

PART II

NEURONAL COMMUNICATION

8.

SYNAPSE STRUCTURE

For the nervous system to function, neurons must be able to communicate with each other, and they do this through structures called synapses. At the synapse, the terminal of a presynaptic cell comes into close contact with the cell membrane of a postsynaptic neuron.

Resources

- Key Takeaways
- Test Yourself
- Video Version

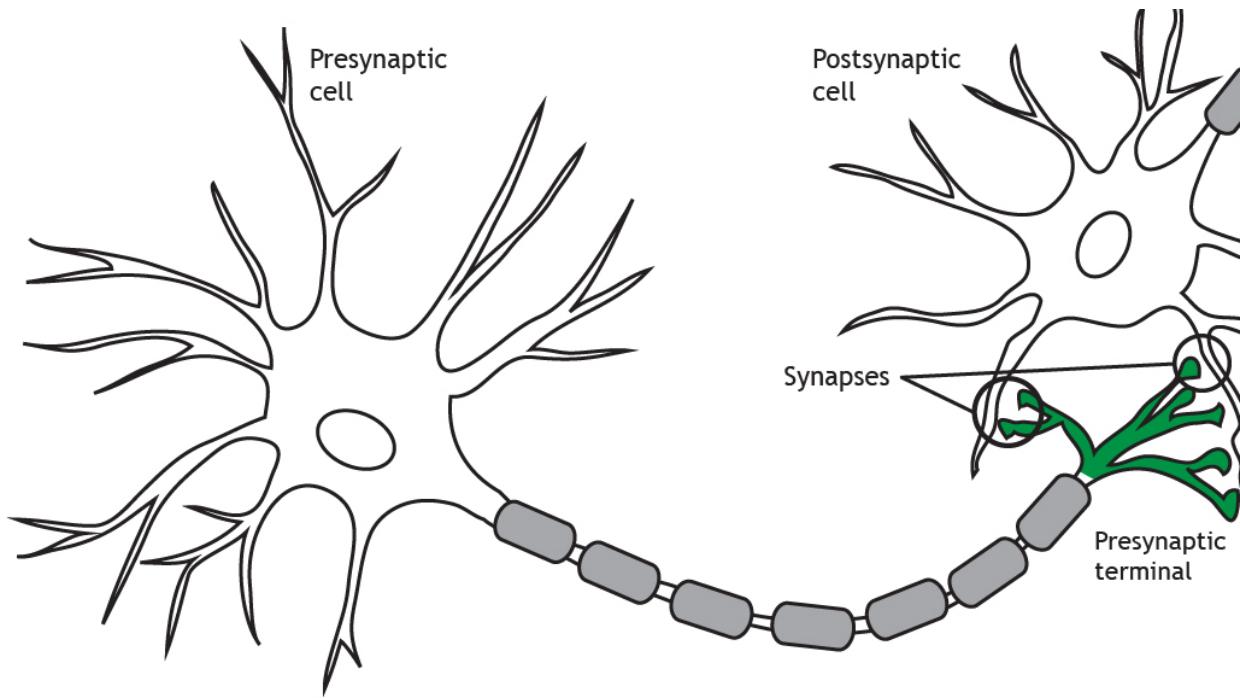


Figure 8.1. The terminal of a presynaptic neuron comes into close contact with a postsynaptic cell at the synapse. 'Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Synapse Types

There are two types of synapses: electrical and chemical.

Electrical

Electrical synapses are a direct connection between two neurons. Cell membrane proteins called connexons form gap junctions between the neurons. The gap junctions form pores that allow ions to flow between neurons, so as an action potential propagates in the presynaptic neuron, the influx of sodium can move directly into the postsynaptic neuron and depolarize the cell. The response in the postsynaptic cell is almost immediate, with little to no delay between signaling in the pre- and postsynaptic neurons.



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Animation 8.1. Membrane-bound proteins called connexons form gap junctions between presynaptic and postsynaptic neurons. This allows for direct exchange of ions between neurons. An action potential in the presynaptic neuron will cause an immediate depolarization of the postsynaptic membrane because the sodium ions will cross the membrane through the gap junctions. ‘Electrical Synapse – Ion Flow’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Since the gap junctions allow diffusion of ions without any obstruction, the signal can flow bidirectionally through an electrical synapse. The electrochemical gradients will drive direction of ion flow.



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Animation 8.2. Since an electrical synapse is a direct, physical connection between two neurons, ions are able to flow either direction across the gap junction. ‘Bidirectional Electrical Synapse’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Additionally, small molecules like ATP or second messengers can also move through the gap junctions. These signaling molecules play an important role in cellular mechanisms, which we will see in a later chapter.



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Animation 8.3. Gap junctions are large enough to allow the flow of small cellular molecules like ATP or second messengers. ‘Electrical Synapse – Small Molecules’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Chemical

Chemical synapses do not form physical connections between the pre- and postsynaptic neurons. Instead, a space called the synaptic cleft exists between the presynaptic terminal and the postsynaptic membrane.

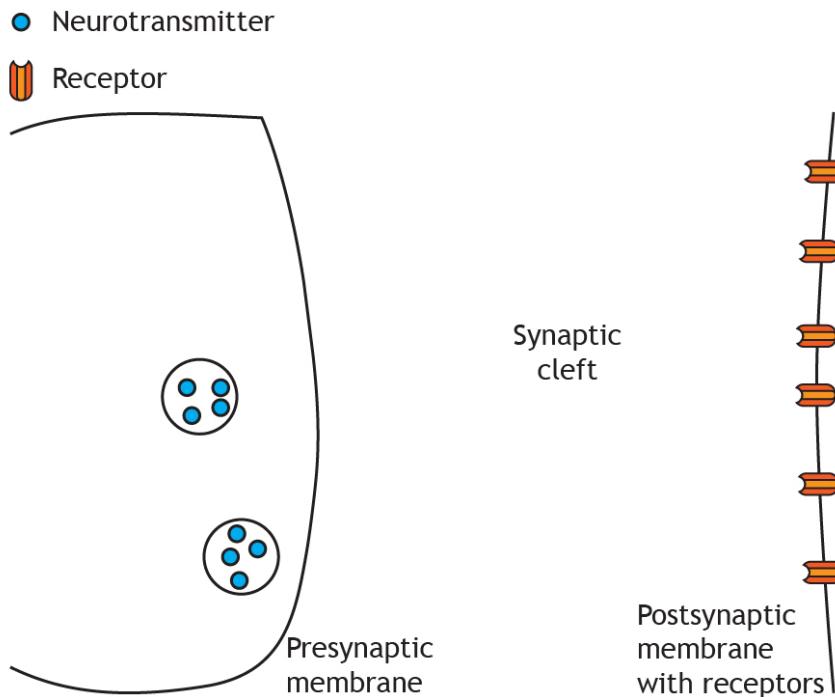


Figure 8.2. A chemical synapse does not make direct contact between the two neurons. The presynaptic terminal and the postsynaptic membrane are separated by the synaptic cleft. Neurotransmitters are stored in the presynaptic cell, and the postsynaptic cell has neurotransmitter receptors in the membrane. ‘Chemical Synapse’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Figure 8.2. A chemical synapse does not make direct contact between the two neurons. The presynaptic terminal and the postsynaptic membrane are separated by the synaptic cleft.

Neurotransmitters are stored in the presynaptic cell, and the postsynaptic cell has neurotransmitter receptors in the membrane. ‘Chemical Synapse’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

At a chemical synapse, the depolarization of an action potential reaching the presynaptic terminal causes release of neurotransmitters, which act on specialized receptors located in the cell membrane of the postsynaptic neuron. The structure and function of chemical synapses make them slower than electrical synapses and permit signaling in only one direction.



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Animation 8.4. An action potential causes release of neurotransmitters from the presynaptic terminal into the synaptic cleft. The transmitters then act on neurotransmitter receptors in the postsynaptic membrane. ‘Chemical Synapse – Neurotransmitter Release’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Synapse Location

As we discuss synaptic transmission, we will focus mainly on axodendritic synapses, in which the presynaptic terminal synapses on the dendrites of the postsynaptic cell. But synapses can also be located between the terminal and the cell body of the postsynaptic cell, called axosomatic, or even between the terminal and the axon of the postsynaptic cell, called axoaxonic.

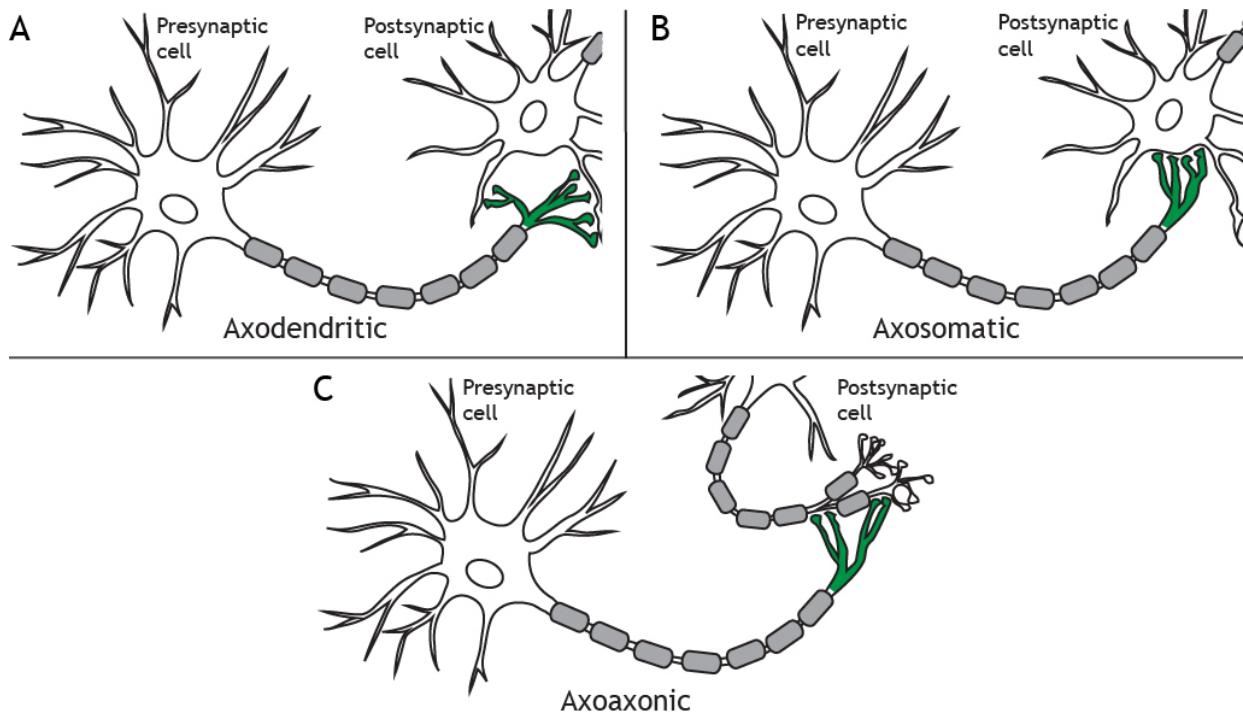


Figure 8.3. A) Axodendritic synapses occur when the presynaptic terminal makes a synaptic connection with the dendrite of a postsynaptic neuron. B) Axosomatic synapses occur when the presynaptic terminal makes a synaptic connection with the cell body of a postsynaptic neuron. C) Axoaxonic synapses occur when the presynaptic terminal makes a synaptic connection with the axon of a postsynaptic neuron. 'Chemical Synapse Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Electrical synapses make direct contact between neurons, are faster than chemical synapses, and can be bidirectional
- Chemical synapses form a synaptic cleft between the neurons and are unidirectional
- Synapses can occur between the presynaptic terminal and the postsynaptic dendrites

(axodendritic), cell body (axosomatic), or axon (axoaxonic)

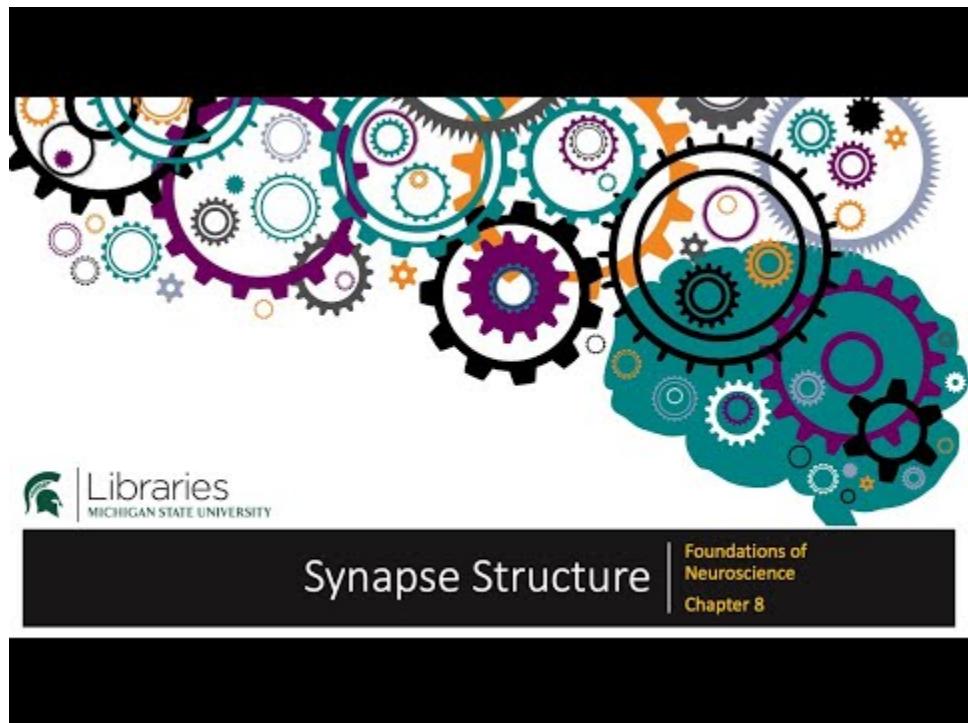
Test Yourself!



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Video Version of Lesson



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9.

NEUROTRANSMITTER SYNTHESIS AND STORAGE

A few criteria must be met for a molecule to be called a neurotransmitter. First, the transmitter must be synthesized within in the presynaptic neuron. Second, the transmitter must be released by the presynaptic neuron in response to stimulation. Third, when a postsynaptic neuron is treated with the transmitter by a researcher, the molecule must cause the same effect in the postsynaptic neuron as when it is released by a presynaptic neuron.

There are two main categories of neurotransmitters: small molecule transmitters and peptide transmitters.

Synthesis and storage of these neurotransmitter groups differ. Small molecule neurotransmitters are synthesized and stored in the terminal for fast release. Neuropeptides are synthesized in the cell body and must be transported to the terminal, which can lead to slower release. Additionally, a neuron typically will synthesize and release only one type of small molecule neurotransmitter but can synthesize and release more than one neuropeptide.

Resources

- Key Takeaways
- Test Yourself
- Video Version

Small Molecule Transmitters

The small molecule transmitters can be divided into two main groups: amino acid neurotransmitters and biogenic amines, also called monoamines. In addition to acting as neurotransmitters, the amino acids glutamate and glycine are used to synthesize proteins in all cell types throughout the body. GABA (γ -Aminobutyric acid) is a metabolite of glutamate but is not used in protein synthesis in the body. The biogenic amines include serotonin and histamine, and the subgroup the catecholamines

dopamine, norepinephrine, and epinephrine. Acetylcholine does not fit into either division but is still considered a small molecule neurotransmitter.

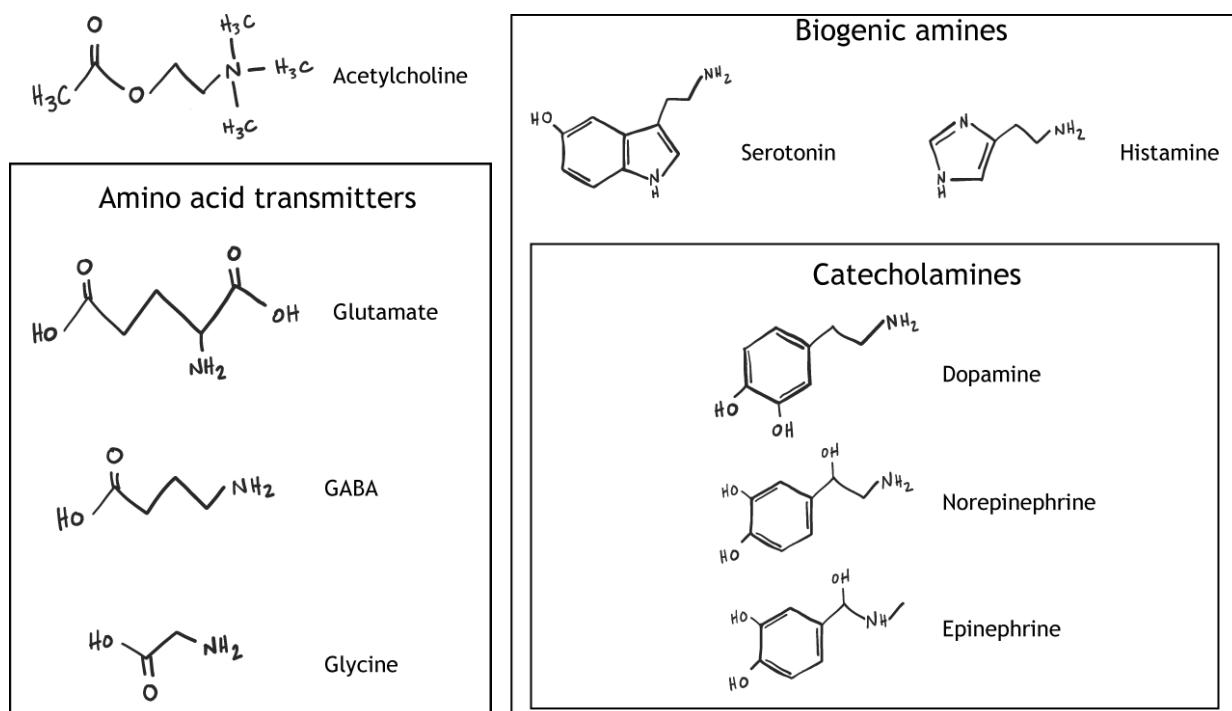


Figure 9.1. Small molecule neurotransmitters can be subdivided into groups based on chemical structure. Amino acid transmitters include glutamate, GABA, and glycine. The biogenic amines include serotonin and histamine, and the catecholamines, a subgroup of the biogenic amines, include dopamine, norepinephrine, and epinephrine. Acetylcholine does not fit into a group. ‘Small Molecule Neurotransmitters’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Synthesis and Storage of Small Molecule Transmitters

Most small molecule neurotransmitters are synthesized by enzymes that are located in the cytoplasm (the exception is norepinephrine, see below). This means that small molecule neurotransmitters can be synthesized and packaged for storage in the presynaptic terminal using enzymes present in the terminal.

Acetylcholine

Acetylcholine is best known for its role at the neuromuscular junction, the synapse between a motor neuron and the muscle fiber. In the presynaptic terminal, acetylcholine is synthesized from acetyl coenzyme A (acetyl CoA) and choline via the enzyme choline acetyltransferase. The level of enzyme activity is the rate-limiting step in the synthesis pathway. Acetylcholine is packaged into vesicles for storage in the terminal via the vesicular acetylcholine transporter (VAChT).

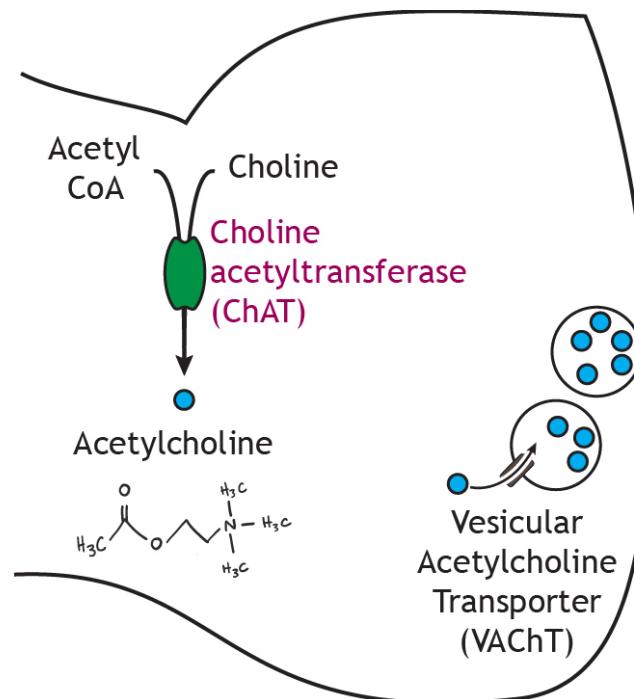


Figure 9.2. Acetylcholine is synthesized from acetyl CoA and choline by choline acetyltransferase, the rate-limiting step in the pathway. Acetylcholine is then packaged into vesicles by vesicular acetylcholine transporter. 'Acetylcholine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Glutamate

Glutamate is an amino acid transmitter and is the primary excitatory neurotransmitter in the brain. In the presynaptic terminal, glutamine is converted into glutamate via the enzyme glutaminase, which is the rate-limiting step in the synthesis pathway. Glutamate is packaged into vesicles for storage via the vesicular glutamate transporter.

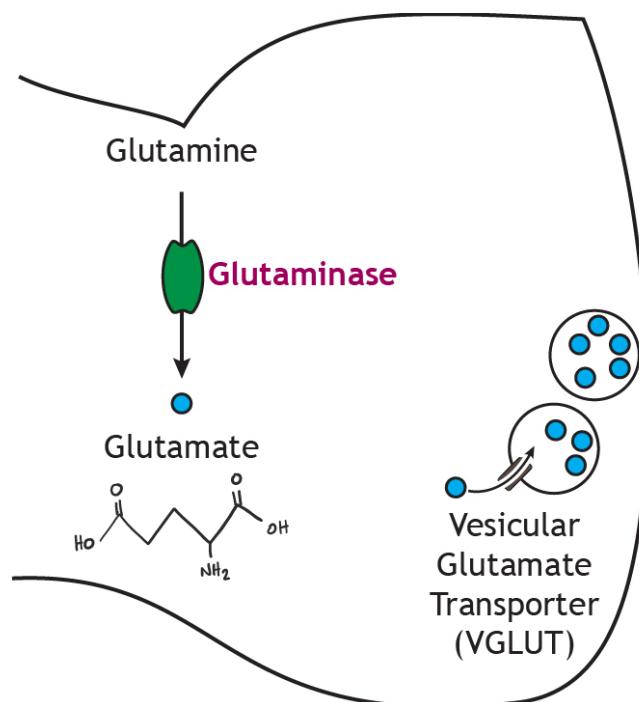


Figure 9.3. Glutamate is synthesized from glutamine by glutaminase, the rate-limiting step in the pathway. Glutamate is then packaged into vesicles by vesicular glutamate transporter. 'Glutamate Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

GABA

Glutamate is then used to synthesize GABA, another amino acid transmitter and the primary inhibitory neurotransmitter in the brain. In the presynaptic terminal, glutamate is converted into GABA via the enzyme glutamic acid decarboxylase, which like the other synthesis pathways is the rate-limiting step. GABA is packaged into vesicles for storage in the terminal via the vesicular inhibitory amino acid transporter.

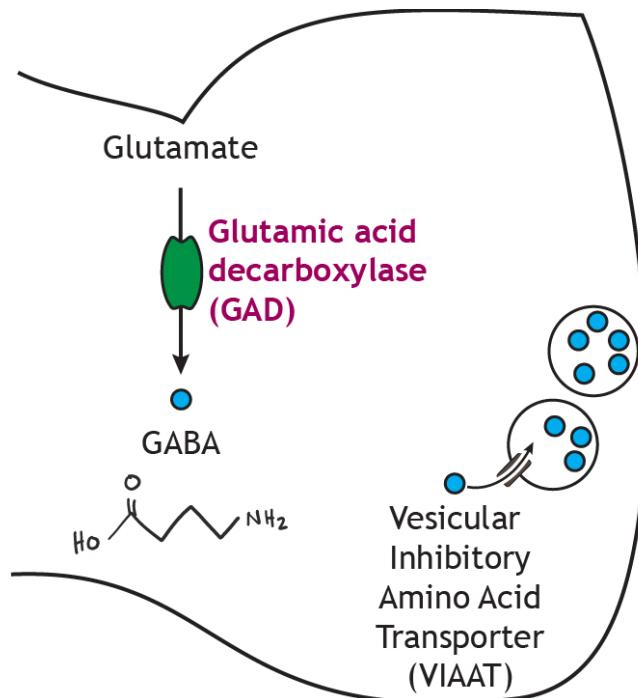


Figure 9.4. GABA is synthesized from glutamate by glutamic acid decarboxylase, the rate-limiting step in the pathway. GABA is then packaged into vesicles by vesicular inhibitory amino acid transporter. 'GABA Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Glycine

Glycine is another inhibitory amino acid neurotransmitter, but unlike GABA, it is more common in the spinal cord than in the brain. Serine hydroxymethyltransferase converts the amino acid serine into glycine in the presynaptic terminal. The rate limiting step for glycine synthesis occurs earlier in the pathway prior to serine synthesis. Glycine is packaged into vesicles by the vesicular inhibitory amino acid transporter like GABA.

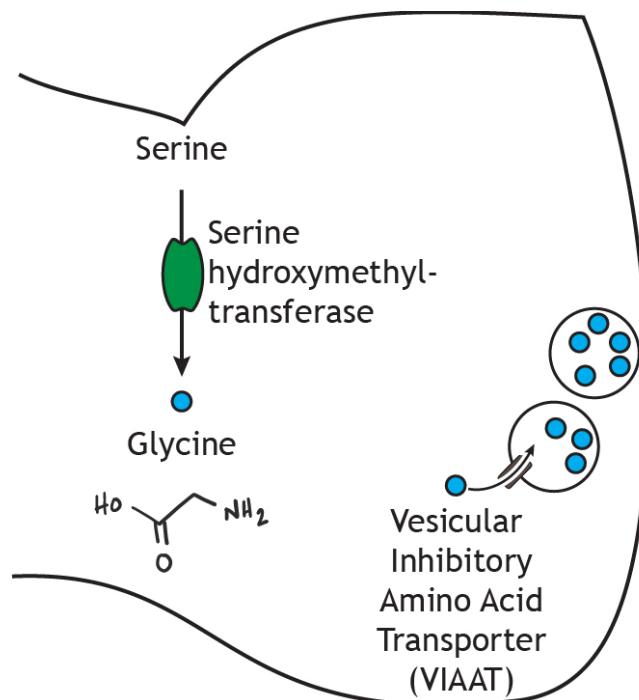


Figure 9.5. Glycine is synthesized from serine by serine hydroxymethyltransferase. Glycine is then packaged into vesicles by vesicular inhibitory amino acid transporter. 'Glycine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Dopamine

Dopamine, a catecholamine transmitter, plays many roles in the nervous system, but it is best known for its roles in reward and movement. In the presynaptic terminal, the amino acid tyrosine is converted into DOPA via tyrosine hydroxylase, which is the rate limiting step in the synthesis of all the catecholamines. DOPA is then converted to dopamine by DOPA decarboxylase. Dopamine is packaged into synaptic vesicles by the vesicular monoamine transporter.

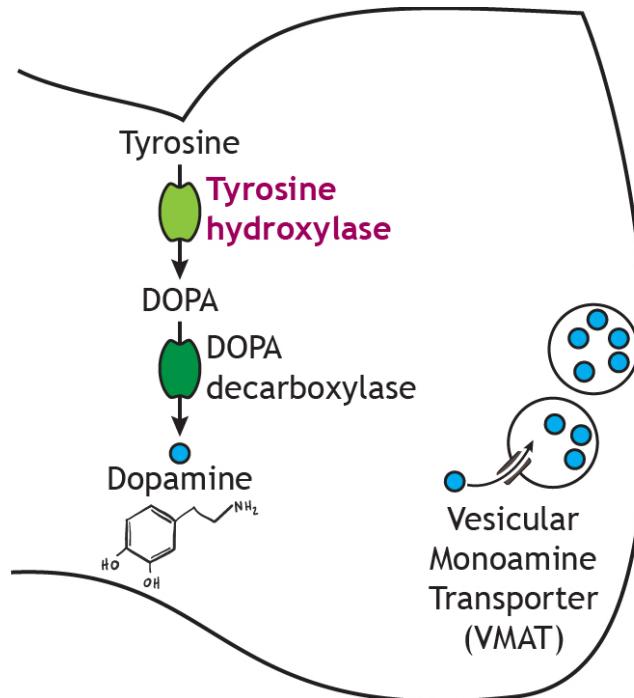


Figure 9.6. Dopamine is synthesized in a two-step process. Tyrosine is converted into DOPA by tyrosine hydroxylase, the rate-limiting step in the pathway. Then dopamine is synthesized from DOPA by DOPA decarboxylase. Dopamine is then packaged into vesicles by vesicular monoamine transporter. 'Dopamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Norepinephrine

In neurons that release norepinephrine, which is another catecholamine transmitter, once dopamine is packaged into the synaptic vesicles, a membrane-bound enzyme called dopamine beta-hydroxylase converts dopamine into norepinephrine. Therefore, unlike the other small molecule neurotransmitters, norepinephrine is synthesized within the vesicles, not in the cytoplasm. Like dopamine, the rate limiting step of this synthesis pathway is the activity of tyrosine hydroxylase.

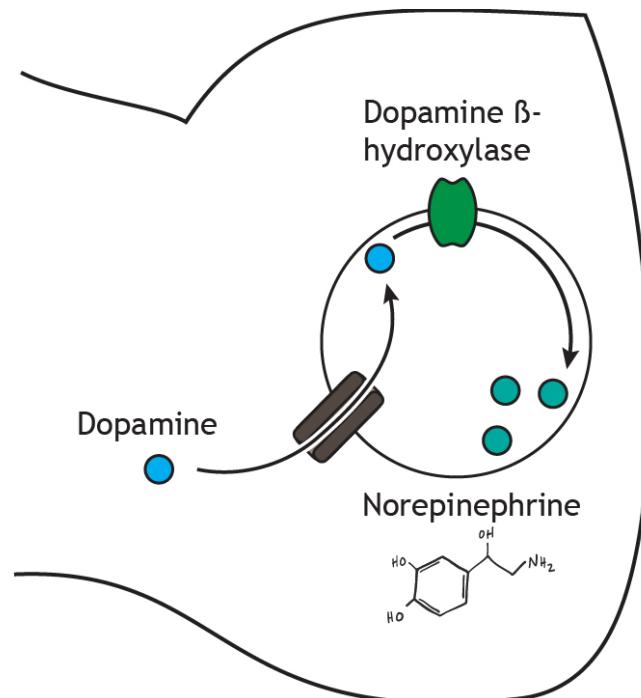


Figure 9.7. Norepinephrine is synthesized from dopamine by dopamine beta-hydroxylase after packaging into vesicles. 'Norepinephrine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Epinephrine

Epinephrine, also called adrenaline, is a catecholamine, but it is often considered a hormone instead of a neurotransmitter. Epinephrine is primarily released by the adrenal medulla into the circulation; it is used as a neurotransmitter in only a small number of neurons. Epinephrine is synthesized from norepinephrine in the cytoplasm by the enzyme phenylethanolamine-N-methyltransferase, so epinephrine synthesis requires norepinephrine to exit the vesicles where it was synthesized. After synthesis in the cytoplasm, epinephrine is repackaged into vesicles via the vesicular monoamine transporter.

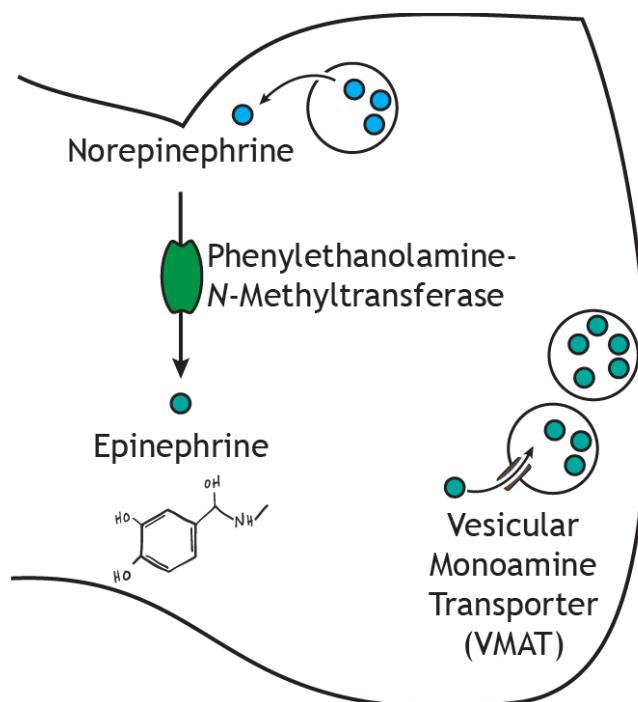


Figure 9.8. Epinephrine is synthesized from norepinephrine by phenylethanolamine-N-methyltransferase in the cytoplasm. Epinephrine is then packaged into vesicles by vesicular monoamine transporter. 'Epinephrine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Serotonin

Serotonin, a biogenic amine neurotransmitter, is known for its role in mood. Tryptophan is converted into 5-hydroxytryptophan by tryptophan hydroxylase. This is also the rate-limiting step of the synthesis pathway. Then aromatic L-amino acid decarboxylase converts the 5-hydroxytryptophan into serotonin. Serotonin is packaged into vesicles by the vesicular monoamine transporter similar to the other monoamine neurotransmitters: dopamine and epinephrine.

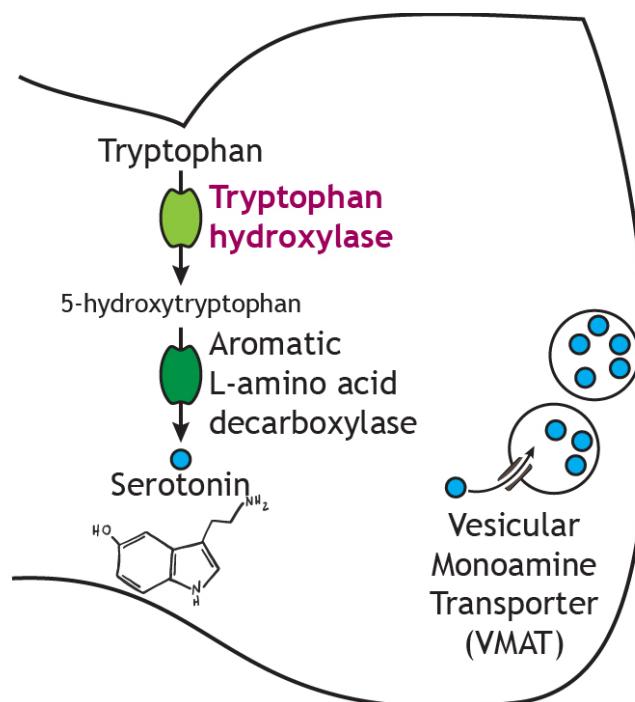


Figure 9.9. Serotonin is synthesized in a two-step process. Tryptophan is converted into 5-hydroxytryptophan by tryptophan hydroxylase, the rate-limiting step in the pathway. Then serotonin is synthesized from 5-hydroxytryptophan by aromatic L-amino acid decarboxylase. Serotonin is then packaged into vesicles by vesicular monoamine transporter. ‘Serotonin Synthesis’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Histamine

Finally, histamine is another biogenic amine transmitter that is synthesized from histidine through the action of histidine decarboxylase, the rate limiting step of the pathway. Like the other monoamine neurotransmitters, it is packaged into synaptic vesicles via the vesicular monoamine transporter.

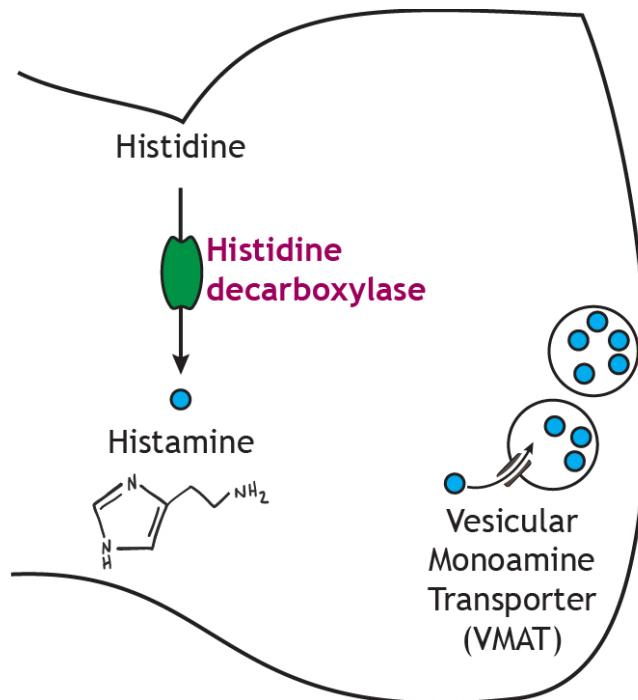


Figure 9.10. Histamine is synthesized from histidine by histidine decarboxylase, the rate-limiting step in the pathway. Histamine is then packaged into vesicles by vesicular monoamine transporter. 'Histamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Synthesis and Storage of Neuropeptides

Neuropeptides are a short string of amino acids and are known to have a wide range of effects from emotions to pain perception. Unlike small molecule neurotransmitters, neuropeptides are synthesized in the cell body and transported to the axon terminal. Like other proteins, neuropeptides are synthesized from mRNA into peptide chains made from amino acids. In most cases, a larger precursor molecule called the prepropeptide is translated into the original amino acid sequence in the rough endoplasmic reticulum. The prepropeptide is processed further to the propeptide stage. The remaining processing and packaging of the final neuropeptide into a vesicle occurs in the Golgi apparatus. The peptides are packaged into vesicles that are significantly larger than the vesicles that store the small molecule transmitters. These large vesicles must then move from the soma to the terminal.

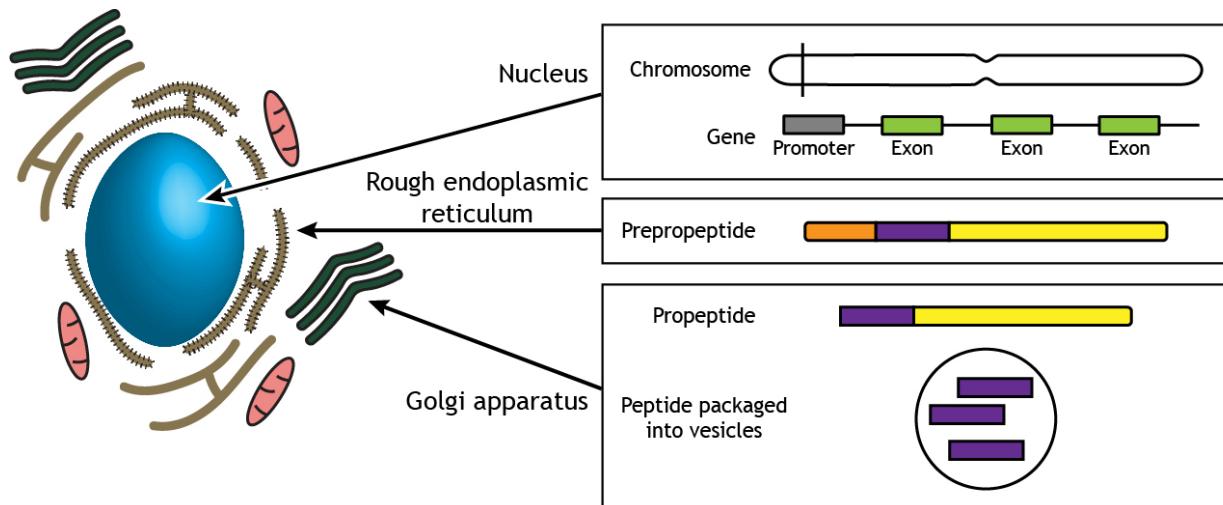


Figure 9.11. Neuropeptide synthesis occurs in the cell body. Each neuropeptide is encoded by a gene on the DNA located in the nucleus. mRNA is translated into an amino acid sequence for a precursor molecule called a prepropeptide in the rough endoplasmic reticulum. Further processing and packaging of the neuropeptide into vesicles occurs in the Golgi apparatus. ‘Neuropeptide Synthesis’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Axonal Transport

The packaged peptides need to be transported to the presynaptic terminals to be released into the synaptic cleft. Organelles, vesicles, and proteins can be moved from the cell body to the terminal via anterograde transport or from the terminal to the cell body via retrograde transport. Anterograde transport can be either fast or slow.

The packaged neuropeptides are transported to the synaptic terminals via fast anterograde axonal transport mechanisms.

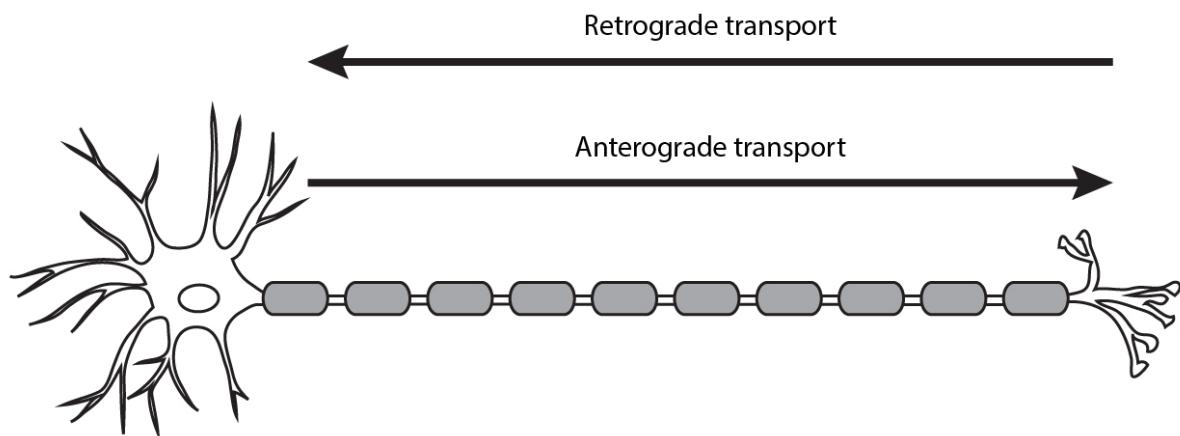


Figure 9.12. Cellular components need to be able to move throughout the cell to have proper functioning. Anterograde transport moves components from the cell body toward the terminal. Retrograde transport moves components from the terminal toward the cell body. 'Axonal Transport' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Small molecule neurotransmitters are synthesized and packaged into vesicles in the presynaptic terminal
- Neuropeptide transmitters are synthesized and packaged into vesicles in the cell body and are transported to the terminal via fast axonal transport
- Each small molecule neurotransmitter has a rate limiting step that controls the rate of synthesis
- Neuropeptides rely on axonal transport mechanisms to move from the soma to the terminal

Test Yourself



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Video Version of Lesson



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10.

NEUROTRANSMITTER RELEASE

Action Potential

As we have covered, when an action potential propagates down the axon to the presynaptic terminal, the electrical signal will result in a release of chemical neurotransmitters that will communicate with the postsynaptic cell.



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Resources

- Key Takeaways
- Test Yourself
- Additional Review
- Video Version

Animation 10.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. ‘Action Potential Propagation’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation

Ion flow in Terminal

When the action potential reaches the terminal, there is an influx of sodium ions. This inward current causes a depolarization of the terminal, activating voltage-gated calcium channels. There is a strong electrochemical gradient that moves calcium into the terminal.



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Animation 10.2. An action potential causes an influx of sodium in the terminal. The depolarization opens voltage-gated calcium channels, and calcium ions flow into the terminal down their electrochemical gradient. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. ‘Terminal Calcium Influx’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Active Zones

The voltage-gated calcium channels are concentrated in the presynaptic terminal at active zones, the regions of the membrane where small molecule neurotransmitters are released. At active zones, some synaptic vesicles are docked and are ready for immediate release upon arrival of the action potential. Other neurotransmitter-filled vesicles remain in a reserve pool outside of the active zone.

Vesicles filled with neuropeptides do not dock at active zones. They are located outside of the active zone, further away from the membrane and the high density of voltage-gated calcium channels and are therefore slower to release than the small molecule transmitters.

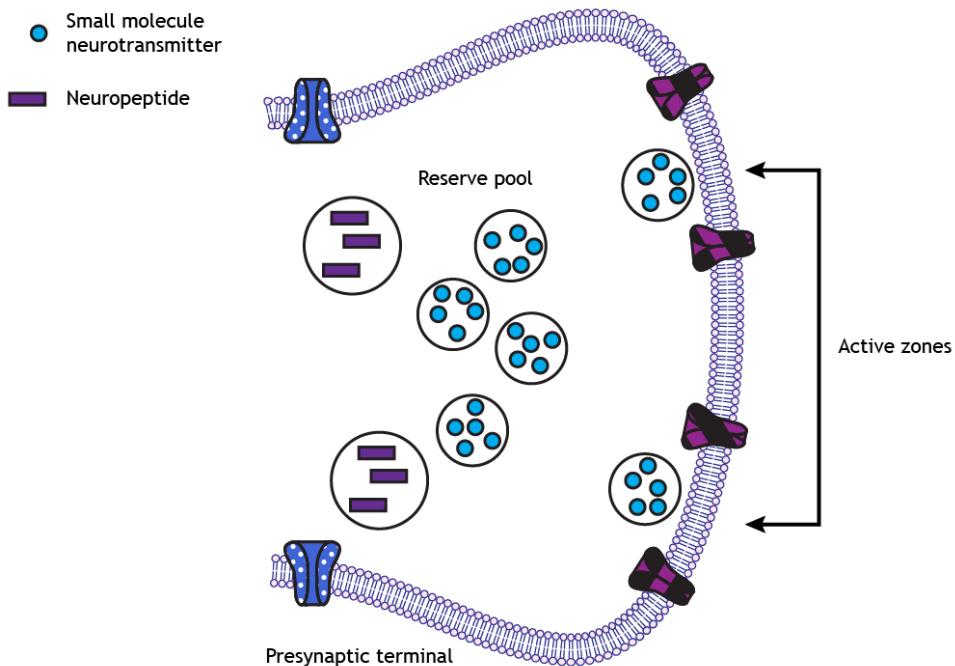


Figure 10.1. Some synaptic vesicles filled with small molecule neurotransmitters dock at active zones on the presynaptic membrane, ready for immediate release. Other synaptic vesicles remain nearby in reserve pools, ready to move into empty active zones. Neuropeptide-filled vesicles do not dock at active zones. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Active Zones' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Vesicle Docking

Docking of synaptic vesicles packaged with small molecule neurotransmitters occurs through the interaction of three membrane-bound proteins called SNARE proteins. Synaptobrevin is called a v-SNARE because it is located on the Vesicular membrane. Syntaxin and SNAP-25 are called t-SNARES because they are located on the terminal membrane, which is the Target membrane. The interaction of these three proteins leads to vesicle docking at the active zone.

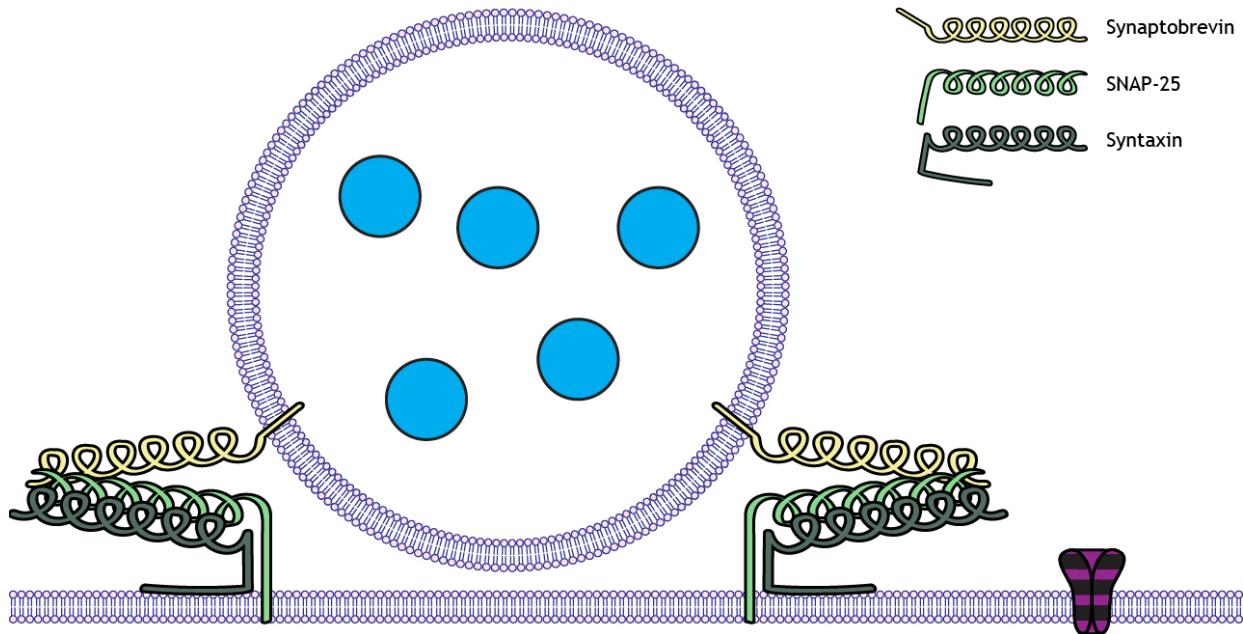


Figure 10.2. Synaptic vesicles filled with small molecule neurotransmitters are able to dock at active zones by the interaction of v- and t-SNARE proteins. Synaptobrevin is embedded in the membrane of the vesicle whereas SNAP-25 and Syntaxin are embedded in the presynaptic terminal membrane. The purple, striped channels represent voltage-gated calcium channels. 'SNARE proteins' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Exocytosis

The influx of calcium through the voltage-gated calcium channels initiates the exocytosis process that leads to neurotransmitter release. Calcium enters the cell and interacts with another vesicle-bound protein called synaptotagmin. This protein is a calcium sensor, and when calcium is present at the active zone, synaptotagmin interacts with the SNARE proteins. This is the first step toward exocytosis of the synaptic vesicle.



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Animation 10.3. Calcium enters the cell when the voltage-gated channels open. In the presence of calcium, synaptotagmin, a protein bound to the vesicular membrane interacts with the SNARE proteins. The purple, striped channels represent voltage-gated calcium channels. ‘Synaptotagmin’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation

Once synaptotagmin interacts with the SNARE proteins, the synaptic vesicle membrane fuses with the presynaptic terminal membrane, exocytosis occurs, and the neurotransmitters released.



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Animation 10.4. Once the synaptotagmin-SNARE protein complex forms, the synaptic vesicle membrane fuses with the terminal membrane, and the neurotransmitters are released into the synaptic cleft through exocytosis. The purple, striped channels represent voltage-gated calcium channels. ‘Transmitter Exocytosis’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Neurotransmitter Action

After exocytosis of the transmitter molecules, they enter the synaptic cleft and bind to receptors on the postsynaptic membrane. Receptors fall into two main categories: ligand-gated channels and G-protein coupled receptors. The next two chapters cover these receptors.

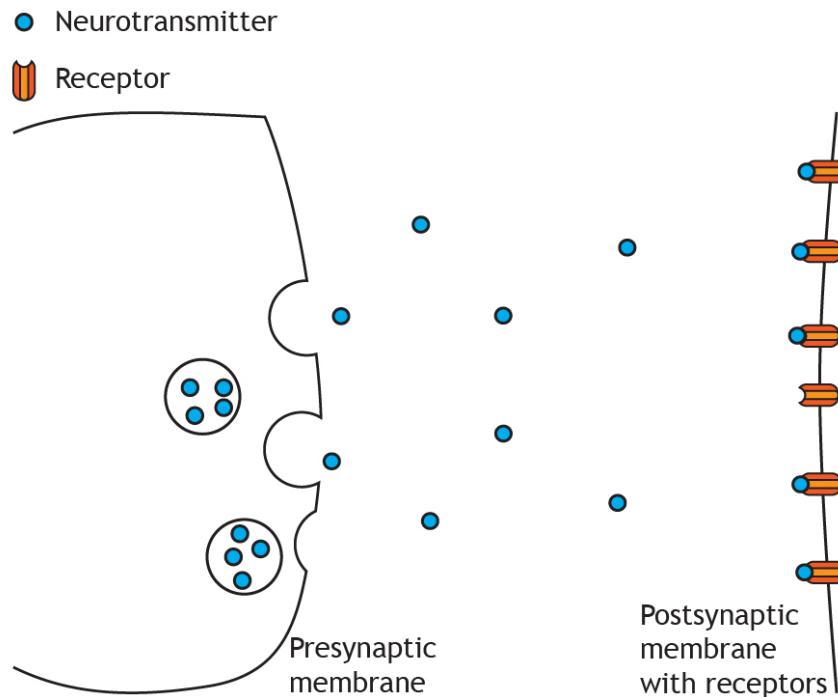


Figure 10.4. After exocytosis of the neurotransmitters into the synaptic cleft, the transmitters bind to receptors present on the postsynaptic membrane. 'Neurotransmitter in Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Neurotransmitter release is dependent on the influx of calcium into the terminal
- SNARE proteins are important for vesicle docking at active zones and exocytosis
- Synaptotagmin is a calcium sensor

Test Yourself!



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Additional Review

Describe the events that occur in the presynaptic terminal when an action potential arrives. Include the role of Ca^{2+} .

Answers

Video Version of Lesson



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11.

NEUROTRANSMITTER ACTION: IONOTROPIC RECEPTORS

Ionotropic receptors, also called neurotransmitter-gated or ligand-gated channels, are ion channels that open in response to the binding of a neurotransmitter. They are primarily located along the dendrites or cell body, but they can be present anywhere along the neuron if there is a synapse. Ligand-gated channels are important for receiving incoming information from other neurons.

Resources

- Key Takeaways
- Test Yourself
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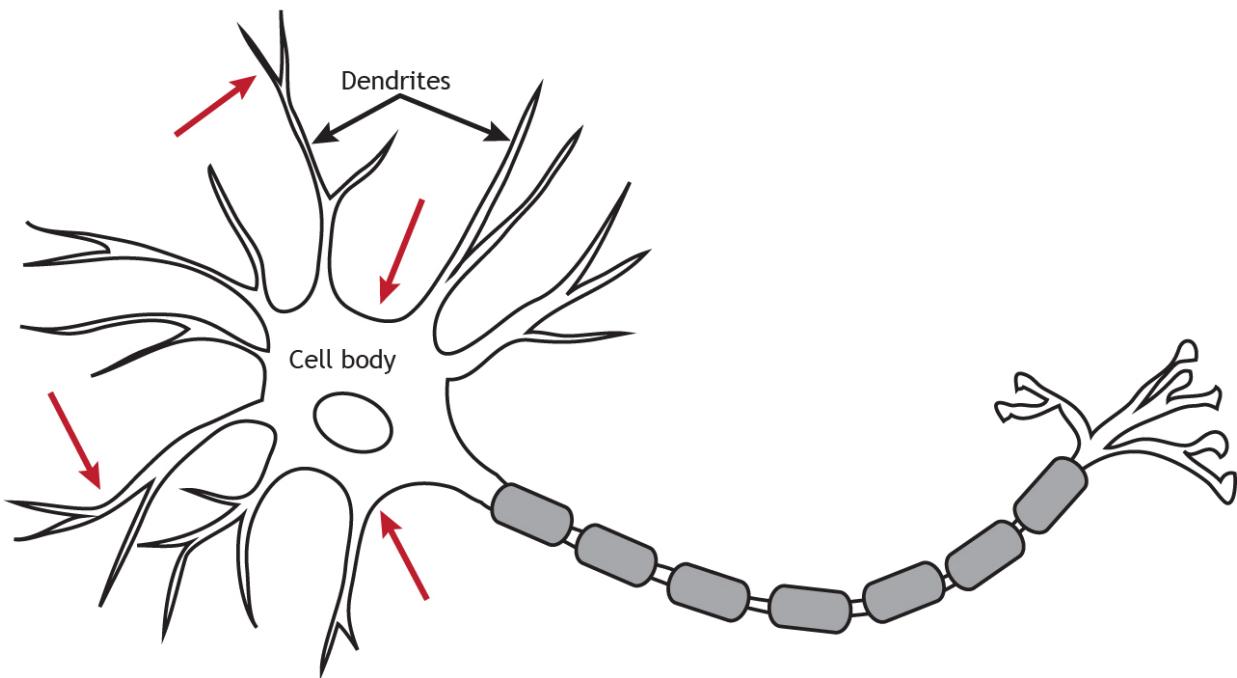


Figure 11.1. Ligand-gated channels critical for receiving incoming synaptic information are primarily located along the dendrites and cell body. 'Receptor Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Although ionotropic receptors are ion channels, they open in a different way than the voltage-gated ion channels needed for propagation of the action potential. The ionotropic receptors are ligand-gated, which means that a specific molecule, such as a neurotransmitter, must bind to the receptor to cause the channel to open and allow ion flow. As seen in previous chapters, the voltage-gated channels open in response to the membrane potential reaching threshold.



A video element has been excluded from this version of the text. You can watch it online here: <https://openbooks.lib.msu.edu/neuroscience/?p=368>

Animation 11.1. Ionotropic receptors, also called ligand-gated channels, are ion channels that are opened by the binding of neurotransmitters. Voltage-gated channels are opened by the membrane

potential of the cell reaching threshold. Both types of channels allow ions to diffuse down their electrochemical gradient. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors; the dotted, blue channels represent voltage-gated sodium channels. ‘Ion Channel Gating’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

The receptors can only be opened by a specific ligand. Neurotransmitters and receptors fit together like a lock and key; only certain neurotransmitters are able to bind to and open certain receptors.



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Animation 11.2. Since neurotransmitter receptors can only bind specific neurotransmitters, glutamate binds to and opens glutamate receptors but has no effect on GABA receptors. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors. ‘Ligand and Receptor’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Glutamate Receptors

Glutamate is the primary excitatory neurotransmitter in the central nervous system and opens non-selective cation channels. There are three subtypes of glutamate receptors. The AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors allow both sodium and potassium to cross the membrane. Although potassium can leave the cell when the receptors open, the electrochemical gradient driving sodium ion movement is stronger than the gradient driving potassium movement, resulting in a depolarization of the membrane potential.



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Animation 11.3. AMPA and kainate glutamate receptors are non-selective ion channels that allow both sodium and potassium to flow across the membrane. When glutamate binds, sodium flows in and potassium flows out. The lined, teal channel represent sAMPA receptors; the checkered, teal channel represents kainate receptors. ‘AMPA and Kainate’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

The NMDA (N-methyl-D-aspartate) receptor requires the binding of glutamate to open, but it is also dependent on voltage. When the membrane potential is below, at, or near rest, a magnesium ion blocks the open NMDA receptor and prevents other ions from moving through the channel. Once the cell depolarizes, the magnesium block is expelled from the receptor, which allows sodium, potassium, and calcium to cross the membrane. The voltage change needed to open the NMDA receptor is usually a result of AMPA receptor activation. Released glutamate binds to both AMPA and NMDA receptors, sodium influx occurs through open AMPA channels, which depolarizes the cell enough to expel the magnesium ion and allow ion flow through the NMDA receptors.



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Animation 11.4. NMDA receptors are opened by a combination of glutamate binding and a voltage trigger. At low levels of stimulation, when the the membrane potential is near rest, a magnesium ion blocks the open NMDA receptor channel preventing ion flow. Ions can flow through open AMPA receptors, which begins to depolarize the membrane. The voltage change eventually expels the magnesium ion from the channel, allowing sodium, potassium, and calcium to cross the membrane. The lined, teal channel represents AMPA receptors; the dotted, violet channel represents NMDA receptors. ‘AMPA and NMDA’ by Casey Henley is licensed under a Creative Commons Attribution

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Nicotinic Acetylcholine Receptors

Like glutamate receptors, nicotinic acetylcholine receptors are non-selective cation channels.

Nicotinic receptors, though, are located primarily outside of the central nervous system. The nicotinic receptors are used at the neuromuscular junction

GABA and Glycine Receptors

GABA and glycine receptors are chloride channels. Since an increase chloride permeability across the membrane is inhibitory, the binding of GABA or glycine to their respective ionotropic receptor will cause inhibition.



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Animation 11.5. GABA and glycine are inhibitory receptors that are selective to chloride. The solid yellow channel represents a GABA receptor; the patterned, yellow channel represents a glycine receptor. ‘GABA and Glycine’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Ionotropic Receptors Cause Postsynaptic Potentials

Postsynaptic potentials (Chapter 5) are a result of ionotropic receptors opening. Excitatory ionotropic

receptors increase sodium permeability across the membrane, whereas inhibitory ionotropic receptors increase chloride permeability. Ion flow through the ionotropic receptors follows the same principles as other ion channels covered so far.

Equilibrium Potential Review

Previously, we covered ion movement through voltage-gated channels and discussed that electrochemical gradients will drive ion movement toward equilibrium. The neuron's membrane potential at which the chemical and electrical gradients balance and equilibrium occurs is the ion's equilibrium potential.



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Animation 11.6. Ions move through open voltage-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the ion's equilibrium potential. In the animation, a voltage-gated sodium channel opens, and sodium flows in until the membrane potential equals approximately +60 mV, sodium's equilibrium potential. The blue, dotted channel represents a voltage-gated sodium channel. 'Equilibrium Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Reversal Potential

This same principle is used for ion movement through ionotropic receptors. The membrane potential at which ion flow through a receptor is at equilibrium is called the reversal potential of the receptor. The direction of ion movement can be predicted if the reversal potential of the receptor is known.

GABA and Glycine – Receptors Selective to One Ion

When an ionotropic receptor that is selective to only one ion opens, the reversal potential of the receptor is the same as the equilibrium potential of the ion. GABA and glycine receptors only allow chloride ions to cross the membrane. Therefore, the reversal potential of a GABA or glycine receptor is equal to the equilibrium potential of chloride, and the binding of GABA or glycine to their respective ionotropic receptor will cause an inhibitory postsynaptic potential (IPSP).



A video element has been excluded from this version of the text. You can watch it online here: <https://openbooks.lib.msu.edu/neuroscience/?p=368>

Animation 11.7. Ions move through open ligand-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the receptor's reversal potential. When the ionotropic receptor only increases permeability for one ion, the receptor's reversal potential is the same as the ion's equilibrium potential. In the animation, a GABA receptor opens, and chloride flows in until the membrane potential equals approximately -65 mV, GABA's reversal potential and chloride's equilibrium potential. Increased chloride permeability causes an IPSP and inhibits the neuron. The yellow, checkered channel represents a GABA receptor. 'GABA Reversal Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Glutamate – Reversal Potential for Receptors that are Non-Selective

However, if the ionotropic receptor allows the flow of more than one ion, or is non-selective, the reversal potential of the receptor does not equal the equilibrium potential of either ion but is somewhere in between. The equilibrium potential of sodium is approximately +60 mV, and the equilibrium potential of potassium is approximately -80 mV. A glutamate receptor is a non-selective cation channel that allows the flow of both ions, and the reversal potential of the receptor is 0 mV. This means that if the neuron's membrane potential is negative, the driving forces acting on sodium are stronger than the driving forces acting on potassium, so more sodium will flow in than potassium

will flow out, and the membrane potential will depolarize, causing an excitatory postsynaptic potential (EPSP).



A video element has been excluded from this version of the text. You can watch it online here: <https://openbooks.lib.msu.edu/neuroscience/?p=368>

Animation 11.8. The reversal potential of an ionotropic receptor that is not selective to one ion will fall between the equilibrium potentials of the permeable ions. Glutamate receptors allow the flow of both sodium and potassium ions, so the reversal potential for the receptor is approximately 0 mV. More sodium will flow into the cell than potassium flows out, resulting in a depolarization of the membrane. The line, teal channel represents a glutamate receptor. ‘Glutamate Reversal Potential – Rest’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

If the membrane potential reached the reversal potential of the glutamate receptor, the electrochemical gradients acting on sodium and potassium would balance, so overall ion flow in both directions would be equal, and the membrane potential would not change.



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Animation 11.9. At the reversal potential, there is no net ion flow in either direction. An equal number of sodium ions enter the cell as potassium ions leave. Since there is no change in voltage at the reversal potential, if the receptor remained open, the membrane potential would stay at 0 mV. ‘Glutamate Reversal Potential – 0 mV’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Key Takeaways

- Ionotropic receptors are ligand-gated ion channels that open when a specific neurotransmitter binds
- For receptors selective to one ion, the reversal potential equals the ion's equilibrium potential
- For receptors not selective for only one ion, the reversal potential is a value between the ions' equilibrium potentials
- Glutamate is an excitatory neurotransmitter that opens non-selective cation channels that allow the influx of sodium, causing an EPSP
- GABA and glycine are inhibitory neurotransmitters that open chloride channels, causing an IPSP

Test Yourself!



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Additional Review

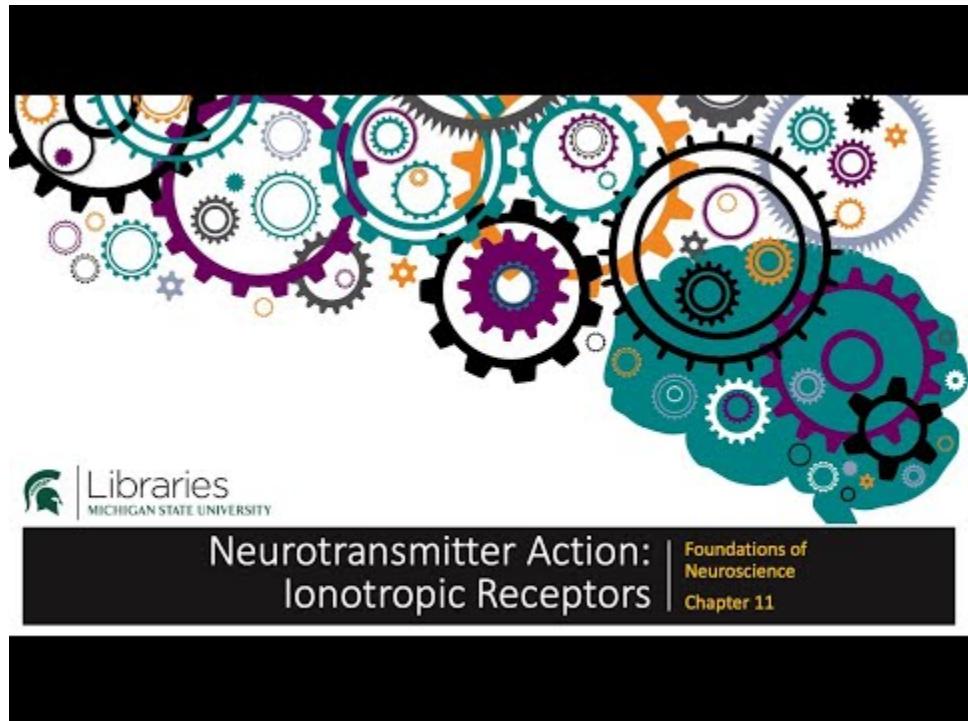
A postsynaptic neuron (Cell A) is at rest at -60 mV and receives input from five separate glutamate neurons and one GABA neuron. Changes in the postsynaptic membrane potential can be measured by a recording electrode located in the cell body.

Draw the change in the postsynaptic membrane potential would you expect to see after each of the following manipulations:

1. One presynaptic glutamate neuron fires one action potential and releases neurotransmitter
2. The presynaptic GABA neuron fires one action potential and releases neurotransmitter
3. One presynaptic glutamate neuron fires five action potentials and releases neurotransmitter

Answers

Video Version of Lesson



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12.

NEUROTRANSMITTER ACTION: G-PROTEIN-COUPLED RECEPTORS

Resources

- Key Takeaways
- Test Yourself
- Additional Review
- Video Version

G-protein-coupled receptors (GPCRs), also called metabotropic receptors, are membrane-bound proteins that activate G-proteins after binding neurotransmitters. Like ionotropic receptors, metabotropic receptors are primarily located along the dendrites or cell body, but they can be present anywhere along the neuron if there is a synapse. Metabotropic receptors are also important for receiving incoming information from other neurons. GPCRs have slower effects than ionotropic receptors, but they can have long-lasting effects, unlike the brief action of a postsynaptic potential.

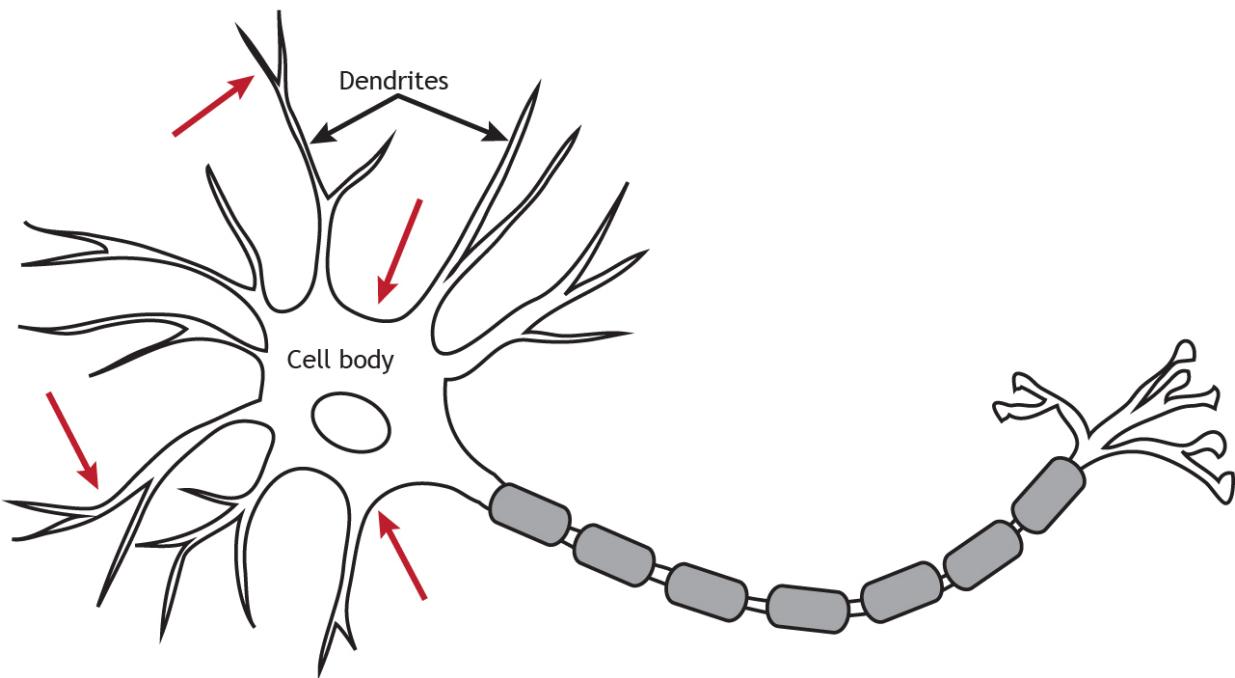


Figure 12.1. Metabotropic receptors critical for receiving incoming synaptic information are primarily located along the dendrites and cell body. 'Receptor Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

G-Proteins

G-proteins are enzymes with three subunits: alpha, beta, and gamma. In the resting state of the G-protein complex, the alpha subunit is bound to a GDP molecule. There are multiple types of alpha subunits, and each initiate different cellular cascades in the neuron.

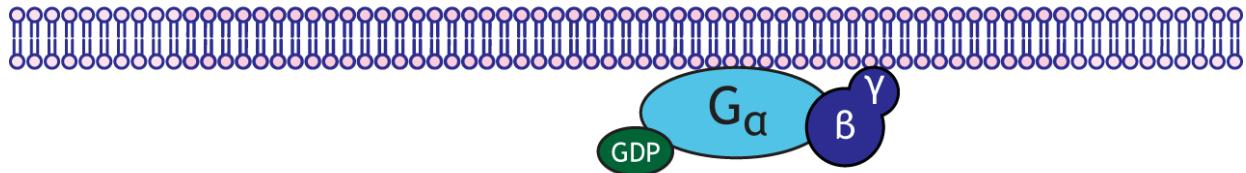


Figure 12.2. The unactivated G-protein complex in the cell consists of three subunits (alpha, beta, and gamma) and a bound GDP molecule. 'G-protein Complex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

G-Protein Coupled Receptors

When a neurotransmitter binds to a GPCR, the receptor is able to interact with an inactivated G-protein complex. The complex that binds is specific to the receptor; different metabotropic receptors for the same neurotransmitter can have different effects in the cell due to which G-protein binds. Once coupled to the receptor, the GDP molecule is exchanged for a GTP molecule, and the G-protein becomes activated.



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Animation 12.1. Neurotransmitter binding to a G-protein-coupled receptor causes the inactivated G-protein complex to interact with the receptor. The GDP molecule is then exchanged for a GTP molecule, which activates the G-protein complex. 'G-protein Binding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

After activation, the G-protein complex will separate into the alpha-GTP subunit and the beta-gamma subunit. Both components can alter the function of effector proteins in the cell. Effector protein functions can range from altering ion permeability across the membrane by opening ion channels to initiating second messenger cascades. Second messenger cascades can have long-term,

widespread, and diverse cellular effects including activation of cellular enzymes or altering gene transcription.



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Animation 12.2. Once activated, the G-protein complex will separate into the alpha-GTP subunit and the beta-gamma subunit. These subunits can stimulate or inhibit effector proteins within the cell. ‘G-protein Effects’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Cellular Effects of G-Proteins

Open Ion Channels – Beta Gamma Subunit

In certain situations, the activated beta-gamma subunit can open or close ion channels and change membrane permeability. Muscarinic acetylcholine receptors in the heart use this pathway. When acetylcholine binds to a muscarinic receptor in the heart muscle fiber, the activated beta-gamma subunit opens a type of potassium channel called G-protein-coupled inwardly-rectifying potassium (GIRK) channel, hyperpolarizing the cell. This inhibitory effect explains why acetylcholine or an agonist like atropine slow the heart rate.



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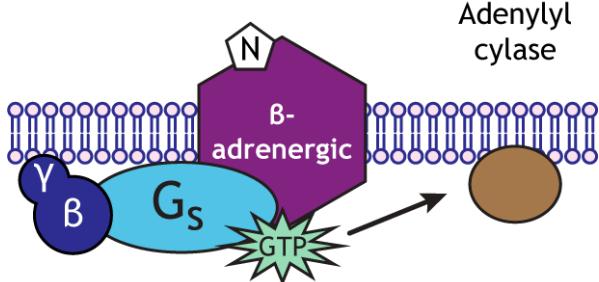
Animation 12.3. Some GPCRs, like the muscarinic acetylcholine receptors in the heart, alter cellular permeability by opening ion channels. The activated beta-gamma subunit of the muscarinic receptor

opens GIRK potassium channels and allows the efflux of potassium. ‘Beta-Gamma Ion Channels’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

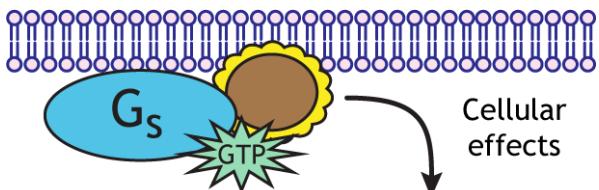
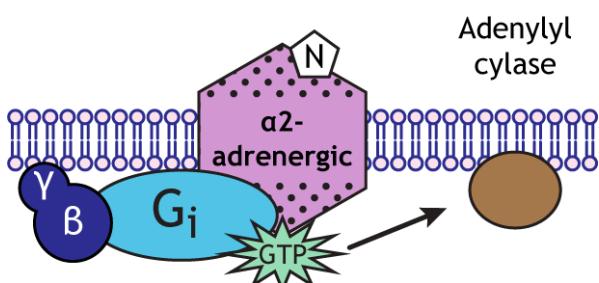
Second Messenger Cascades

In addition to direct effects like the activated beta-gamma subunit opening ion channels, G-proteins can have many indirect actions in the cell through the use of second messenger cascades. The specific second messenger pathway that is activated or suppressed by G-protein action depends on the type of alpha subunit.

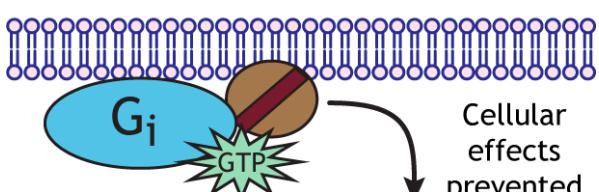
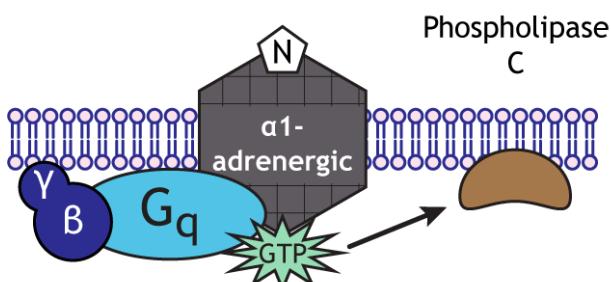
For example, norepinephrine can act on either alpha- or beta-adrenergic receptors. Beta-adrenergic GPCRs couple to a stimulatory G-protein, or G_s , which initiates the cyclic AMP (cAMP) second messenger system by activating the enzyme adenylyl cyclase. Alpha 2-adrenergic receptors, however, couple to an inhibitory G-protein, or G_i , and suppress the activity of adenylyl cyclase. Alpha 1-adrenergic receptors couple to a third type of G-protein, G_q , which activates the phospholipase C pathway. One neurotransmitter can, therefore, cause a wide range of cellular effects after binding to GPCRs, unlike the single function of ion flow through the ionotropic receptors. The pathway initiated by norepinephrine will depend on the type of receptor a specific cell expresses.

A. G_s alpha subunit

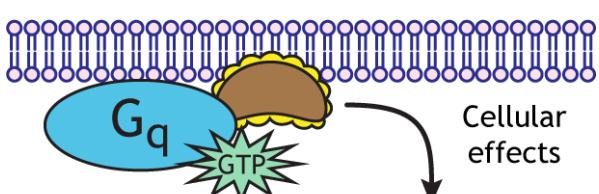
Adenylyl cyclase - Activated

**B. Gi alpha subunit**

Adenylyl cyclase - Inhibited

**C. Gq alpha subunit**

Phospholipase C - Activated



Norepinephrine

Figure 12.3. The second messenger pathway used and whether that pathway is stimulated or inhibited depends on the type of alpha subunit in the G-protein complex. Different receptors couple to different G-protein complexes. This allows one neurotransmitter to initiate multiple types of signaling cascades. A) The norepinephrine beta-adrenergic receptor couples to the G_s subunit and activates adenyl cyclase, which initiates downstream cellular effects. B) The norepinephrine alpha 2-adrenergic receptor couples to the G_i subunit and inhibits adenyl cyclase, which prevents

downstream cellular effects. C) The norepinephrine alpha 1-adrenergic receptor couples to the G_q subunit and activates phospholipase C, which initiates downstream cellular effects. 'Alpha Subunit Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Adenylyl Cyclase / cAMP Second Messenger Cascade

The cyclic AMP (cAMP) second messenger pathway is used by many GPCRs. Activation of the pathway is caused by the G_s alpha subunit and inhibition of the pathway is caused by the G_i alpha subunit. When activated, adenylyl cyclase converts ATP to cAMP in the cytoplasm. cAMP then activates another enzyme called protein kinase A (PKA) by binding to the regulatory subunits, allowing the catalytic (functional) subunits to separate and become active. Protein kinases add a phosphate molecule to proteins, a mechanism called phosphorylation. The addition of the phosphate changes the activity of the protein and how it functions in the cell.



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Animation 12.4. GPCRs that couple to the G_s alpha subunit initiate the adenylyl cyclase / cAMP pathway. The G_s subunit activates adenylyl cyclase, which then converts ATP to cAMP. cAMP binds to and activates protein kinase A (PKA), which phosphorylates proteins in the cell. 'Adenylyl Cyclase Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

The end effects of this pathway will depend on which proteins are targeted. For example, cAMP can gate ion channels and PKA can phosphorylate ion channels altering permeability and membrane potential. Phosphorylation can open the channel, or it may modulate the activity of the channel, making the channel easier to open or remain open longer.



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Animation 12.5. The adenylyl cyclase / cAMP pathway can alter many cellular functions. One example is that both cAMP and PKA can open ion channels. Like ligand-gated channels, there are also cAMP-gated channels, which open after cAMP binding. PKA is able to phosphorylate and modulate ion channel function by converting ATP to ADP. ‘Second Messenger Ion Channel Action’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

In addition to altering ion channel function, PKA can phosphorylate other proteins important for neuron function, such as proteins involved with neurotransmitter synthesis and release. One other critical target of PKA phosphorylation is the transcription factor CREB (cAMP response element binding-protein). Transcription factors bind to DNA in the nucleus and change the rate of gene transcription. Phosphorylation by PKA can cause CREB to initiate transcription of genes, creating new proteins for the neuron. Depending on which genes are transcribed, the effects on the neuron can be long-lasting.

Overall, neurotransmitters working through GPCRs and second messenger cascades like the adenylyl cyclase pathway can cause a diverse range of cellular effects: from opening ion channels, to changing protein activity via phosphorylation, to altering the proteins synthesized in the neuron.



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Animation 12.6. PKA can phosphorylate a number of proteins involved with neuron function. It can target proteins involved with neurotransmitter synthesis, packing, and release, or it can enter the nucleus and phosphorylate CREB, a transcription factor that can initiate gene transcription and protein synthesis. ‘PKA Targets’ by Casey Henley is licensed under a Creative Commons Attribution

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Phospholipase C / IP₃ / DAG Second Messenger Cascade

The G_q alpha subunit initiates a separate signaling pathway in the cell by activating phospholipase C. Phospholipase C targets PIP₂ (phosphatidylinositol 4,5-bisphosphate), which is a phospholipid present in the plasma membrane of the cell. PIP₂ is split into two cellular molecules: IP₃ (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol). DAG remains in the membrane and interacts with protein kinase c (PKC). IP₃ moves to the endoplasmic reticulum where it opens calcium channels and allows calcium to flow into the cytosol.

Calcium is also a second messenger in the cell. One important effect is the binding of calcium to calmodulin protein. This complex can then activate another kinase, the calcium/calmodulin-dependent protein kinase (CaMK). Both PKC and CaMK can phosphorylate specific cellular and nuclear proteins like PKA.



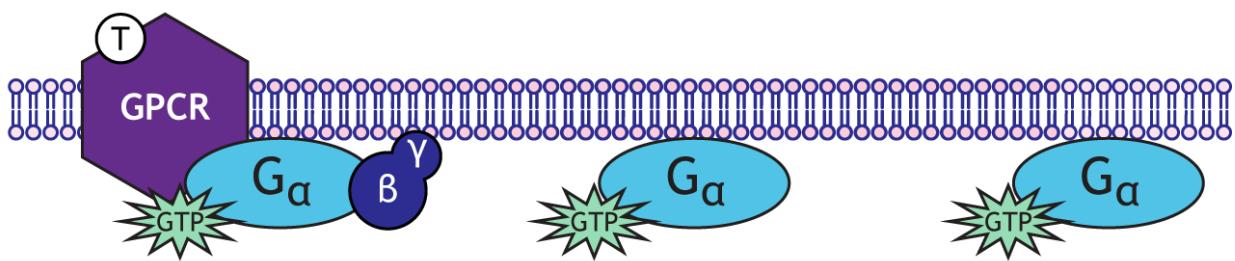
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Animation 12.7. The G_q G-protein subunit activates phospholipase C, which converts the phospholipid PIP₂ in the cell membrane into DAG, another membrane-bound molecule, and IP₃, a cytoplasmic molecule. DAG can interact with PKA, initiating phosphorylation of cellular proteins. IP₃ opens calcium channels in the endoplasmic reticulum, allowing calcium to flow into the cytoplasm. Calcium, another second messenger can have many cellular effects. It can bind to calmodulin, which then activates CaMK, causing phosphorylation of more protein targets. 'IP₃-DAG Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

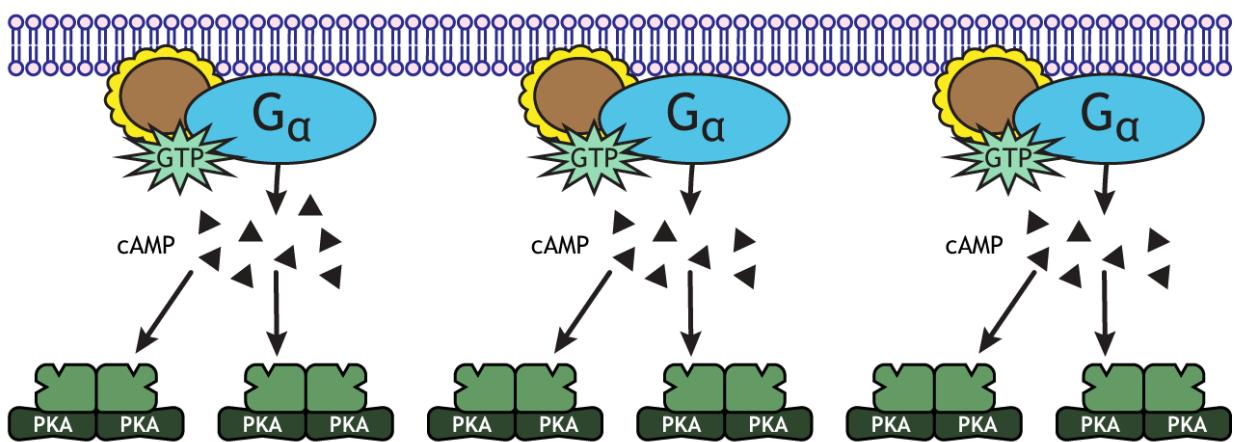
Signal Amplification

One characteristic of GPCR activation is the signal amplification that takes place. One receptor is able to activate more than one G-protein complex. The effector protein activated by the G-protein can create many second messengers, and the activated protein kinases can each phosphorylate multiple cellular proteins. This means that one neurotransmitter can have a significant effect on cellular function.

A. One GPCR can activate multiple G-proteins



B. One effector protein can create multiple second messengers



C. One kinase can phosphorylate multiple cellular proteins

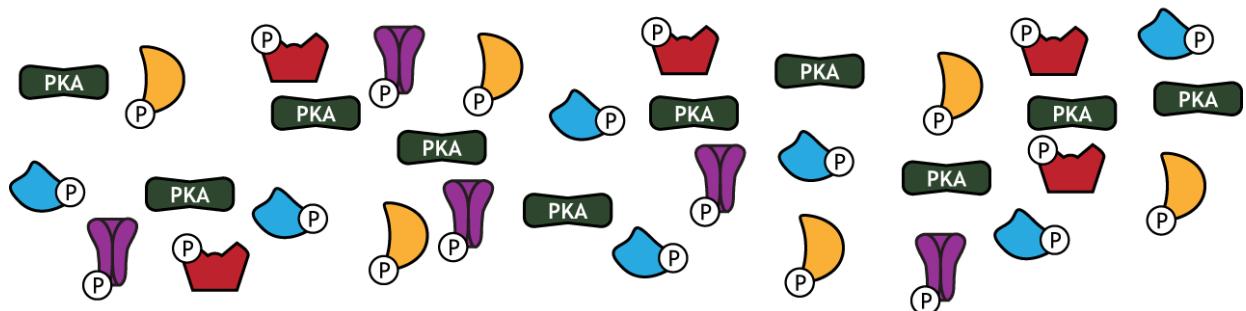


Figure 12.4. The second messenger cascades initiated by GPCRs undergo significant signal amplification. A) Multiple G-proteins can be activated by a GPCR. B) Each effector protein is able to synthesize numerous second messenger molecules. C) Each protein kinase activated by the second messengers can phosphorylate various cellular proteins. 'Signal Amplification' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Signal Termination

Eventually, the cascade initiated by binding of the neurotransmitter to the GPCR needs to end. The alpha subunit of the G-protein is able to convert the bound GTP back to GDP after a short period of time, inactivating the G-protein. The alpha subunit will then interact with a beta-gamma subunit and stay in the resting state until activated by another GPCR. Enzymes in the cell called protein phosphatases find and remove the phosphate groups added to cellular proteins by the protein kinases. And finally, other cellular mechanisms exist to remove calcium from the cytoplasm and degrade other second messengers.

Key Takeaways

- G-protein-coupled receptors rely on the activation of G-proteins to cause cellular changes
- G-protein-coupled receptors have slower effects than ligand-gated receptors
- G-proteins can open ion channels, alter protein function via phosphorylation, and alter gene transcription
- The G_s subunit initiates the adenylyl cyclase / cAMP signaling pathway
- The G_i subunit inhibits the adenylyl cyclase / cAMP signaling pathway
- The G_q subunit initiates the phospholipase C / IP₃ / DAG signaling pathway

Test Yourself!



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view it online here:

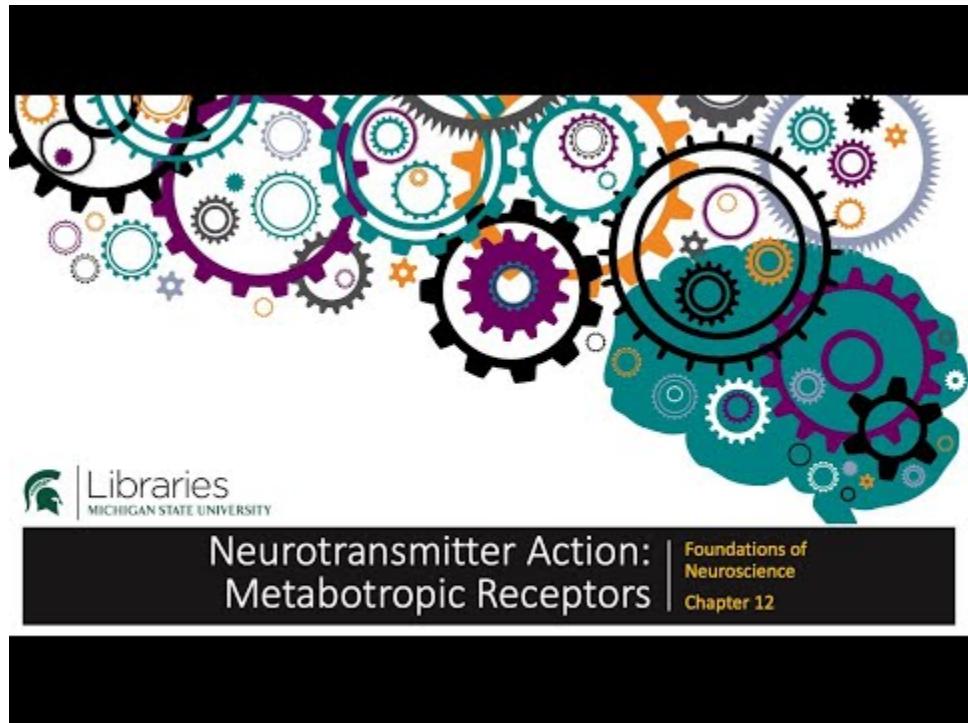
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Additional Review

What are some differences between ionotropic and metabotropic neurotransmitter receptors?

Answers

Video Version of Lesson



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<https://openbooks.lib.msu.edu/neuroscience/?p=397>

13.

NEUROTRANSMITTER CLEARANCE

Resources

- Key Takeaways
- Test Yourself
- Video Version

After neurotransmitters have been released into the synaptic cleft, they act upon postsynaptic receptors, as covered in the previous chapters. That action must be terminated in order for proper neuronal communication to continue. This is accomplished mainly through two processes: neurotransmitter transport and/or degradation. Transport physically removes the neurotransmitter molecule from the synaptic cleft. Degradation breaks down the neurotransmitter molecule by enzyme activity.

Acetylcholine

Acetylcholine action is terminated by acetylcholinesterase, an enzyme present in the synaptic cleft. Acetylcholinesterase degrades acetylcholine into choline and acetate molecules. Choline is then transported back into the presynaptic terminal and used in the synthesis of new acetylcholine.

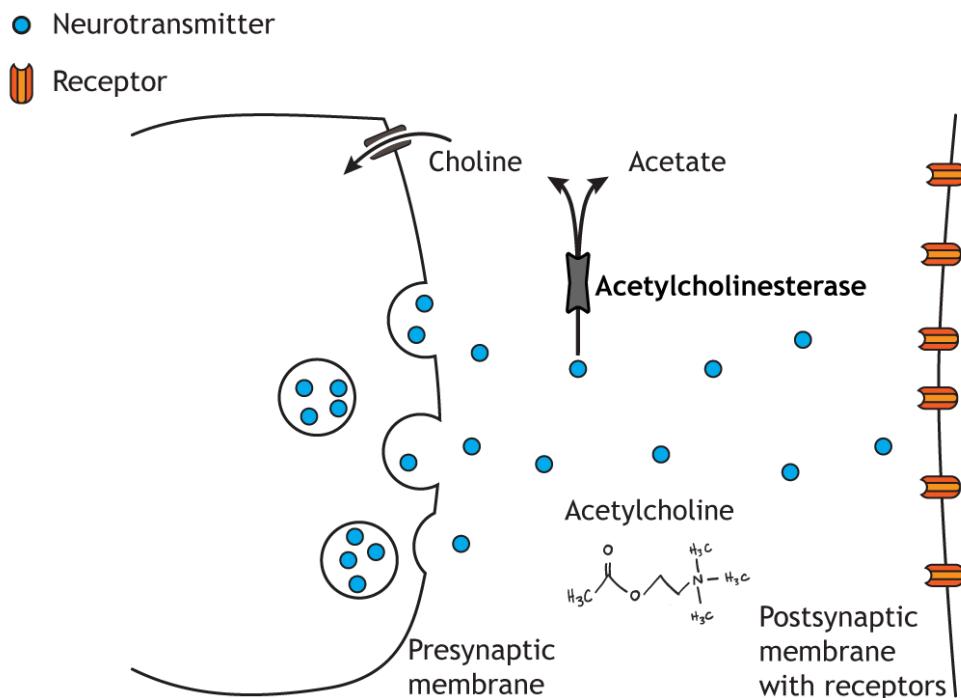


Figure 13.1. Acetylcholine is degraded into choline and acetate within the synaptic cleft via acetylcholinesterase. Choline is then transported back into the presynaptic terminal. 'Acetylcholine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Glutamate

Glutamate action is terminated by two mechanisms. Reuptake of glutamate molecules into the presynaptic terminal can occur, or glutamate can be transported into nearby glial cells. The excitatory amino acid transporters are sodium co-transporters and use the sodium electrochemical gradient to drive neurotransmitter transport. Within glial cells, glutamate is converted into glutamine by glutamine synthetase. Glutamine is then transported out of the glial cell and back into the presynaptic terminal for use in future glutamate synthesis. If glutamate is transported back into the presynaptic terminal, it can be repackaged in synaptic vesicles.

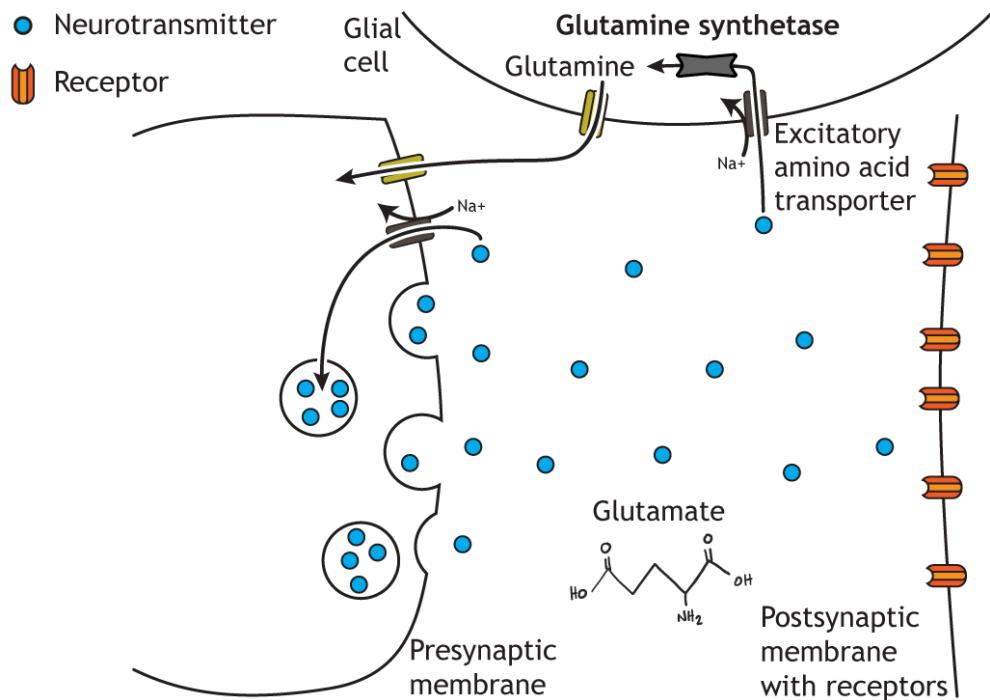


Figure 13.2. Glutamine needs to removed from the synapse. The excitatory amino acid transporter that uses sodium to drive glutamate movement across the membrane can move glutamate into glial cells or back into the presynaptic terminal. In the terminal, glutamate is repackaged into synaptic vesicles. In the glial cells, glutamate is broken down into glutamine by glutamine synthetase. 'Glutamate Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

GABA and Glycine

Like glutamate, GABA and glycine action are terminated by either reuptake into the presynaptic terminal and packaging in synaptic vesicles or through transport into glial cells where breakdown can occur. The GABA and glycine transporter also use the sodium electrochemical gradient to drive the movement of the transmitter across the membrane.

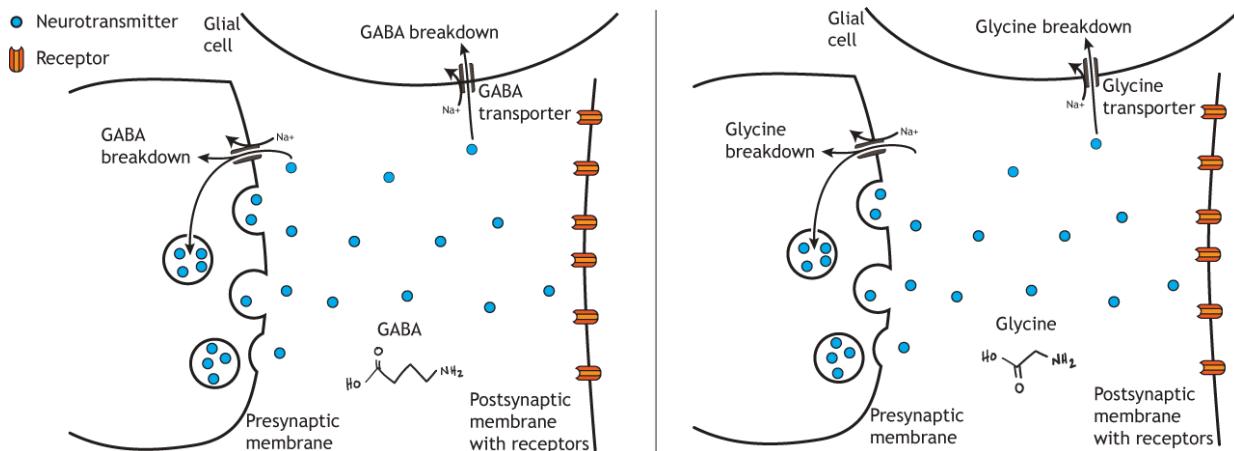


Figure 13.3. GABA and glycine action is terminated by reuptake by sodium co-transporters into either glial cells or back into the presynaptic terminal. In both locations, the neurotransmitters can be broken down by enzymes, whereas in the presynaptic terminal, the transmitters can be repackaged in synaptic vesicles. 'GABA and Glycine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Dopamine

Dopamine action is terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Once inside the cell, dopamine is either degraded via the actions of either monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT), or it is repackaged into vesicles.

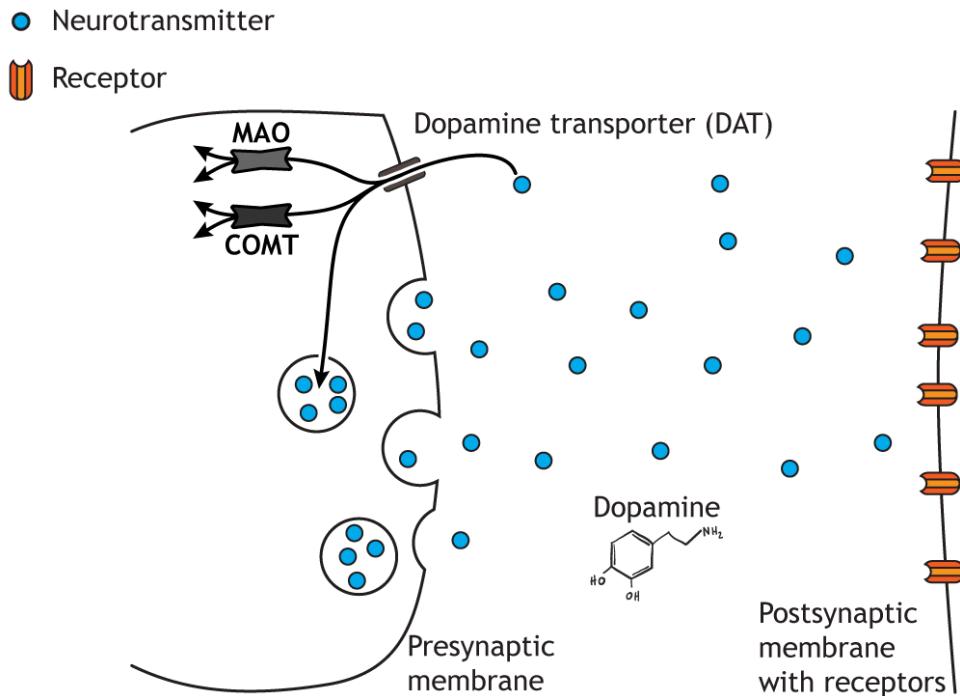


Figure 13.4. Dopamine action is terminated by reuptake into the presynaptic terminal via DAT. Dopamine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Dopamine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Norepinephrine

Norepinephrine follows the same pathway as dopamine. Reuptake into the presynaptic terminal occurs via the norepinephrine transporter (NET), and then the transmitter is either degraded within the cell by MAO or COMT or repackaged into synaptic vesicles.

● Neurotransmitter

● Receptor

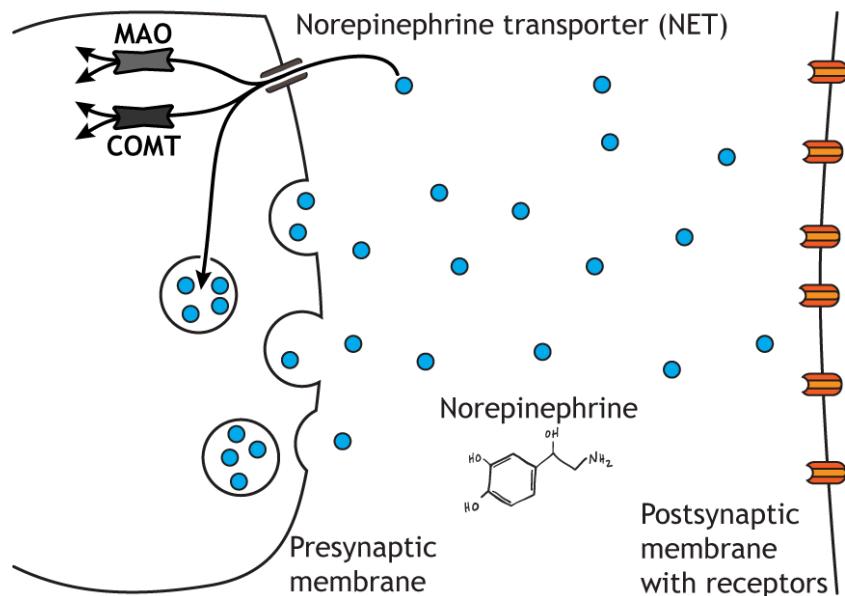


Figure 13.5. Norepinephrine action is terminated by reuptake into the presynaptic terminal via NET. Norepinephrine is then either degraded by MAO or COMT or repackaged into synaptic vesicles.
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Serotonin

Like the other monoamines, serotonin is transported back into the presynaptic terminal via the serotonin transporter (SERT). The difference between serotonin and the catecholamines dopamine and norepinephrine is that monoamine oxidase is the only enzyme used for degradation.

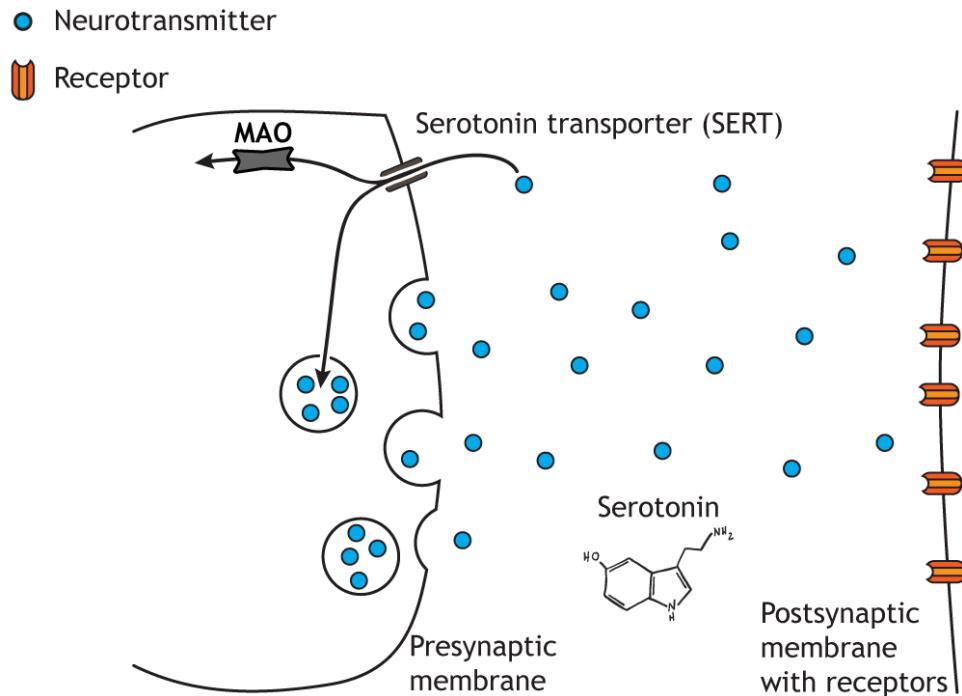


Figure 13.6. Serotonin action is terminated by reuptake into the presynaptic terminal via SERT. Serotonin is then either degraded by MAO or repackaged into synaptic vesicles. 'Serotonin Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Neurotransmitter action in the synapse must be terminated
- This occurs by either
 - reuptake into the presynaptic terminal where enzymatic degradation or repackaging into vesicles occurs
 - transport into glial cells where enzymatic degradation occurs
 - enzymatic degradation in the synapse

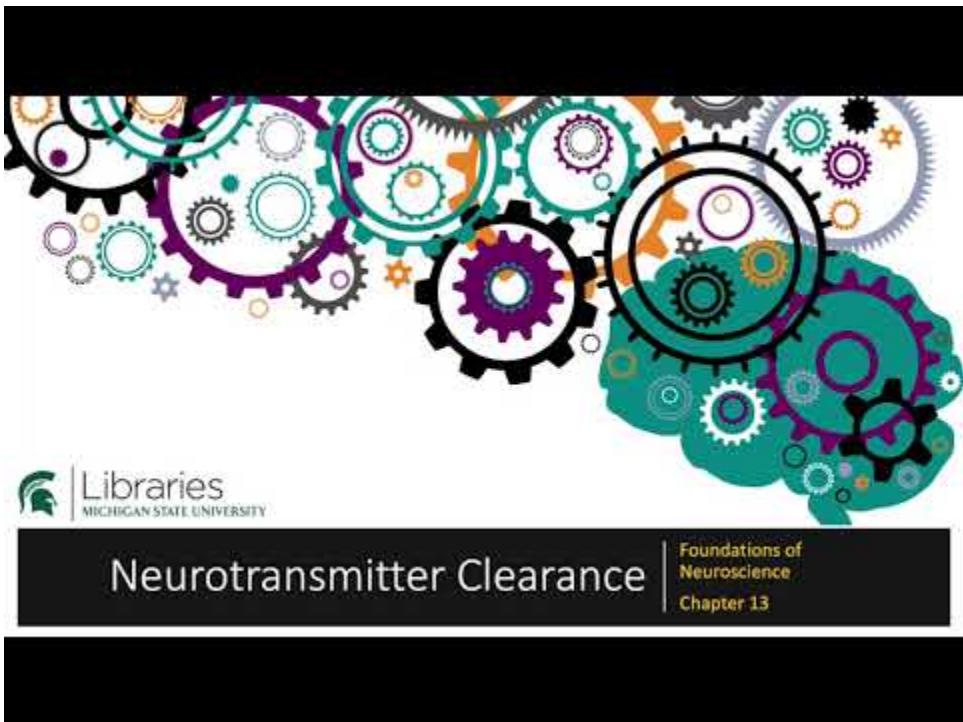
Test Yourself!



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14.

DRUG AND TOXIN EFFECTS

Resources

- Key Takeaways
- Test Yourself
- Video Version

Drugs and toxins can alter neuron functioning in a range of ways, from activation to inhibition and all levels of modulation. Although many drugs exist that alter molecular process typical of many cells, this lesson will focus on neuron-specific targets.

Synaptic Effects

As we have seen, the synapse is an incredibly complex structure, and for small molecule neurotransmitters, the entire “lifecycle” of the transmitter occurs in this space – synthesis, packaging, release, action, and termination. This means there are numerous targets upon which drugs and toxins can act and alter synaptic communication.

Drug Effects on Neurotransmitter Release

Drugs can alter neurotransmitter synthesis pathways, either increasing or decreasing the amount of neurotransmitter made in the terminal, affecting how much transmitter is released. An example of this is administration of L-DOPA, a dopamine precursor molecule that results in increased dopamine production; it is used as a treatment for Parkinson’s Disease.

Neurotransmitter packaging is another site of possible drug action. Reserpine, which has been used to treat high blood pressure, blocks the transport of the monoamine transmitters into vesicles by inhibiting the vesicular monoamine transporter (VMAT). This decrease the amount of neurotransmitter stores and the amount of neurotransmitter released in response to an action potential.

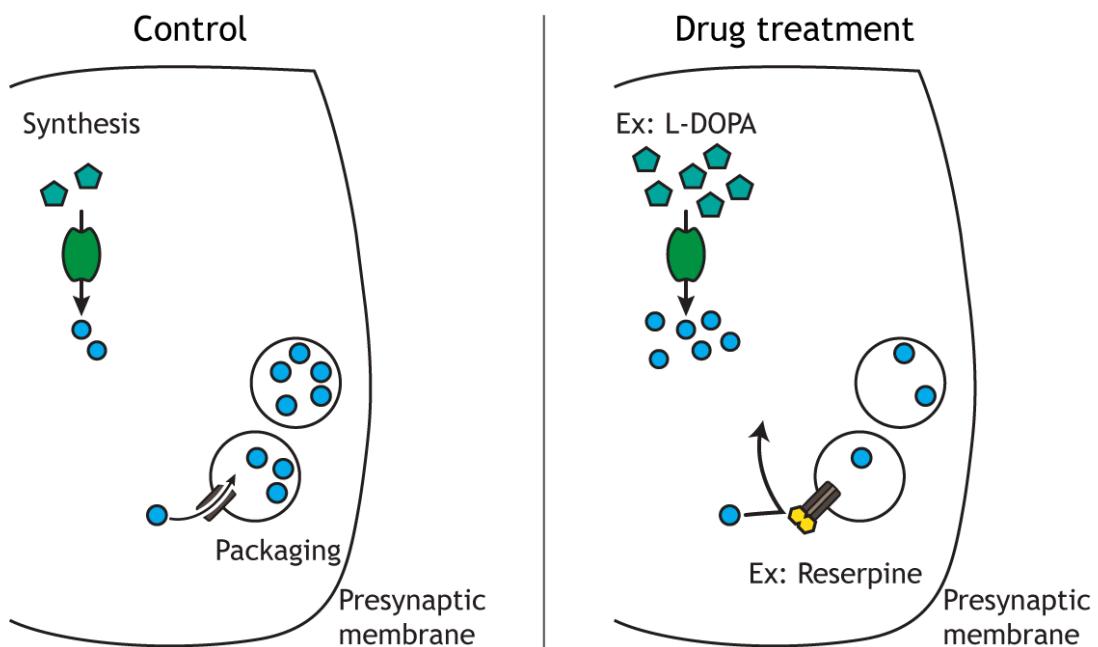


Figure 14.1. Drugs and toxins can alter neurotransmitter synthesis and packaging into synaptic vesicles. L-DOPA increases the synthesis of dopamine in the terminal. Reserpine prevents packaging of the biogenic amines, resulting in low concentrations of transmitter stored in synaptic vesicles. 'Drug Effects on Neurotransmitter Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Drug Effects on the Postsynaptic Membrane

The neurotransmitter receptors are another critical location for drug and toxin action. Agonists mimic neurotransmitter effects, whereas antagonists block neurotransmitter effects. Muscimol, a component of some mushrooms, is an agonist for the ionotropic GABA receptor. Bicuculline, a component of some plants, is an antagonist to this receptor and blocks the action of GABA. Additionally, many chemicals are able to modulate receptors in either a positive or negative fashion. Alcohol binds to the GABA receptor and increases the time the receptor is open when GABA binds.

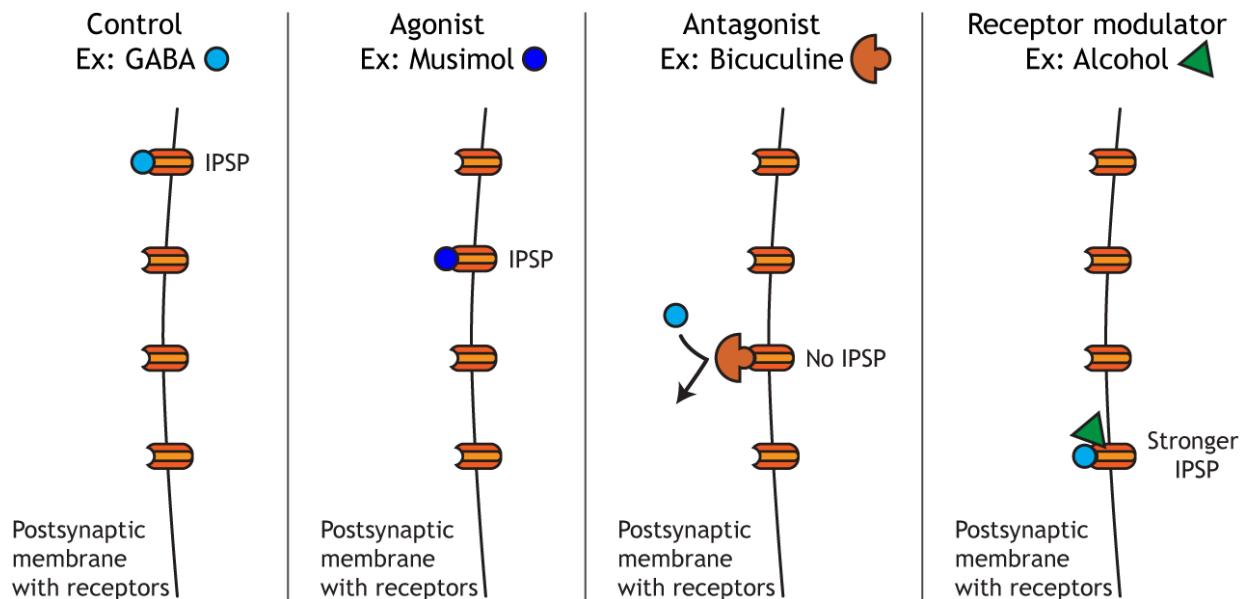


Figure 14.2. Drugs and toxins can alter neurotransmitter receptors on the postsynaptic neuron. A GABA agonist, muscimol, would replicate the actions of GABA and cause an IPSP. A GABA antagonist, bicuculine, would prevent GABA actions resulting in no IPSP. Modulators such as alcohol, alter how the receptor works, so when GABA binds the response is a stronger IPSP than when alcohol is not present. 'Postsynaptic Drug Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Drug Effects on Neurotransmitter Clearance

Finally, neurotransmitter degradation and reuptake can also be altered by drugs and toxins.

Depending on the neurotransmitter, enzymes located in either the synapse or in the terminal are responsible for degradation of the transmitter, and these enzymes can be blocked by drugs.

Organophosphates are found in many pesticides and prevent the action of acetylcholinesterase, the enzyme that breaks down acetylcholine in the synapse. This inhibition increases acetylcholine action on the postsynaptic neuron. Monoamine oxidase inhibitors (MAOIs) prevent monoamine oxidase from degrading the biogenic amine neurotransmitters. MAOIs have been used as antidepressants since they increase the amount of transmitter available. Additionally, drugs can prevent the reuptake of neurotransmitters into the presynaptic terminal. Cocaine blocks the dopamine transporter, which results in increased action of dopamine in the synapse.

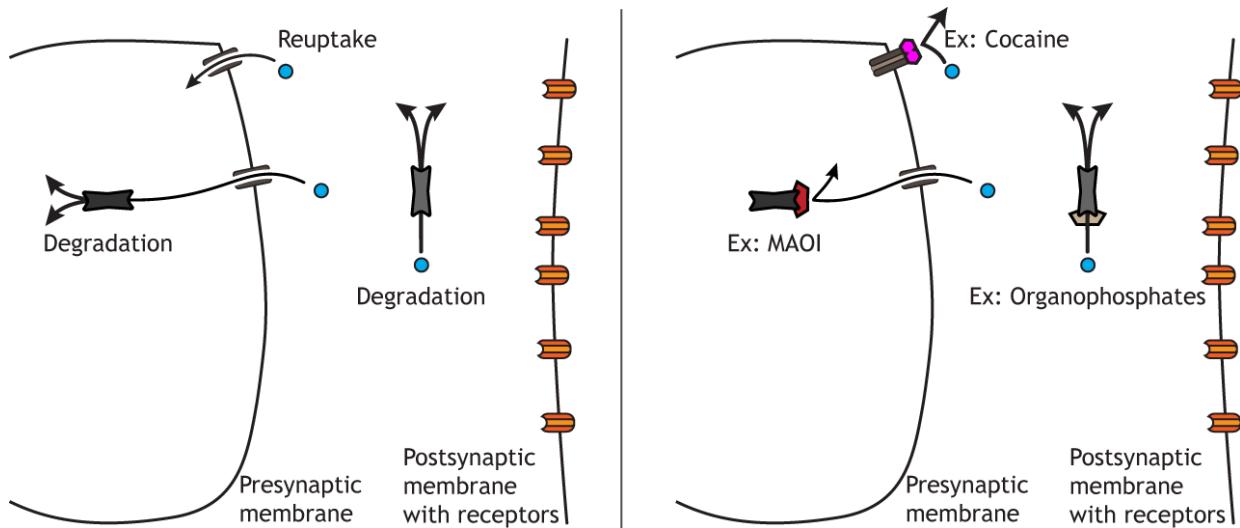


Figure 14.3. Drugs and toxins can alter neurotransmitter degradation and reuptake into the presynaptic terminal. Organophosphates prevent the degradation of acetylcholine in the synapse. MAOIs prevent the degradation of monoamine transmitters in the terminal. Cocaine prevents dopamine from being transported into the presynaptic terminal. All of these effects lead to increased neurotransmitter action and availability. ‘Drug Effects on Neurotransmitter Clearance’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Non-Synaptic Effects

Drugs and toxins can also affect neuron function by acting outside of the synapse. For example, some chemicals change voltage-gated ion channel dynamics. Veratridine, a compound found in plants from the lily family, prevents voltage-gated sodium channels from inactivating. Initially, this causes an increase in neurotransmitter release, but it can quickly lead to excitotoxicity.

Key Takeaways

- There are many ways in which drugs and toxins can alter neuron function

- Effects can be excitatory, inhibitory, or modulatory

Test Yourself!



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15.

EPIGENETICS

Resources

- Key Takeaways
- Video Version

We have seen how neurotransmitter action can alter gene transcription and translation through binding to G-protein coupled receptors. The effectiveness of the signaling cascade on new protein synthesis does depend on some DNA-specific factors. This chapter will briefly cover how genes are transcribed and then how non-sequence, molecular changes to DNA can affect transcription rates.

Central Dogma

DNA to RNA to protein. The central dogma of genetics. It may look simple, but many complex steps must occur for the process to be successful.

DNA

Doubled-stranded DNA (deoxyribonucleic acid) is comprised of four nucleotide bases: adenine (A), thymine (T), guanine (G), and cytosine (C). Adenine and thymine form base pairs whereas guanine and cytosine form pairs. The pairs cause the two strands to coil around each other and form a double helix.

RNA

The single-stranded messenger RNA (ribonucleic acid) is created from the DNA sequence via

complementary base pairing. Like DNA, there are four bases, but in RNA the thymine base is replaced by uracil (U). Messenger RNA (mRNA) leaves the nucleus and interacts with ribosomes to synthesize proteins in a process called translation. The ribosomes pair amino acids to specific three-base sequences called codons. For example, the codon sequence AUG is the start codon and it codes for methionine. The ribosomes will move down the mRNA to find the start codon of the protein and begin translation there, adding a new amino acid for each codon until a stop codon is reached.

Protein

Proteins are synthesized by the linking of amino acids together by the ribosomes. There are 20 amino acids that are each encoded by one or more mRNA codon sequences.

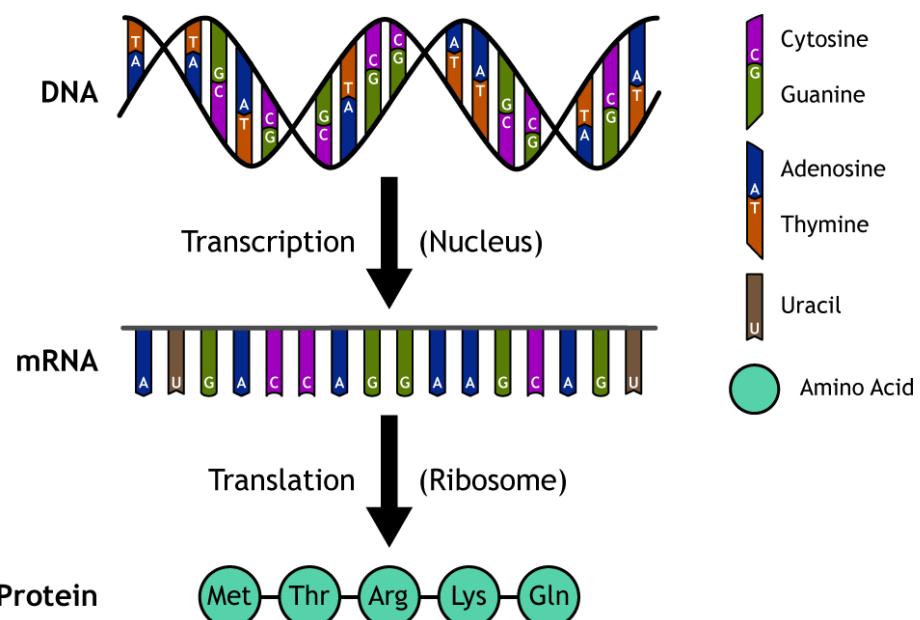


Figure 15.1. The central dogma of genetics. DNA is transcribed into RNA, which is translated into protein. DNA is composed of the nucleotides cytosine, guanine, adenosine, and thymine. RNA is composed of the nucleotides cytosine, guanine, adenosine, and uracil. Protein is composed of amino acids. ‘Central Dogma’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Gene Transcription

In the nucleus, proteins called transcription factors and an RNA polymerase attach to the DNA. The DNA unwinds, the proteins bind, and an mRNA strand is synthesized using the DNA as a template. The mRNA is a complementary sequence to the DNA strand being transcribed.

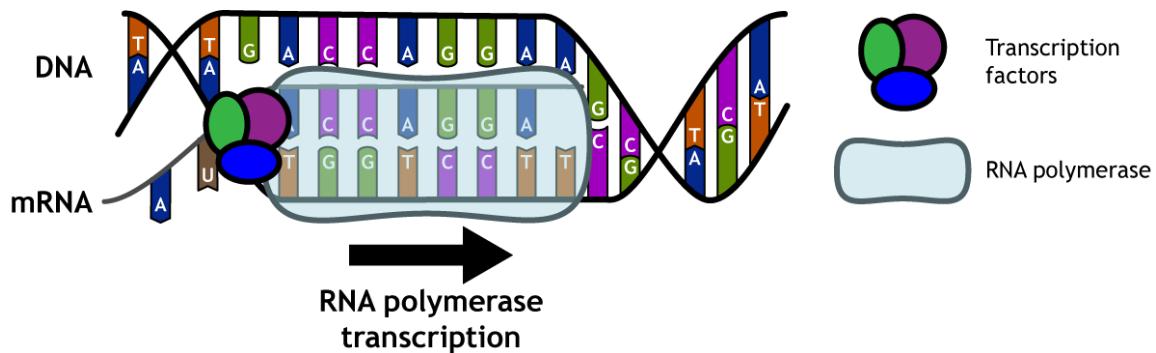


Figure 15.2. The double helix of the DNA unwinds, and proteins including transcription factors and RNA polymerase bind. The mRNA strand is synthesized by the proteins that use the DNA as a template for the nucleotide sequence. 'Transcription' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

DNA Packaging

DNA is not always accessible to those transcription proteins, though. There is so much DNA in each cell, that in order to save space, it is highly condensed in the nucleus. The double helix is wrapped around proteins called histones. The histones are then wrapped into nucleosome strands. The nucleosomes are compacted into denser structures called chromatin. Finally, the chromatin is condensed more and creates chromosomes.

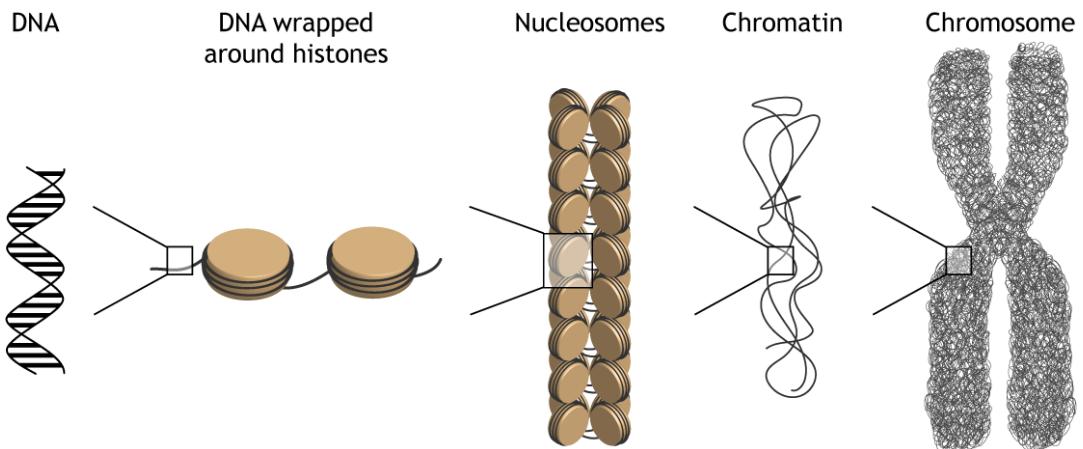


Figure 15.3. DNA is highly condensed within the cell. DNA is wrapped around histone proteins in a structure called nucleosomes. The nucleosomes are compacted into chromatin which is further compacted into chromosomes. 'DNA Packaging' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In order for gene transcription to occur, the strands of DNA must uncoil from the histone bodies to become accessible to the transcriptional machinery.

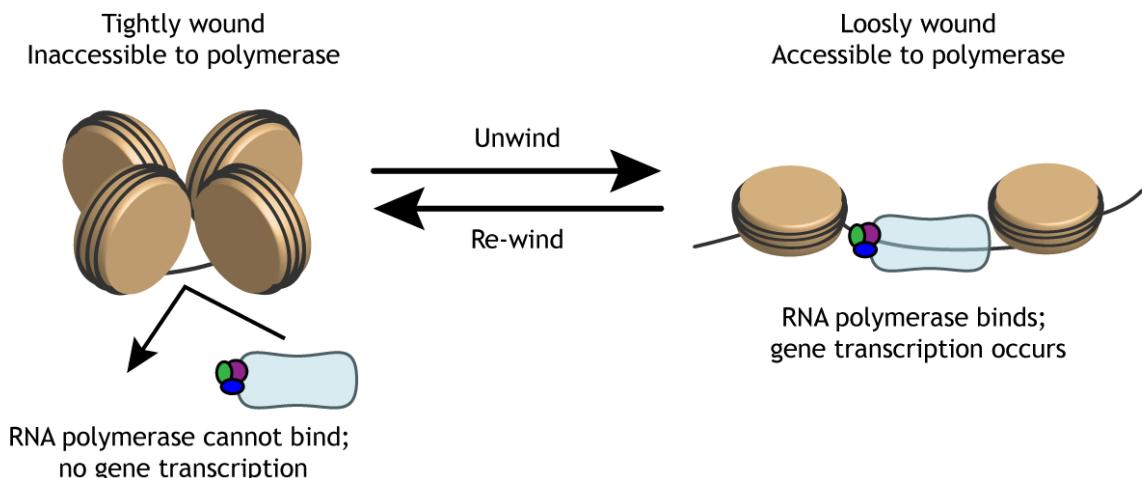


Figure 15.4. When the DNA is wound tightly around histones, the strands are inaccessible to the polymerase proteins and transcription factors. Since these proteins cannot bind, no gene transcription can occur. If the histones unwind, the DNA then becomes accessible to the transcription proteins. RNA polymerase can bind, and gene transcription can take place. 'RNA Polymerase Binding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Epigenetics

Molecules such as methyl groups can be attached to DNA or on the histones. These epigenetic tags can affect how tightly the DNA is wound around the histones. Since gene expression can be altered by modifying how easily the histones unwind and how accessible DNA strands are, epigenetic tags are able to have an indirect effect on gene transcription.

Methyl groups make it more difficult for the polymerase to access the DNA by keeping the DNA coiled around the histones, reducing transcription. When the methyl groups are removed, called demethylation (not to be confused with dimethylation, the addition of two methyl groups), gene expression can increase because the DNA uncoils and is accessible to the transcriptional machinery.

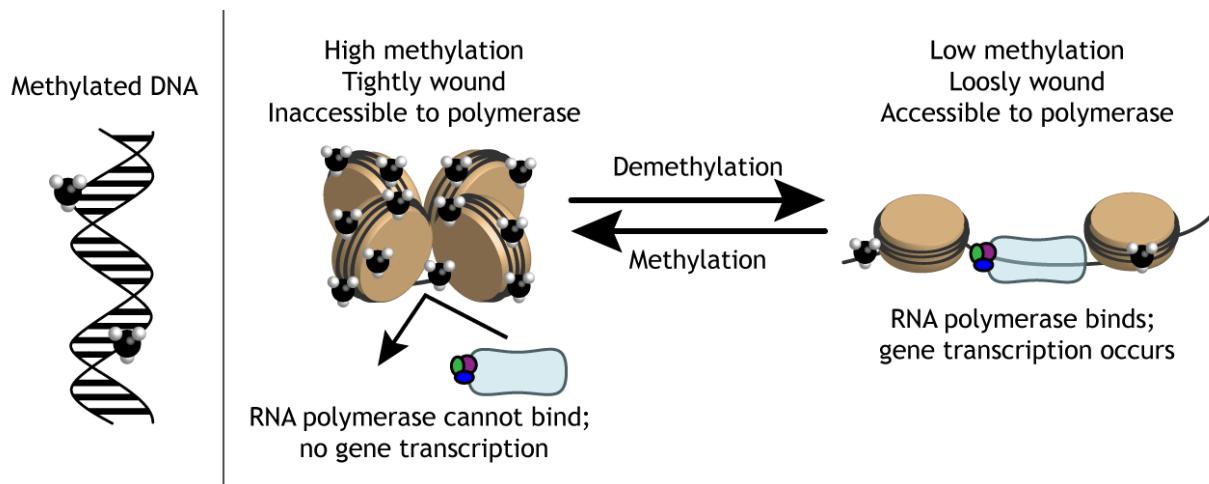


Figure 15.5. Methyl groups attached to DNA affect how accessible genes are to transcription proteins. Highly methylated DNA stays tightly wound around histones, preventing RNA polymerase binding and gene transcription. Low methylation loosens the coils and make the DNA accessible to RNA polymerase, allowing gene transcription. 'DNA methylation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Epigenome is Flexible

An individual's DNA sequence is fixed (excluding mutations that occur due to damage or errors in cell replication), but the epigenome is flexible and can change throughout life. An individual's life experiences, especially during development or other critical periods, are able to alter the epigenome.

Some experiences will increase methylation, sometimes for only certain genes, sometimes genome-

wide, whereas other experiences will decrease it. For example, early life stress can increase the amount of methylation found on the gene that encodes for the receptor that is activated by stress hormones. Increased methylation leads to reduced transcription which has downstream effects on the negative feedback loop on the stress response. Scientists are starting to realize how important the epigenome is in regulating our brain and behavior.

Inherited Epigenome

Additionally, epigenetic modifications are heritable. Recent research is starting to show that experiences of mothers, fathers, and even grandparents can have transgenerational effects. And these effects, once thought only to be inherited from the maternal side, have now been shown to be paternally inherited as well. This means an animal that had early life stress may have increased methylation and changes in gene transcription that is then passed down for generations even if the offspring do not experience the same stressors.

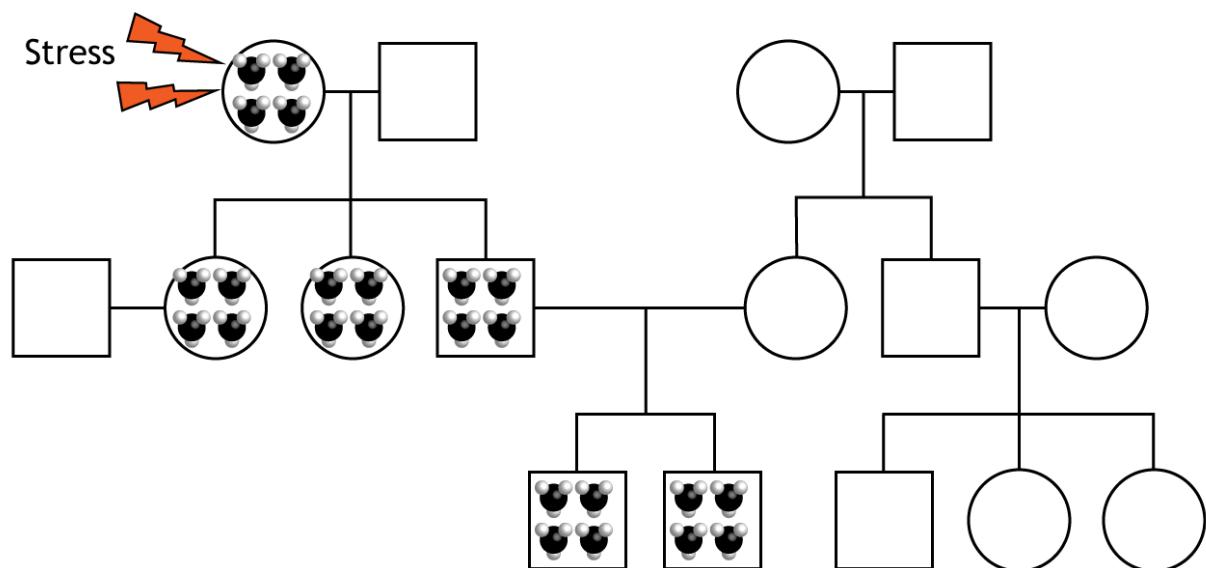


Figure 15.6. Epigenetic factors can be inherited. Stress experienced by a grandparent can increase DNA methylation and that effect can be found in first- and second-generation offspring. 'Transgenerational Methylation Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- DNA is highly condensed in the nucleus
- The DNA must unwind for transcription to take place
- Epigenetic modifications can alter how easily the DNA can unwind
- Epigenetic modifications can be inherited

Video Version of Lesson



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Epigenetics

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Chapter 15

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