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INTRODUCTION

*Foundations of Neuroscience* is aimed at undergraduate students new to the field of neuroscience. The first edition specifically targets students enrolled in Neurobiology at Michigan State University and primarily contains topics covered in that course. For example, only three sensory systems are discussed in this version of the text. Future editions will continue to expand the number of topics and concepts presented.

This OER will be unique in its presentation of neuroscience content. The text will be divided into short, easily digestible chapters that focus on one concept. Pairing the text with images and animations will provide students with multiple ways of learning the content. The text is written with the undergraduate student that is new to neuroscience in mind. Neuroscience terminology will be introduced in an easy-to-understand manner, and supporting content will be clear and concise to minimize cognitive load not associated with understanding new material.

Each chapter will end with an interactive quiz for student self-evaluation of the content. All quiz answers (i.e. both correct and incorrect) will provide feedback, so students can
self-check their understanding at the end of each concept and receive immediate feedback about their learning.
PART I
NEURON STRUCTURE & FUNCTION
Overview

Neurons are the basic units of the brain. Their main function is to send electrical signals over short and long distances in the body, and they are electrically and chemically excitable. The function of the neuron is dependent on the structure of the neuron. The typical neuron consists of the dendrites, cell body, axon (including the axon hillock), and presynaptic terminal.
Figure 1.1. A typical neuron. Dendrites branch out from the cell body, where the nucleus is located. The axon hillock is located where the cell body transitions into the axon. The axon begins at the axon hillock and ends at the presynaptic terminal, which can branch into multiple terminals. ‘Neuron’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

**Dendrites**

Dendrites, shown here in green, are processes that branch out in a tree-like fashion from the cell body. They are the main target for incoming signals received from other cells. The number of inputs a neuron receives depends on the complexity of the dendritic branching. Dendrites may also have small protrusions along the branches known as spines. Spines, illustrated in the inset box, are the sites of some synaptic contacts. Spines increase the surface area of the
dendritic arbor, which may be an important factor in receiving communication.

![Diagram of a neuron with dendrites and cell body](image)

Figure 1.2. Dendrites branch out from the soma. Their function is to receive information from other neurons. Some dendrites have small protrusions called spines that are important for communicating with other neurons. ‘Dendrites’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

**Cell Body**

The cell body, shown here in green and also known as the soma, contains the nucleus and cellular organelles, including endoplasmic reticulum, Golgi apparatus, mitochondria, ribosomes, and secretory vesicles. The nucleus houses the DNA of the cell, which is the template for all proteins synthesized in the cell. The organelles, illustrated in the inset box, in the soma are responsible for cellular mechanisms like
protein synthesis, packaging of molecules, and cellular respiration.

Figure 1.3. The cell body, or soma, of the neuron contains the nucleus and organelles that are commonly found in other cell types and are important for basic cellular functions. These organelles include mitochondria, endoplasmic reticulum, and Golgi apparatus. ‘Soma’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axon

The axon, highlighted in green, is usually a long, single process that begins at the axon hillock and extends out from the cell body. The axon hillock is located where the cell body transitions into the axon. Axons can branch in order to communicate with more than one target cell.
Figure 1.4. The axon is a long single projection that begins at the axon hillock, the region between the cell body and the axon. The axon terminates at the presynaptic terminal. ‘Axon’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Action Potential

The axon transmits an electrical signal, called an action potential, from the axon hillock to the presynaptic terminal where the electrical signal will result in a release of chemical neurotransmitters to communicate with the next cell. The action potential is a very brief change in the electrical potential, which is the difference in charge between the inside and outside of the cell. During the action potential, the electrical potential across the membrane moves from a negative value to a positive value and back.
Animation 1.1. 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.

Myelin

Many axons are also covered by a myelin sheath, a fatty substance that wraps around portions of the axon and increases action potential speed. There are breaks between the myelin segments called Nodes of Ranvier, and this uncovered region of the membrane regenerates the action potential as it
propagates down the axon in a process called saltatory conduction. There is a high concentration of voltage-gated ion channels, which are necessary for the action potential to occur, in the Nodes of Ranvier.

![Axon Characteristics](image)

**Axon Characteristics**

**Axon Length**

The length of an axon is variable depending on the location of the neuron and its function. The axon of a sensory neuron in your big toe needs to travel from your foot up to your spinal
cord, whereas an interneuron in your spinal cord may only be a few hundred micrometers in length.

Figure 1.6. Axons vary in length. Spinal interneurons, neurons that fully exist within the spinal cord, can have short axons, whereas sensory or motor neurons, which need to reach from the spinal cord to the appropriate body region, for example the toe, have long axons. ‘Axon Length’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axon Diameter

Axon diameter is also variable and can be used to differentiate different types of neurons. The diameter affects the speed at which the action potential will propagate. The larger the
diameter, the faster the signal can travel. Additionally, larger diameter axons tend to have thicker myelin.

Figure 1.7. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. ‘Axon Diameter’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Presynaptic Terminal

The axon terminates at the presynaptic terminal or terminal bouton. The terminal of the presynaptic cell forms a synapse with another neuron or cell, known as the postsynaptic cell. When the action potential reaches the presynaptic terminal, the neuron releases neurotransmitters into the synapse. The neurotransmitters act on the postsynaptic cell. Therefore,
neuronal communication requires both an electrical signal (the action potential) and a chemical signal (the neurotransmitter). Most commonly, presynaptic terminals contact dendrites, but terminals can also communicate with cell bodies or even axons. Neurons can also synapse on non-neuronal cells such as muscle cells or glands.

The terms presynaptic and postsynaptic are in reference to which neuron is releasing neurotransmitters and which is receiving them. Presynaptic cells release neurotransmitters into the synapse and those neurotransmitters act on the postsynaptic cell.
Variations in Structure

Although these typical structural components can be seen in all neurons, the overall structure can vary drastically depending on the location and function of the neuron. Some neurons, called unipolar, have only one branch from the cell body, and the dendrites and axon terminals project from it. Others, called bipolar, have one axonal branch and one dendritic branch. Multipolar neurons can have many processes branching from the cell body. Additionally, each of the projections can take many forms, with different branching.
characteristics. The common features of cell body, dendrites, and axon, though, are common among all neurons.

Figure 1.10. Neuron structure is variable, but the main components of cell body (shown in black), dendrites (shown in brown), and axon (shown in blue) are common among all neurons. ‘Neuron Types’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
• Each structural component of the neuron has an important function
• Overall structure of the cell can vary depending on location and function of the neuron

Test Yourself!

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/neuroscience/?p=5

Additional Review

1. Draw a neuron and identify the following
2. Describe functions of each neuronal structure depicted in your model.
3. Predict what would happen to neuron function if myelin was destroyed.
2. ION MOVEMENT

Overview

Ion flow into and out of the neuron is a critical component of neuron function. Ions move in predictable ways, and the control of ion movement affects the cell at rest and while sending and receiving information from other neurons.

Phospholipid Bilayer Prevents Ion Movement

The neuronal membrane is composed of lipid molecules that form two layers. The hydrophilic heads of the molecules align on the outside of the membrane, interacting with the intra- and extracellular solution of the cell, whereas the hydrophobic tails are arranged in the middle, forming a barrier to water and water-soluble molecules like ions. This barrier is critical to neuron function.
Ion Channels Allow Ion Movement

Embedded throughout the neuronal membrane are ion channels. Ion channels are proteins that span the width of the cell membrane and allow charged ions to move across the membrane. Ions cannot pass through the phospholipid bilayer without a channel. Channels can be opened in a number of different ways. Channels that open and close spontaneously are called leak or non-gated channels. Channels that open in response to a change in membrane potential are called voltage-gated. Channels that open in response to a chemical binding are called ligand-gated. Other mechanisms like stretch of the membrane or cellular mechanisms can also lead to the opening of channels.
Channels can be specific to one ion or allow the flow of multiple ions.

Figure 2.2. The phospholipid bilayer with embedded ion channels. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Membrane with Channels’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Ion channels control ion movement across the cell membrane because the phospholipid bilayer is impermeable to the charged atoms. When the channels are closed, no ions can move into or out of the cell. When ion channels open, however, then ions can move across the cell membrane.

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=52

Animation 2.1. When ion channels in the membrane are
closed, ions cannot move into or out of the neuron. Ions can only cross the cell membrane when the appropriate channel is open. For example, only sodium can pass through open sodium channels. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Ion Movement’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View static image of animation.

Gradients Drive Ion Movement

Ions move in predictable ways. Concentration and electrical gradients drive ion movement. Ions will diffuse from regions of high concentration to regions of low concentration. Diffusion is a passive process, meaning it does not require energy. As long as a pathway exists (like through open ion channels), the ions will move down the concentration gradient.

In addition to concentration gradients, electrical gradients can also drive ion movement. Ions are attracted to and will move toward regions of opposite charge. Positive ions will move toward regions of negative charge, and vice versa.

For discussion of ion movement in this text, the
combination of these two gradients will be referred to as the electrochemical gradient. Sometimes the concentration and electrical gradients driving ion movement can be in the same direction; sometimes the direction is opposite. The electrochemical gradient is the summation of the two individual gradients and provides a single direction for ion movement.

Animation 2.2. Concentration and electrical gradients drive ion movement. Ions diffuse down concentration gradients from regions of high concentration to regions of low concentration. Ions also move toward regions of opposite electrical charge. ‘Gradients’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View static image of animation.
When Gradients Balance, Equilibrium Occurs

When the concentration and electrical gradients for a given ion balance, meaning they are equal in strength but in different directions, that ion will be at equilibrium. Ions still move across the membrane through open channels when at equilibrium, but there is no net movement in either direction meaning there is an equal number of ions moving into the cell as there are moving out of the cell.

Animation 2.3. When an ion is at equilibrium, which occurs when the concentration and electrical gradients acting on the ion balance, there is no net movement of the ion. The ions continue to move across the membrane through open channels, but the ion flow into and out of the cell is equal. In this animation, the membrane starts and ends with seven positive ions on each side even though the ions move through the open channels. ‘Ion Equilibrium’ by Casey Henley is
The phospholipid bilayer prevents ion movement into or out of the cell.
Ion channels allow ion movement across the membrane.
Electrochemical gradients drive the direction of ion flow.
At equilibrium, there is no net ion movement (but ions are still moving).
Additional Review

1. Explain how chemical and electrical gradients affect ion flow.
2. Explain ion movement at equilibrium.
3. MEMBRANE POTENTIAL

Membrane Potential

The membrane potential is the difference in electrical charge between the inside and the outside of the neuron. This is measured using two electrodes. A reference electrode is placed in the extracellular solution. The recording electrode is inserted into the cell body of the neuron.
Figure 3.1. The membrane potential is measured using a reference electrode placed in the extracellular solution and a recording electrode placed in the cell soma. The membrane potential is the difference in voltage between these two regions. ‘Measuring Membrane Potential’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Terminology

There is more than one way to describe a change in membrane potential. If the membrane potential moves toward zero, that is a depolarization because the membrane is becoming less polarized, meaning there is a smaller difference between the charge on the inside of the cell compared to the outside. This is also referred to as a decrease in membrane potential. This means that when a neuron’s membrane
potential moves from rest, which is typically around -65 mV, toward 0 mV and becomes more positive, this is a decrease in membrane potential. Since the membrane potential is the difference in electrical charge between the inside and outside of the cell, that difference decreases as the cell’s membrane potential moves toward 0 mV.

If the membrane potential moves away from zero, that is a hyperpolarization because the membrane is becoming more polarized. This is also referred to as an increase in membrane potential.

Figure 3.2. A decrease in membrane potential is a change that moves the cell’s membrane potential toward 0 or depolarizes the membrane. An increase in membrane potential is a change that moves the cell’s membrane potential away from 0 or hyperpolarizes the membrane. ‘Membrane Potential Terms’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Voltage Distribution

At rest, ions are not equally distributed across the membrane. This distribution of ions and other charged molecules leads to the inside of the cell having a more negative charge compared to the outside of the cell.

A closer look shows that sodium, calcium, and chloride are concentrated outside of the cell membrane in the extracellular solution, whereas potassium and negatively-charged molecules like amino acids and proteins are concentrated inside in the intracellular solution.

Figure 3.3. The inside of the neuron has a more negative charge than the outside of the neuron. ‘Membrane Potential’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Figure 3.4. For a typical neuron at rest, sodium, chloride, and calcium are concentrated outside the cell, whereas potassium and other anions are concentrated inside. This ion distribution leads to a negative resting membrane potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. ‘Membrane at Rest’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ion Distribution Creates Electrochemical Gradients

These concentration differences lead to varying degrees of electrochemical gradients in different directions depending on the ion in question. For example, the electrochemical gradients will drive potassium out of the cell but will drive sodium into the cell.
Figure 3.5. The distribution of ions on either side of the membrane lead to electrochemical gradients for sodium and potassium that drive ion flow in different directions. If the membrane is permeable to sodium, ions will flow inward. If the membrane is permeable to potassium, ions will flow outward. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Gradients Across Membrane’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Equilibrium Potential

The neuron’s membrane potential at which the electrical and concentration gradients for a given ion balance out is called the ion’s equilibrium potential. Let’s look at sodium in more detail:
When sodium channels open, the neuron’s membrane becomes permeable to sodium, and sodium will begin to flow across the membrane. The direction is dependent upon the electrochemical gradients. The concentration of sodium in the extracellular solution is about 10 times higher than the intracellular solution, so there is a concentration gradient driving sodium into the cell. Additionally, at rest, the inside of the neuron is more negative than the outside, so there is also an electrical gradient driving sodium into the cell.

As sodium moves into the cell, though, these gradients change in driving strength. As the neuron’s membrane potential become positive, the electrical gradient no longer works to drive sodium into the cell. Eventually, the concentration gradient driving sodium into the neuron and the electrical gradient driving sodium out of the neuron balance with equal and opposite strengths, and sodium is at equilibrium. The membrane potential of the neuron at which equilibrium occurs is called the equilibrium potential.
potential of an ion, which, for sodium, is approximately +60 mV.

Animation 3.1. At rest, both the concentration and electrical gradients for sodium point into the cell. As a result, sodium flows in. As sodium enters, the membrane potential of the cell decreases and becomes more positive. As the membrane potential changes, the electrical gradient decreases in strength, and after the membrane potential passes 0 mV, the electrical gradient will point outward, since the inside of the cell is more positively charged than the outside. The ions will continue to flow into the cell until equilibrium is reached. An ion will be at equilibrium when its concentration and electrical gradients are equal in strength and opposite in direction. The membrane potential of the neuron at which this occurs is the equilibrium potential for that ion. Sodium’s equilibrium potential is approximately +60 mV. The dotted, blue channels represent sodium
channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Sodium Gradients’ 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.

Calculate Equilibrium Potential with Nernst Equation

The gradients acting on the ion will always drive the ion towards equilibrium. The equilibrium potential of an ion is calculated using the Nernst equation:

\[ E_{ion} = \frac{61}{z} \log \frac{[ion]_{outside}}{[ion]_{inside}} \]

The constant 61 is calculated using values such as the universal gas constant and temperature of mammalian cells.
Z is the charge of the ion

$[\text{Ion}]_{\text{inside}}$ is the intracellular concentration of the ion

$[\text{Ion}]_{\text{outside}}$ is the extracellular concentration of the ion

An Example: Sodium’s Equilibrium Potential

$$E_{\text{ion}} = \frac{61}{z} \log \frac{[\text{ion}]_{\text{outside}}}{[\text{ion}]_{\text{inside}}}$$

For Sodium:

$z = 1$

$[\text{Ion}]_{\text{inside}} = 15 \text{ mM}$

$[\text{Ion}]_{\text{outside}} = 145 \text{ mM}$

$$E_{\text{ion}} = \frac{61}{1} \log \frac{145}{15} = 60 \text{ mV}$$

Predict Ion Movement by
Comparing Membrane Potential to Equilibrium Potential

It is possible to predict which way an ion will move by comparing the ion’s equilibrium potential to the neuron’s membrane potential. Let’s assume we have a cell with a resting membrane potential of -70 mV. Sodium’s equilibrium potential is +60 mV. Therefore, to reach equilibrium, sodium will need to enter the cell, bringing in positive charge. On the other hand, chloride’s equilibrium potential is -65 mV. Since chloride is a negative ion, it will need to leave the cell in order to make the cell’s membrane potential more positive to move from -70 mV to -65 mV.
Figure 3.6. A) If a cell is at rest at -70 mV, sodium ions will flow into the cell to move the cell’s membrane potential toward sodium’s equilibrium potential of +60 mV. B) At the same resting membrane potential, chloride would flow out of the cell, taking away its negative charge, making the inside of the cell more positive and moving toward chloride’s equilibrium potential of -65 mV. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Moving Toward Equilibrium’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
# Potential Values

We will use the following ion concentrations and equilibrium potentials:

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside concentration (mM)</th>
<th>Outside concentration (mM)</th>
<th>Equilibrium Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>15</td>
<td>145</td>
<td>+60 mV</td>
</tr>
<tr>
<td>Potassium</td>
<td>125</td>
<td>5</td>
<td>-85 mV</td>
</tr>
<tr>
<td>Chloride</td>
<td>13</td>
<td>150</td>
<td>-65 mV</td>
</tr>
</tbody>
</table>

Table 3.1. Intra- and extracellular concentration and equilibrium potential values for a typical neuron at rest for sodium, potassium, and chloride.

## Key Takeaways

- Moving the membrane potential toward 0 mV is a decrease in potential; moving away from 0 mV is an increase in potential
- The distribution of ions inside and outside of
the cell at rest vary among the different ions; some are concentrated inside, some are concentrated outside

- Equilibrium potentials are calculated using the Nernst equation
- To predict ion movement, compare the current membrane potential of the neuron with the ion’s equilibrium potential. Determine which way the ion needs to move to cause that membrane potential change (i.e. does the ion need to move into the cell or out of the cell?)

Test Yourself!

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/neuroscience/?p=752
1. Define resting membrane potential (Vm) of a cell.
2. Explain the differences between the resting membrane potential and the equilibrium potential.
3. Using the concentration values from the table above, calculate the equilibrium potential of potassium using the Nernst equation.
Overview

As covered in the previous chapter, at rest there is an uneven distribution of ions on either side of the membrane. The inside of the neuron is more negatively charged than the outside.
Permeability at Rest

How the ions are distributed across the membrane plays an important role in the generation of the resting membrane potential. When the cell is at rest, some non-gated, or leak, ion channels are actually open. Significantly more potassium channels are open than sodium channels, and this makes the membrane at rest more permeable to potassium than sodium.
Figure 4.2. At rest, the distribution of ions across the membrane varies for different ions. Additionally, at rest, more potassium non-gated ion channels (emphasized by green circles) are open than sodium channels (emphasized by the blue circle). The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. ‘Channels at Rest’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Potassium Can Cross Membrane at Rest

Since the membrane is permeable to potassium at rest due to
the open non-gated channels, potassium will be able to flow across the membrane. The electrochemical gradients at work will cause potassium to flow out of the cell in order to move the cell’s membrane potential toward potassium’s equilibrium potential of -80 mV.

Animation 4.1. Electrochemical gradients drive potassium out of the cell, removing positive charge, making the cell’s membrane potential more negative, in the direction of potassium’s equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. ‘Potassium Flow at 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.
You might ask, though, if the cell has these open non-gated ion channels, and ions are moving at rest, won’t the cell eventually reach potassium’s equilibrium potential if the membrane is only permeable to potassium?

If the only structural element involved in ion flow present in the cell membrane were the open non-gated potassium channels, the membrane potential would eventually reach potassium’s equilibrium potential. However, the membrane has other open non-gated ion channels as well. There are fewer of these channels compared to the potassium channels, though. The permeability of chloride is about half of that of potassium, and the permeability of sodium is about 25 to 40 times less than that of potassium. This leads to enough chloride and sodium ion movement to keep the neuron at a resting membrane potential that is slightly more positive than potassium’s equilibrium potential.
Animation 4.2. The membrane is most permeable to potassium at rest, and this leads to potassium efflux. However, the membrane is also permeable to chloride and sodium, and the flow of these ions keep the resting membrane potential more positive than potassium’s equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. ‘Ion Flow at 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.

Maintenance of Gradients

As ions move across the membrane both at rest and when the neuron is active, the concentrations of ions inside and outside of the cell would change. This would lead to changes in the electrochemical gradients that are driving ion movement. What, then, maintains the concentration and electrical gradients critical for the ion flow that allows the neuron to function properly?

The sodium-potassium pump is the key. The pump uses energy in the form of ATP to move three sodium ions out of the cell and two potassium ions in. This moves the ions against their electrochemical gradients, which is why it
requires energy. The pump functions to keep the ionic concentrations at proper levels inside and outside the cell.

Animation 4.3. The sodium-potassium pump is embedded in the cell membrane and uses ATP to move sodium out of the cell and potassium into the cell, maintaining the electrochemical gradients necessary for proper neuron functioning. Three intracellular sodium ions enter the pump. ATP is converted to ADP, which leads to a conformational change of the protein, closing the intracellular side and opening the extracellular side. The sodium ions leave the pump while two extracellular potassium ions enter. The attached phosphate molecule then leaves, causing the pump to again open toward the inside of the neuron. The potassium ions leave, and the cycle begins again. ‘Sodium-Potassium Pump’ by 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.
Calculating Membrane Potential with Goldman Equation

It is possible to calculate the membrane potential of a cell if the concentrations and relative permeabilities of the ions are known. Recall from the last chapter, the Nernst equation is used to calculate one ion’s equilibrium potential. Knowing the equilibrium potential can help you predict which way one ion will move, and it also calculates the membrane potential value that the cell would reach if the membrane were only permeable to one ion. However, at rest, the membrane is permeable to potassium, chloride, and sodium. To calculate the membrane potential, the Goldman equation is needed.

**The Goldman Equation**

\[ V_m = 61 \cdot \log \left( \frac{P_K [K^+]_{\text{outside}} + P_{Na} [Na^+]_{\text{outside}} + P_{Cl} [Cl^-]_{\text{inside}}}{P_K [K^+]_{\text{inside}} + P_{Na} [Na^+]_{\text{inside}} + P_{Cl} [Cl^-]_{\text{outside}}} \right) \]

Like the Nernst equation, the constant 61 is calculated using values such as the universal gas constant and temperature of mammalian cells.

\( P_{\text{ion}} \) is the relative permeability of each ion.
[Ion]_{\text{inside}} \text{ is the intracellular concentration of each ion}

[Ion]_{\text{outside}} \text{ is the extracellular concentration of each ion}

Example: The Neuron at Rest

\[ V_m = 61 \cdot \log \frac{P_K [K^{+}]_{\text{outside}} + P_{Na} [Na^{+}]_{\text{outside}} + P_{Cl} [Cl^{-}]_{\text{inside}}}{P_K [K^{+}]_{\text{inside}} + P_{Na} [Na^{+}]_{\text{inside}} + P_{Cl} [Cl^{-}]_{\text{outside}}} \]

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside concentration (mM)</th>
<th>Outside concentration (mM)</th>
<th>Relative permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>15</td>
<td>145</td>
<td>0.04</td>
</tr>
<tr>
<td>Potassium</td>
<td>125</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Chloride</td>
<td>13</td>
<td>150</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 4.1. Intra- and extracellular concentration and relative permeability values for a typical neuron at rest for sodium, potassium, and chloride.
Key Takeaways

- Non-gated (leak) potassium channels are open at rest causing potassium to have the highest permeability at rest.
- Other ion channels (chloride and sodium) are also open, but fewer are open than potassium.
- The resting membrane potential of a typical neuron is relatively close to the equilibrium potential for potassium.
- The sodium-potassium pump is responsible for maintaining the electrochemical gradients needed for neuron functioning.

\[ V_m = 61 \times \log \frac{1[5] + 0.04[145] + 0.4[13]}{1[125] + 0.04[15] + 0.4[150]} = -65mV \]
Test Yourself!

In the example above, we calculated the resting membrane potential of a typical neuron at rest.

1. What would happen to the membrane potential if the extracellular concentration of potassium was changed from 5 mM to 50 mM?
2. What would happen to the membrane potential if the extracellular concentration of potassium returned to 5 mM but the extracellular concentration of sodium was
changed from 145 mM to 100 mM?

3. Changing the extracellular concentration of which ion (potassium or sodium) has a significant effect on the membrane potential?

4. Why do you think this is?

From memory, draw a neuronal membrane at rest.

- Include structural elements critical for ion movement.
- Label each type of ion channel
- Illustrate appropriate state (open, closed, inactivated) of each channel.
5. POSTSYNAPTIC POTENTIALS

Overview

When the neuron is at rest, there is a baseline level of ion flow through leak channels. However, the ability of neurons to function properly and communicate with other neurons and cells relies on ion flow through channels other than the non-gated leak channels. We will cover how these channels open in a later lesson. This chapter will examine ion flow through these channels after a stimulus and how the membrane potential changes in response.

Postsynaptic Potentials

Postsynaptic potentials are changes in membrane potential that move the cell away from its resting state. For our purposes, postsynaptic potentials are measured in the dendrites and cell bodies. Ion channels that are opened by a
stimulus allow brief ion flow across the membrane. A stimulus can range from neurotransmitters released by a presynaptic neuron, changes in the extracellular environment like exposure to heat or cold, interactions with sensory stimuli like light or odors, or other chemical or mechanical events. The change in membrane potential in response to the stimulus will depend on which ion channels are opened by the stimulus.

Animation 5.1. A stimulus can cause ion channels in the membrane of the cell body or dendrites to open, allowing ion flow across the membrane. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Postsynaptic 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.
Excitatory Postsynaptic Potentials (EPSPs)

An excitatory postsynaptic potential (EPSP) occurs when sodium channels open in response to a stimulus. The electrochemical gradient drives sodium to rush into the cell. When sodium brings its positive charge into the cell, the cell’s membrane potential becomes more positive, or depolarizes. This change is called a depolarization because the cell’s membrane potential is moving toward 0 mV, and the membrane is becoming less polarized. At 0 mV, there is no potential or polarization across the membrane, so moving toward 0 would be a decrease in potential. This depolarization increases the likelihood a neuron will be able to fire an action potential, which makes this ion flow excitatory. Therefore, an EPSP is an excitatory change in the membrane potential of a postsynaptic neuron.

A postsynaptic potential is typically brief, with ion channels closing quickly after the stimulus occurs. If there is not another stimulus, the cell will return to the resting membrane potential.
Animation 5.2. When a stimulus opens sodium channels, sodium rushes into the cell because the equilibrium potential of sodium is +60 mV. This causes an excitatory depolarization called an excitatory postsynaptic potential (EPSP). After the stimulus, the ion channels close, and the membrane potential returns to rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘EPSP’ 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.

Inhibitory Postsynaptic Potentials (IPSPs)

An inhibitory postsynaptic potential, or IPSP, on the other hand, is caused by the opening of chloride channels. The equilibrium potential of chloride is -65 mV, so if the neuron is at rest at -60 mV, when chloride channels open, the
electrochemical gradients drive chloride to flow into the cell. Chloride brings its negative charge into the cell, causing the cell’s membrane potential to become more negative, or hyperpolarize. This change is called a hyperpolarization because the cell’s membrane potential is moving away from 0 mV, and the membrane is becoming more polarized. An IPSP decreases the likelihood a neuron will be able to fire an action potential, which makes this ion flow inhibitory. Therefore, an IPSP is an inhibitory change in the membrane potential of a postsynaptic neuron.

Like an EPSP, an IPSP is also typically brief, and the membrane potential will return to rest if not additional stimulation occurs.

Animation 5.3. When a stimulus opens chloride channels, and the resting membrane potential is more positive than chloride’s equilibrium potential of -65 mV, chloride rushes into the cell. This causes an inhibitory hyperpolarization called an inhibitory postsynaptic potential (IPSP). After the stimulus, the ion channels close, and the membrane potential
returns to rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘IPSP’ 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 Resting Membrane Potential is Critical

In the previous example, the resting membrane potential of that cell was -60 mV, so chloride moved into the cell. If the resting membrane potential was instead equal to chloride’s equilibrium potential of -65 mV, then chloride would be at equilibrium and move into and out of the cell, and there would be no net movement of the ion. Even though this would lead to no change in membrane potential, the opening of chloride channels continues to be inhibitory. Increased chloride conductance would make it more difficult for the cell to depolarize and to fire an action potential.

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Animation 5.4. If the cell is at rest at chloride’s equilibrium potential, when a stimulus opens the chloride channels, there will be no net movement of chloride in either direction because chloride will be at equilibrium. Since there is no net movement, there will also be no change in membrane potential because there is an equal amount of ion flow into and out of the cell. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘IPSP at Equilibrium’ 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 resting membrane potential of the cell was more negative than chloride’s equilibrium potential, for example, at -70 mV, then chloride would leave the cell, in order to move the membrane potential toward -65 mV. This would result in a depolarization of the membrane potential. However, the overall effect is still inhibitory because once the cell reaches -65 mV, the driving forces acting on chloride would try to keep the cell at that membrane potential, making it more difficult
for the cell to depolarize further and fire an action potential.

A good rule of thumb is to remember that opening of sodium channels is excitatory whereas opening of chloride channels is inhibitory.

Animation 5.5. If the cell is at rest at chloride’s equilibrium potential, when a stimulus opens the chloride channels, chloride will leave the cell, removing its negative charge. This causes a depolarization in the membrane potential, but it is still inhibitory since chloride movement will try to keep the cell near -65 mV. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Inhibitory Depolarization’ 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.
Summation of Inputs

If an excitatory stimulus is followed by additional excitatory stimuli, the sodium channels will either remain open or additional sodium channels will open. The increased sodium conductance will cause the EPSPs to summate, depolarizing the cell further than one EPSP alone. Each neuron has a threshold membrane potential at which the cell will fire an action potential. The summation of EPSPs causes the neuron to reach that threshold.

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Animation 5.6. Excitatory stimuli that occur quickly in succession lead to summation of EPSPs. This leads to increased depolarization of the membrane potential compared to a single EPSP. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘Summated EPSP Ion Flow’ by Casey Henley is licensed under a Creative Commons Attribution Non-
Summation can occur in two ways. Temporal summation occurs when one presynaptic input stimulates a postsynaptic neuron multiple times in a row. Spatial summation occurs when multiple presynaptic inputs each stimulate the postsynaptic neuron at the same time. Both types of summation result in a depolarization of a higher magnitude than when only one excitatory input occurs.

Figure 5.1 EPSPs can summate via temporal or spatial summation. Temporal summation occurs when a presynaptic neuron, Input 1 in the figure, stimulates the postsynaptic neuron multiple times in a row. Spatial summation occurs when more than one presynaptic neuron, Inputs 1 through 4 in the figure, each stimulate the postsynaptic neuron at the same time. The EPSPs of each stimulation will add together to cause a stronger depolarization of the membrane potential of the postsynaptic neuron than one excitatory stimulus alone. ‘Synaptic Summation” by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
In addition to the summation of excitatory inputs, EPSPs can also summate with inhibitory inputs. The addition of an inhibitory stimulus will result in either a weaker depolarization compared to a single excitatory stimulus or possibly no depolarization at all, depending on the strength of the inhibitory input.

Figure 5.2. If an inhibitory input, Input 3 in the figure, stimulates the postsynaptic neuron at the same time as an excitatory input, Input 1 in the figure, the result is a decrease in the amount of depolarization or the complete prevention of depolarization, depending on the strength of the inhibitory input. 'EPSP and IPSP Summation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In the case of combined inhibitory and excitatory stimuli, both chloride and sodium channels will open. As sodium
enters the cell trying to move the membrane potential to +60 mV, the equilibrium potential of sodium, chloride will also enter, trying to keep the cell near -65 mV, the equilibrium potential of chloride.

Animation 5.7. When an inhibitory input and an excitatory input stimulate a postsynaptic neuron at the same time, chloride and sodium channels open. Due to the equilibrium potentials of the two ions, both will flow into the cell. Sodium tries to depolarize the cell, whereas chloride tries to keep the cell near rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. ‘EPSP and IPSP 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.
• Postsynaptic potentials occur in the dendrites or cell body
• Excitatory postsynaptic potentials are caused by sodium channels opening
• Inhibitory postsynaptic potentials are caused by chloride channels opening
• Since the resting membrane of a typical neuron is usually very close to chloride’s equilibrium potential, knowing and comparing these two values is important for determining direction of ion flow when chloride channels open
• Input effects, whether excitatory or inhibitory, can summate and affect the postsynaptic neuron’s membrane potential
can view it online here:
https://openbooks.lib.msu.edu/neuroscience/?p=142
As covered in Chapter 1, the action potential is a very brief change in the electrical potential, which is the difference in charge between the inside and outside of the cell. During the action potential, the electrical potential across the membrane moves from a negative resting value to a positive value and back.
Figure 6.1. 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, will rapidly become positive, and then rapidly return to rest during an action potential. ‘Action Potential’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Propagation

The propagation of the action potential from the axon hillock down the axon and to the presynaptic terminal results in release of chemical neurotransmitters that communicate with a postsynaptic neuron.
Animation 6.1. The action potential moves down the axon beginning at the axon hillock. The action potential moving down a myelinated axon will jump from one Node of Ranvier to the next. This saltatory conduction leads to faster propagation speeds than when no myelin in present. When the action potential reaches the synaptic terminal, it causes the release of chemical neurotransmitter. ‘Action Potential Propagation’ by [Casey Henley](https://openbooks.lib.msu.edu/neuroscience/?p=161) is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0) 4.0 International License. View [static image of animation](https://openbooks.lib.msu.edu/neuroscience/?p=161).

**Voltage-Gated Ion Channels**

The change in membrane potential during the action potential is a function of ion channels in the membrane. In the previous lessons, we have learned about the principles of ion movement and have discussed non-gated (leak) channels at rest, as well as ion channels involved in the generation of
postsynaptic potentials. In this chapter, we will examine a different type of ion channel: voltage-gated ion channels. For our purposes, these channels are located primarily at the axon hillock, along the axon and at the terminal. They are necessary for the propagation of the action potential.

Figure 6.2. Voltage-gated channels critical for the propagation of the action potential are located at the axon hillock, down the axon at the Nodes of Ranvier, and in the presynaptic terminal. ‘Voltage-Gated Channel Location’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Voltage-gated channels allow ions to cross the membrane using the same ion movement principles covered in previous lessons. The main difference between voltage-gated channels and leak channels are how they are opened or “gated”. Voltage-gated channels open when the cell’s membrane potential reaches a specific value, called threshold. The
neuron reaches threshold after enough EPSPs summate together.

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Animation 6.2. As EPSPs summate, a result of ion movement not shown in the animation, the cell’s membrane potential will depolarize. Reaching threshold causes voltage-gated ion channels to open. Once the channels are open, ions will move toward equilibrium. In the animation, sodium ions flow inward. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. ‘Voltage-Gated Channel’ 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 Action Potential

The action potential begins when the cell’s membrane
potential reaches threshold. Once initiated in a healthy, unmanipulated neuron, the action potential has a consistent structure and is an all-or-nothing event. It will run through all the phases to completion.

The rising phase is a rapid depolarization followed by the overshoot, when the membrane potential becomes positive. The falling phase is a rapid repolarization followed by the undershoot, when the membrane potential hyperpolarizes past rest. Finally, the membrane potential will return to the resting membrane potential.
Rising Phase

The rising phase is caused by the opening of voltage-gated sodium channels. These ion channels are activated once the cell’s membrane potential reaches threshold and open immediately. The electrochemical gradients drive sodium into the cell causing the depolarization.
Animation 6.3. Voltage-gated sodium channels open once the cell’s membrane potential reaches threshold. The rapid influx of sodium results in a large depolarization called the rising phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. ‘Rising Phase’ 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.

Falling Phase

The falling phase of the action potential is caused by the inactivation of the sodium channels and the opening of the potassium channels. After approximately 1 msec, the sodium channels inactivate. The channel becomes blocked, preventing ion flow. At the same time, the voltage-gated potassium channels open. This allows potassium to rush out
of the cell because of the electrochemical gradients, taking its positive charge out of the cell, and repolarizing the membrane potential, returning the cell’s membrane potential moves back near rest.

Like the voltage-gated sodium channels, the voltage trigger for the potassium channel is when the cell’s membrane potential reaches threshold. The difference is that the sodium channels open immediately, whereas the potassium channels open after a delay.

Animation 6.4. After approximately 1 msec, the voltage-gated sodium channels inactivate, which prevents any further ion flow into the cell. Although the voltage-gated potassium channels are activated in response to the cell reaching threshold, their opening is delayed and occurs alone with the sodium channel inactivation. This allows an efflux of potassium ions, which causes the repolarization of the falling phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent
Undershoot

As the membrane potential returns to resting level, the sodium channels will de-inactivate, returning to the closed position, ready to be opened by a voltage change again. The potassium channels will also close, but they remain open long enough to cause a hyperpolarizing undershoot as potassium continues to move toward its equilibrium potential of -80 mV.

Animation 6.5. Once the cell’s membrane potential repolarizes, the voltage-gated sodium channels de-inactivate and return to their closed state. The voltage-gated potassium channels remain open long enough for the undershoot to occur as potassium continues to flow out of the cell. The
dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. ‘Undershoot’ 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.

Return to Rest

Once the voltage-gated channels close, the sodium-potassium pumps will reestablish the proper ionic concentrations needed for the electrochemical gradients. This action along with open leak channels will return the cell to its resting membrane potential.

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Animation 6.6. Once the voltage-gated potassium channels close, the sodium-potassium pump will work to re-establish the electrochemical gradients and return the cell to its resting membrane potential. ‘Return to Rest’ by Casey Henley is
Refractory Periods

Each neuron does have a maximum firing rate, though. And even if the stimulus continues to increase in strength, the neuron cannot fire at a higher frequency. The maximum firing rate of a cell is determined by the status of the ion channels in the neuronal membrane during the different phases of the action potential.

The Absolute Refractory Period

During the absolute refractory period, a second action potential cannot be fired under any circumstances regardless of the strength of the stimulus. The voltage-gated sodium channels are either open (during the rising phase) or inactivated (during the falling phase).

The Relative Refractory Period

When the cell repolarizes and the voltage-gated sodium channels de-inactivate and return to a closed state, the cell is
again able to fire another action potential. However, during the end of the falling phase and the undershoot, voltage-gated potassium channels are still open. During the undershot, while the neuron is hyperpolarized, a larger-than-normal stimulus is needed to make the cell reach threshold again. This segment of the action potential is called the relative refractory period. Action potentials can be fired, but a stronger stimulus is needed than when the cell is at rest.
Figure 6.6. The maximum firing rate of a neuron is determined by the refractory periods. A) During the absolute refractory period no additional action potentials can be fired because the voltage-gated sodium channels are either already open (rising phase) or inactivated (falling phase). In these states, they cannot be opened again to begin a second action potential. B) The relative refractory period occurs when the voltage-gated sodium channels are closed, but the voltage-gated potassium channels remain open, causing a hyperpolarization of the membrane. Action potentials can be fired during this time, but a stronger stimulus is required to reach threshold compared to when the cell is at rest. The dotted, blue channels represent voltage-gated sodium
channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. “Refractory Periods” by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

**Action Potential Characteristics**

For a given cell, all action potentials have the same characteristics; they depolarize to the same membrane potential value and take the same amount of time. However, different neurons may exhibit different action potential characteristics. Likewise, if a neuron has a change in its environment, like altered extracellular ion concentrations, the shape of the action potential would change due to a change in the electrochemical gradients. For example, if the external concentration of sodium is decreased, the equilibrium potential of sodium, as well as the strength of the electrochemical gradients will change, which will result in a slower rate of rise and a lower amplitude of the action potential.
Figure 6.4. A) A neuron kept under the same conditions will display action potentials of similar height and length. B) However, if cellular conditions change, so will the action potential characteristics. If extracellular sodium levels are decreased compared to control levels, the action potential will show a slower rate of rise and a decreased height. ‘Low Sodium Action Potential’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
Stimulus Strength

The strength of a stimulus needs to be encoded by the neurons. We need to be able to perceive the difference, for example, between a dim light and a bright one. The frequency or rate of action potential firing informs the nervous system of stimulus strength.

Since the height of the action potential is always the same for a given neuron, the strength of the stimulus is determined by the frequency of action potential firing. A weak stimulus would cause fewer action potentials to be fired than a strong stimulus.
Figure 6.5. Information about the strength of a stimulus is encoded by the rate of action potential firing. A) A weak stimulus results in few action potentials being fired. B) A strong stimulus results in many action potentials firing in a row. ‘Stimulus Strength’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Direction of Propagation

The action potential moves down the axon due to the influx of sodium depolarizing nearby segments of axon to threshold.
Animation 6.7. A voltage change that reaches threshold will cause voltage-gated sodium channels to open in the axonal membrane. The influx of sodium causes the rising phase of the action potential, but the ion flow also depolarizes nearby axon regions. As the depolarization reaches threshold, the action potential moves down the axon. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. ‘Action Potential Movement’ 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.

Action potentials only move in one direction, though, from the cell body to the presynaptic terminal. The refractory period keeps the action potential from moving backward down the axon. As the action potential moves from one Node of Ranvier to the next, the inactivated sodium channels in the previous axon segment prevent the membrane from depolarizing again. Therefore, the action potential can only
move forward toward axon segments with closed sodium channels ready for rising phase depolarization.

Figure 6.7. Action potentials only travel in one direction. The inactivated sodium channels prevent the action potential from moving backward down the axon. Blue dotted channels: sodium channels; green striped channels: potassium channels. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'No Backward Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Speed of Propagation

Presence of Myelin

The presence of myelin leads to a significant increase in action potential conduction speed compared to an unmyelinated axon. For a myelinated axon, the action potential “jumps” between Nodes of Ranvier in a process called saltatory conduction. The nodes have a high density of voltage-gated
channels, and the action potential is able to skip the axon segments covered by the myelin. In an unmyelinated axon, the action potential moves in a continuous wave. In addition to the saltatory conduction process, the presence of myelin also insulates the axon, preventing charge loss across the membrane, which also increases speed of the action potential.

Animation 6.8. The action potential moves down an unmyelinated axon like a wave, opening voltage-gated channels along the length of the axon. In a myelinated axon, though, the action potential is able to skip portions of the axon that are covered by the myelin; the action potential jumps from node to node and travels further down the axon in the same amount of time. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. ‘Action Potential Speed’ 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.
Diameter of Axon

The diameter of the axon also affects speed. The larger the diameter of the axon, the faster the propagation of the action potential down the axon. A larger axon leads to less resistance against the flow of ions, so the sodium ions are able to move more quickly cause the regeneration of the action potential in the next axon segment.

Figure 6.8. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. ‘Axon Diameter’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
Key Takeaways

- The voltage-gated ion channels are located along the axon hillock and axon; they open in response to the membrane potential reaching a threshold value
- The rising phase of the action potential is a result of sodium influx
- The falling phase of the action potential is a result of potassium efflux
- Action potentials are all-or-none (postsynaptic potentials are graded)
- Action potential have the same height of depolarization for a given cell under typical conditions
- The neuron cannot fire a second action potential during the absolute refractory phase
- The neuron can fire a second action potential during the relative refractory phase, but it requires a stronger stimulus than when the neuron is at rest
- Stimulus strength is coded by frequency of action potential firing
• Action potential travel in one direction due to the presence of inactivated voltage-gated sodium channels
• Speed of propagation relies on presence and thickness of myelin and diameter of axon

Test Yourself!

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/neuroscience/?p=161

Additional Review

From memory, draw an action potential.
1. Label the main phases (rising, falling, etc...) and include threshold
2. Identify the change in potential (depolarization, repolarization, hyperpolarization)
3. Describe the state (open, closed, inactivated) of the ion channels at each phase

From memory, draw the neuronal membrane during each refractory period.
7.

VOLTAGE CLAMP

Overview

In the previous chapter, we covered ion flow and membrane potential changes that occur during the action potential in the neuron. We have this level of understanding about how ions move during the action potential because of a special technique called a voltage clamp experiment that was used in the 1950s. The voltage clamp method allows researchers to study voltage-gated ion channels by controlling the membrane potential of a neuron.

The Voltage Clamp Experiment

Initial Set-Up

To conduct a voltage clamp experiment, a portion of the axon, which would include the cell membrane and all the
voltage-gated ion channels located there, is removed from a neuron and placed into a solution that mimics that of physiological extracellular solution. The ion concentrations across the membrane, as well as the electrochemical gradients, would remain the same.

Figure 7.1. To conduct a voltage clamp experiment, a portion of the axon is removed from the neuron. The axon is placed in a special solution that is similar to physiological extracellular solution. ‘In Vitro Axon’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Measuring the Membrane Potential

The initial step in the voltage clamp method is to measure the membrane potential of the axon. A recording electrode is placed into the axon, and a reference electrode is placed into the extracellular solution. The voltage difference between these two electrodes is the membrane potential of the axon.
Clamping the Voltage

The researchers running the experiment can set a desired membrane potential for the cell. The equipment then compares the desired membrane potential with the measured membrane potential from the electrodes. If these values differ, current is injected into the cell to change the measured membrane potential and make it equal to the desired potential.
Repeat

The equipment continues this cycle for the length of the experiment. It constantly measures and compares the actual membrane potential with the desired potential, and then uses
current to correct any changes, “clamping” the potential at one value.

Figure 7.4. The voltage clamp cycle repeats continuously. The actual membrane potential of the axon is measured, compared to the set desired potential value, and then current is passed into the axon to keep the actual membrane potential equal to the desired potential. ‘Voltage Clamp Cycle’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
At Rest

Let's work through the system with an example. Here is an axon bathed in the extracellular solution. The resting membrane potential is measured at -65 mV.

Figure 7.5. Measure the membrane potential. The membrane potential of this axon at rest is -65 mV. ‘Voltage Clamp Example at Rest’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
Set Clamped Membrane Potential Value

For this experiment, the desired membrane potential value is 0 mV.

Figure 7.6. Set desired membrane potential. The set value for this experiment is 0 mV. 'Voltage Clamp Example Set Value' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
Compare Actual and Set Membrane Potential Values

The equipment will determine that the actual membrane potential of the cell is not correct (-65 mV compared to 0 mV), so the cell must depolarize to reach the set value.

Figure 7.7. Compare measured membrane potential to desired potential. The actual membrane potential of the axon is at -65 mV, so the cell needs to be depolarized to reach the desired potential of 0 mV. ‘Voltage Clamp Example Comparison’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
Adjust Membrane Potential

To make the axon move from its resting membrane potential to 0 mV, the current electrode will pass positive current into the cell, depolarizing the cell until the membrane potential reaches the set value.

Figure 7.8. Correct actual membrane potential. To depolarize this axon from rest at -65 mV to the desired clamp value of 0 mV, positive current will be injected into the cell. The membrane potential will then depolarize to 0 mV and remain there. ‘Voltage Clamp Example Current’ by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.
Function During Voltage Clamp

The important aspect of the depolarization seen in the example is that it is above threshold. Moving the membrane potential above threshold will activate the voltage-gated ion channels. Sodium channels will open immediately, and sodium will begin rushing into the cell. This influx of positive ions would normally cause change the membrane potential to depolarize, but the voltage clamp equipment will measure the ion flow and inject a current of equal strength and opposite charge into the axon to maintain the membrane potential at 0 mV. This happens almost instantly and is a constant process, so as the ion flow changes, so does the injected current.

Animation 7.1. Clamping the cell at 0 mV will result in current being passed into the axon to depolarize the membrane potential. This depolarization is above threshold, so the
voltage-gated ion channels in the membrane will be activated. Sodium will enter the axon through the open sodium channels. The voltage clamp equipment will inject current equal in strength and opposite in charge to the sodium influx in order to keep the membrane potential of the axon at 0 mV. The membrane potential will remain at 0 mV because the injected current offsets any change that would normally occur due to ion flow. ‘Voltage Clamp Sodium 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 ion channels function as expected during the voltage clamp experiment, the voltage-gated sodium channels will inactivate, and the delayed voltage-gated potassium channels will open because, like the sodium channels, they are also activated when the membrane potential reaches threshold. This causes the ion flow to change from inward to outward. Normally, potassium efflux would cause a repolarization of the membrane potential, but the voltage clamp equipment will again inject a current that is equal in strength and opposite in charge to the potassium flow to keep the membrane potential steady at 0 mV.

A video element has been excluded from this version of the text. You can watch it online.
Animation 7.2. The voltage-gated sodium channels will inactivate, and the potassium channels will open. Potassium will then flow out of the axon. Similar to the sodium influx, the voltage clamp equipment will inject current equal in strength and opposite in charge to the potassium efflux in order to keep the membrane potential of the axon at 0 mV. ‘Voltage Clamp Potassium 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.

Data Collection

Researchers can determine how much current is moving through the voltage-gated ion channels by observing how much current the equipment must inject into the cell to keep the membrane potential steady. If the equipment has to inject negative current in for 2 milliseconds, then the researchers know that positive ions were flowing in for 2 milliseconds. So the voltage-clamp set up allowed researchers in the 1950s to
learn about how the voltage-gated ion channels were functioning during an action potential.

Key Takeaways

- The membrane potential does not change during a voltage clamp experiment
- Voltage-gated ion channels are still able to function normally and allow ion flow
- If the clamped membrane potential is above threshold, the voltage-gated channels will act as if the cell is firing an action potential
- The equipment must compensate for the neuron’s ion flow by injecting current into the axon. The amount of current needed to keep the membrane potential steady is equal and opposite to the current actually flowing in the cell
Additional Review

You conduct a voltage clamp experiment where you move the membrane potential from rest at -65 mV to 0 mV. You collect the following data:
The membrane potential of a neuron is clamped at 0 mV. An initial inward current is seen, followed by an outward current.

Describe what causes the observed ion flow, including information about which ion(s) is/are moving and in which direction.
PART II

NEURONAL COMMUNICATION
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.
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.

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.
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.

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.

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.

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=307

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) A xoaxonic 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!

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/neuroscience/?p=307
Overview

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 neurotransmitters 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.

Small Molecule Transmitters

The small molecule transmitters can be divided into two main groups: amino acid neurotransmitters and biogenic amines. 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 (Ɣ-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.
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 in the synthesis pathway. GABA is packaged into vesicles for storage in the terminal via the vesicular inhibitory amino acid transporter.
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.
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.

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 norepinephrine.

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 histadine decarboxylase, the rate limiting step of the pathway. Like the
other monoamine neurotransmitters, it is packaged into synaptic vesicles via the vesicular monoamine transporter.

![Histamine Synthesis](https://example.com/histamine-synthesis.png)

**Figure 9.10.** Histamine is synthesized from histadine 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 vesicle must then move from the soma to the terminal using fast axonal transport mechanisms.

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 molecules 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

An interactive or media element has been excluded from this version of the text. You can view it online here:

https://openbooks.lib.msu.edu/neuroscience/?p=328
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.

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.
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](image.png)

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](https://creativecommons.org/licenses/by-nc-sa/4.0) is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0) 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.

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.
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
Additional Review

Describe the events that occur in the presynaptic terminal when an action potential arrives. Include the role of Ca2+.
NEUROTRANSMITTER ACTION: IONOTROPIC RECEPTORS

Overview

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.
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.
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.
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 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.

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 represents AMPA 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 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 Non-Commercial
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.
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).

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 open, 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).
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.
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!

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/neuroscience/?p=368
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:

- One presynaptic glutamate neuron fires one action potential and releases neurotransmitter
- The presynaptic GABA neuron fires one action potential and releases neurotransmitter
- One presynaptic glutamate neuron fires five action potentials and releases neurotransmitter
Overview

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.
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.

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=397
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.

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=397

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.
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<sub>i</sub>, and suppress the activity of adenylyl cyclase. Alpha 1-adrenergic receptors couple to a third type of G-protein, G<sub>q</sub>, 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.
Figure 12.3. The second messenger pathway use 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 adenylyl cyclase, which initiates downstream cellular effects. B) The norepinephrine alpha 2-adrenergic receptor couples to the $G_i$ subunit and inhibits adenylyl 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.
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 Gs alpha subunit and inhibition of the pathway is caused by the Gi 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.

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=397
Animation 12.4. GPCRs that couple to the G<sub>s</sub> alpha subunit initiate the adenylyl cyclase / cAMP pathway. The G<sub>s</sub> 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.

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=397

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.

A video element has been excluded from this version of the text. You can watch it online.
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 Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Phospholipase C / IP₃ / DAG Second Messenger Cascade

The Gq 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).
IP$_3$ 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.

Animation 12.7. The G$_q$ G-protein subunit activates phospholipase C, which converts the phospholipid PIP$_2$ in the cell membrane into DAG, another membrane-bound molecule, and IP$_3$, a cytoplasmic molecule. DAG can interact with PKA, initiating phosphorylation of cellular proteins. IP$_3$ 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. ‘IP$_3$-DAG Pathway’ by Casey Henley is licensed under a Creative Commons
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.
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.

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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 Gs subunit initiates the adenylyl cyclase / cAMP signaling pathway
- The Gi subunit inhibits the adenylyl cyclase / cAMP signaling pathway
- The Gq subunit initiates the phospholipase C / IP3 / DAG signaling pathway

Test Yourself!

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Additional Review
What are some differences between ionotropic and metabotropic neurotransmitter receptors?
Overview

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.
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.
Serotonin action is terminated by reuptake into the presynaptic terminal via SERT. Serotonin is then either degraded by MAO or repackaged into synaptic vesicles.

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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https://openbooks.lib.msu.edu/neuroscience/?p=412
Overview

Drugs and toxins can have many effects on a neuron, from activation to inhibition and all levels of modulation. Understanding how neurons typically function is important in being able to understand the role of drugs and toxins.

Effects at the Terminal

There are many ways in which drugs and toxins can alter neuron functioning. Drugs can alter neurotransmitter synthesis pathways. An example of this is treatment with L-DOPA, a dopamine precursor molecule that results in increased dopamine production and is used as a treatment in 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
norepinephrine into vesicles, depleting neurotransmitter stores.

Action at the neurotransmitter receptors is another critical location for drug and toxin action. Agonists mimic neurotransmitter effects, whereas antagonists block neurotransmitter effects. Nicotine is an agonist for the ionotropic acetylcholine receptor, which is also called the nicotinic acetylcholine receptor. Bungarotoxin, a component of some snake venom, is an antagonist to this receptor and blocks the action of acetylcholine. Additionally, many
chemicals are able to modulate receptors. Barbiturates bind to the GABA receptor and increase the time the receptor is open when GABA binds.

![Diagram of neurotransmitter receptors](image-url)

**Figure 2.** Drugs and toxins can alter neurotransmitter receptors on the post-synaptic neuron in multiple ways. Receptor Drug Effects by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

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. Certain chemicals are able to inhibit these degradative enzymes. 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. 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 3. Drugs and toxins can alter neurotransmitter degradation and reuptake into the presynaptic terminal.

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**Effects on Ion Channels**

Drugs are also able to have effects on neuronal communication by acting outside of the synaptic cleft. 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 cellular firing, but it can quickly lead to excitotoxicity.
EPIGENETICS

Central Dogma

DNA to RNA to protein. The central dogma of genetics. It may look simple, but much has to occur in the cell for this process to be successful.
Figure 1. The central dogma of genetics. DNA is translated into RNA, which is translated into protein. Central Dogma by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Transcription

In the nucleus, proteins called polymerases and transcription factors attach to the DNA, and then copy the sequence into RNA.
DNA isn’t always accessible to those proteins, though. There is so much DNA in each cell, that in order to save space, it is condensed into chromatin, which consists of DNA wrapped around proteins called histones.

Epigenetic tags on the DNA or histones affects how tightly the DNA is wound around the histones. Methyl groups can be attached to DNA, usually on CG pairs, or on the histones themselves.
In order for transcription and gene expression to occur, the strands of DNA must uncoil from the histone bodies to become accessible to the transcriptional machinery. Gene expression can be altered by modifying how easily the histones unwind and how accessible DNA strands are.
Figure 4. Transcription proteins cannot bind DNA when it is tightly wound around histones. The DNA must first uncoil and become accessible to RNA polymerase and associated proteins. 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.

Epigenetic tags on the DNA or histones affects how tightly the DNA is wound around the histones. Methyl groups can be attached to DNA, usually on CG pairs, or on the histones themselves. These methyl groups make it more difficult for the polymerase to access the DNA, by keeping the DNA coiled around the histones, and this reduces transcription. When the methyl groups are removed, called demethylation, gene expression can increase because the DNA uncoils and is accessible to the transcriptional machinery. The location and number of methyl groups on the DNA is part of the epigenome. The epigenome, therefore, plays an important role in the control of the physical structure of the genome.
Figure 5. Methyl groups attached to DNA affect how accessible genes are to transcription proteins. Highly methylated DNA stays tightly wound around histones. Demethylated DNA uncoils and transcription of those genes can occur. 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 experiences, especially during development, 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
had 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.

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.

Figure 6. Epigenetic factors can be inherited. Transgenerational Effects by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
PART III
SENSORY SYSTEMS
GENERAL PRINCIPLES OF SENSORY SYSTEMS

Each sensory system is obviously quite different in the type of stimulation that it responds to and the manner in which environmental stimuli is converted to neuronal signaling. However, there are many principles that can be generalized across sensory systems.

Sensory transduction

Our sensory systems work by converting different types of stimuli in the environment (i.e. visible light, sound waves, chemical molecules) into action potentials in the nervous system. This conversion is called sensory transduction and occurs in all sensory systems.

Receptive fields

Receptive fields are easiest to understand in the visual and
somatosensory systems. The receptive field for a neuron is the region of the retina or skin where a stimulus (light or touch) will evoke a response in the neuron. Receptive fields in the auditory system can consist of a certain frequency of sound and/or the location of sound in space.

Receptive fields can vary in size and shape depending on the characteristics of neuron (i.e. type, location in body, location in pathway). Receptive fields become more complex as information travels to the brain.

Lateral Inhibition

Lateral inhibition is a process used by sensory systems to enhance the perception of signals, particularly at edges, points, or other changes in the stimulus. It occurs because overlapping receptive fields can inhibit each other. This inhibition enhances the perceived differences between the stimulus and the area not stimulated.

Neural Coding

There are a number of different ways in which the nervous system encodes complex information. Two that are common within the sensory systems are line coding and population coding.
Labeled Line Coding

In the labeled line coding of information, one cell encodes for one type of sensory quality. Pain is a good example of this. If a pain receptor is activated, the resulting sensation will be pain, regardless of the manner in which the receptor is stimulated. In other words, the sensory neurons are specifically tuned to one sensory stimulus. If that receptor-cell type was dysfunctional, the sensation will not be perceived. For example, there is a mutation that prevents sodium channels in pain receptors (but not other cell types) from working. When this mutation occurs, the subject cannot feel pain.

Population Coding

In populating coding, one cell can encode more than one sensory modality, and it is the combination of many cells that make up the perception. An example of this is color vision. Each color photoreceptor is most sensitive to a specific color (blue, green, or red), but a range of wavelengths can elicit changes in firing rates in the neuron. Therefore, the responses from a population of color photoreceptors must be combined to perceive the full spectrum of color.

Higher level processing of taste and olfaction also uses population coding – sometimes the sense of smell is needed in addition to the sense of taste to fully perceive a flavor. Have you ever been congested from a cold and food just doesn’t taste
the same? That’s due to this combining of the senses for a full perception.

Pathways

In general, the route sensory information takes from the periphery to the central nervous system is similar among most of the systems. Environmental stimuli become encoded by a specialized receptor in the periphery. Information then enters the central nervous system via the spinal cord or brainstem and relays through the thalamus, a structure that sits deep in the forebrain. The only sensory system that does not relay through the thalamus is the olfactory system. The thalamus then sends projections out to the primary cortical regions for each sensory system.

Role of the Thalamus

It’s common to hear that sensory information “relays” through the thalamus on the way to the cortex (for example, in the paragraph above). This language can give the impression that the thalamus is only responsible for making sure the sensory signal gets from periphery to the cortex. This greatly underestimates the thalamic role. The thalamus is known to contribute to the processing and modification of the sensory signal.
17.

SOMATOSENSORY: SKIN

Receptors

Our somatosensory systems allows us to interact with our environment through the sensation of touch. Touch can come in many forms: pressure, vibration, stretch, motion, edges, points, etc. We can feel all these different modalities because of the presence of specialized sensory receptors located in the skin. And when this information is combined in the central nervous system, we are able to determine the location, strength, duration, movement, and object shape and texture of the object interacting with the skin.
Receptive Fields

The sensory receptors have special characteristics that allow them to respond to the different stimuli. One characteristic is the receptive field of the receptor. The receptive field is the space on the skin that, when touched, will activate that receptor.
Figure 2. Each mechanoreceptor will be activated by a specific region of skin, and that region is the neuron’s receptive field. Receptive Field Action by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Merkel cells and Meissner corpuscles, both of which are located near the skin surface, have small receptive fields. Ruffini endings and Pacinian corpuscles are located deeper in the skin layers. These two receptor types have larger receptive fields than the Merkel cells and Meissner corpuscles.
Figure 3. Receptive field sizes vary depending on the underlying mechanoreceptor type and location. Mechanoreceptor Receptive Fields by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive field sizes vary among different body regions. Even within one receptor type (e.g. Meissner corpuscles), receptive fields in regions like the fingers or lips are smaller than in regions like the back or leg. This allows us to have finer spatial resolution with locating and identifying objects using our
fingers. The smaller receptive fields in these regions are a result of a higher density of receptors in the skin.

High receptor density
Small receptive fields
Fine two-point discrimination

Low receptor density
Large receptive fields
Coarse two-point discrimination

Example: Hand
Example: Back

Figure 4. Density of mechanoreceptors can affect the size of the receptive field for each receptor. High density leads to smaller receptive fields and varies by location on the body. Receptive Field Location by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Two-Point Discrimination

Receptive field sizes are important because they allow us to locate a stimulus on our bodies. Larger receptive fields are not as precise as smaller receptive fields. One measure of receptive field size is two-point discrimination, which determines the minimum distance needed between two stimuli to perceive two separate points on the skin and not one.
Figure 5. The size and density of the receptive fields affect the sensitivity of the skin, which can be measured by the two-point discrimination test. Two-Point Discrimination by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Adaptation Rate

Another important characteristic of the somatic sensory receptors is that of adaptation rate. Fibers that are slowly adapting show action potential firing throughout the entire time a stimuli is present. Merkel cells and Ruffini endings are
both slowly adapting fibers. Slowly adapting fibers are most useful for determining a stimulus’ pressure and shape.

Animation 1. Slowly adapting mechanoreceptors continuing firing action potentials throughout the duration of a stimulus. Slowly Adapting Mechanoreceptor by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Rapidly adapting fibers fire action potentials when a stimulus changes (e.g. starts, stops, gets stronger or weaker) but not when a stimulus is constant. This firing makes rapidly adapting fibers specialized for detecting movement and vibration. Meissner and Pacinian corpuscles are rapidly adapting.

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=493
Animation 2. Rapidly adapting mechanoreceptors firing action potentials when the strength of the stimulus changes. Rapidly Adapting Mechanoreceptor by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

**Sensory Transduction**

In previous chapters we discussed ion channels that are gated by voltage changes in the neuron and channels that are gated by neurotransmitters. In the somatosensory channel, we find ion channels that are gated by physical distortion or stretch of the membrane. These channels can open by stretch of the membrane itself or indirectly through movement of intra- or extracellular proteins that are linked to the channels. Sodium and calcium flow into the cell, causing both a depolarization and the initiation of second messenger cascades. If enough stimulus is applied, the depolarization reaches threshold of the axon and an action potential is sent toward the spinal cord.
Animation 3. Mechanoreceptors respond to touch stimuli via stretch-gated non-selective cation channels. The channels can either open due to movement of the membrane itself or due to proteins associated with the channels. Stretch Channels by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Lateral Inhibition

Understanding the basics of how receptive fields function is important for understanding lateral inhibition. We have previously examined receptive fields that are excitatory. If a stimulus is present within the receptive field, the sensory receptor cell is activated. However, receptive fields are more complex. There is a region outside of the excitatory center that is inhibitory. If a stimulus is present near but not within the center of a cell’s receptive field, this will lead to a decrease in firing rate.
Figure 1. Receptive fields have an central excitatory region and a surrounding inhibitory region. Lateral Inhibition Receptive Fields by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC
In the following example, there are three sensory neurons, and the excitatory regions of their receptive fields are adjacent to one another. The inhibitory regions, therefore, overlap. These sensory receptor cells innervate neurons in the central nervous system (we will discuss the pathway in detail below). When no stimulus is present, each of the CNS neurons will show a baseline firing rate.
Figure 2. Neurons in the sensory pathway have a baseline firing rate when no stimulus is present. Lateral Inhibition Baseline by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
If a stimulus touches the excitatory region of the receptive field of cell B, it will end up increasing the firing rate of cell E because cell B directly innervates cell E. Cell B also innervates inhibitory interneurons, though, and these interneurons make connections with the nearby CNS neurons. Since these synapses are inhibitory, the neurons will have a decrease in firing rate from baseline.
Figure 3. If a stimulus is present, it will activate the excitatory regions of some receptive fields and the inhibitory regions of others. The presence of inhibitory interneurons function to decrease the firing rate of nearby second-order neurons.
The result is that the perception of the stimulus is enhanced compared to the actual stimulus strength.
Figure 4. Due to lateral inhibition, the perceived stimulus strength, particularly at points or edges, is enhanced compared to the actual stimulus. Lateral Inhibition Stimulus Strength by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Afferent fibers have their cell bodies located in the dorsal root ganglion, a structure that lies just outside of the spinal cord. The axons of these first-order neurons enter the ipsilateral dorsal side of the spinal cord. Some axon collaterals terminate in the spinal cord and are important for reflexes. The main axon branch ascends to the brain, terminating in the dorsal column nucleus located in the brainstem. Projections from the second-order neurons in the dorsal column nucleus cross the midline and ascend via a white matter tract called the medial lemniscus. The axons terminate in the ventral posterior nucleus of the thalamus. The thalamic neurons then project to the primary somatosensory cortex located in the postcentral gyrus in the parietal lobe.
Figure 5. Somatosensory information from the neck and body travels through the dorsal column – medial lemniscus pathway. Axons enter the spinal cord and ascend through the dorsal column to the medulla where decussation occurs. Information continues to the thalamus via the medial lemniscus, and then reaches the somatosensory cortex. Somatosensory Pathway by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway from the Head (Trigeminal Pathway)

Sensory receptors in the face and head send info to the brain via cranial nerve V, the trigeminal nerve. The first-order neurons project to the ipsilateral trigeminal nucleus in the brainstem. The second-order neurons cross the midline and project up to the ventral posterior nucleus of the thalamus. These neurons then send projections to the somatosensory cortex.
Somatotopic Organization

As covered earlier, the touch receptors each correspond to a specific region of skin. As information ascends to the CNS, the receptive fields of each higher-order neuron increases in size and complexity, but even cortical neurons are associated with a specific region of the body. Cortical neurons are organized by the region of the body they represent, so neurons that respond to sensation in the fingers are located close to the neurons that respond to sensation in the hand. This creates a somatotopic map of the body in the primary somatosensory cortex. Regions with high receptor density in the skin, and thusly fine two-point discrimination, have more cortical space devoted to them. This means that the cortical representation of the body
is not true to actual physical proportions. A homunculus is a cartoon representation of what a body would look like if the cortical representation was proportional to actual body size. The hands and lips would be excessively large while the torso, arms, and legs, would be relatively small.

Figure 7. The body is mapped onto the somatosensory cortex. Regions with high touch sensitivity, and therefore high mechanoreceptor density, have more cortical space dedicated to their processing. Somatotopic map by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
The somatotopic map can rearrange under certain conditions. This characteristic is called plasticity. Amputation or loss of a finger, for example, will lead to the associated cortical space to be functionally remapped by input from neighboring regions of the hand. The cortical neurons do not die, they begin to be activated by a different region of the body. Likewise, cortical representation can expand with use or practice. Repeated training of certain fingers can lead to an increase in cortical space mapped to those digits. Cortical plasticity is believed to underlie the phenomenon of the perception of phantom limbs after amputation. In these cases, subjects that have lost a region of their body can sometimes still “feel” the missing part.
Figure 8. Cortical activity can be measured when peripheral receptive fields are stimulated. However, the cortex is plastic and when peripheral changes occur, like amputation of a finger in this example, nearby cortical regions will overtake the space of the “lost” body region. Plasticity by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Anatomy of the Retina

The retina is the light-sensitive region in the back of the eye where the photoreceptors, the specialized cells that respond to light, are located. The retina covers the entire back portion of the eye, so it’s shaped like a cup. In the middle of the cup is the fovea, the region of highest visual acuity.
Cells of the Retina

In addition to the photoreceptors, there are four other cell types in the retina. The photoreceptors synapse on bipolar cells, and the bipolar cells synapse on the ganglion cells. Horizontal and amacrine cells allow for communication laterally between the neurons.
Figure 2. There are five cell types in the retina. Retinal Neurons by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Direction of Information

When light strikes the retina, it must pass through all the cell layers to activate the photoreceptors, which then starts the synaptic communication back toward the ganglion cells.

Figure 3. When light enters the eye, it must cross through the ganglion and bipolar cell layer before reaching the photoreceptors. Then the neuronal communication moves in the opposite direction from the photoreceptors toward the ganglion cells. Direction of Light by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptors

The photoreceptors are the specialized receptors that respond to light. There are two types of photoreceptors: rods and cones. Rods are more sensitive to light, making them primarily responsible for vision in low-lighting conditions. Cones are less sensitive to light and are responsible for color vision.
vision. These photoreceptors are most active in daylight conditions.

The photoreceptors are responsible for converting light into electrical signals. For our purposes, to examine the function of the photoreceptors, we will A) focus on rods and B) assume the cells are moving from either an area of dark to an area of light or vice versa, so there is no set “resting” baseline point for the photoreceptors. For the “typical” neurons we covered in previous chapters, we usually assumed they were at rest at -65mV, and that is where we would begin when looking at
membrane potential changes. For photoreceptors, the starting point will be relative to the lighting change.

Photoreceptors do not fire action potentials; they respond to light changes with graded potentials (depolarization or hyperpolarization). Despite this, the photoreceptors still release glutamate onto the bipolar cells. The amount of glutamate released changes along with the membrane potential, so a hyperpolarization will lead to less glutamate being released.
Figure 5. Photoreceptors respond with graded potentials when moving from light to dark or vice versa. The direction of change in the membrane potential leads to an increase or decrease in glutamate release. Photoreceptors Moving by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Sensory Transduction

In the dark, the photoreceptor has a membrane potential that is more depolarized than the “typical” neuron we examined in previous chapters (photoreceptor membrane potential is around -40mV). This is because photoreceptors have open ion channels that allow the influx of sodium and calcium. These channels are gated by the presence of cyclic GMP (cGMP), a molecule important in second-messenger cascades.

When the photoreceptor moves into the light, the cell hyperpolarizes. Light enters the eye, reaches the photoreceptors, and causes a conformational change in special protein called opsin. This change activates a G-protein called transducin, which then activates a protein called phosphodiesterase (PDE). PDE breaks down cGMP, and with less cGMP, the cGMP-gated ion channels that were open in the dark close. The decrease in cation flow into the cell causes the photoreceptor to hyperpolarize.

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=438

Animation 1. Photoreceptors hyperpolarize when exposed to
light because the light causes a conformational change in the opsin protein, which activates transducin, leading PDE to convert cGMP to GMP. Without cGMP, the cation channels close, preventing the influx of positive ions, hyperpolarizing the cell. Phototransduction by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Transmission of Information within Retina

Bipolar Cells

Photoreceptors synapse onto bipolar cells in the retina. There are two types of bipolar cells: ON and OFF. These cells respond in opposite ways to the glutamate released by the photoreceptors. Like photoreceptors, the bipolar cells do not fire action potential and only respond with graded postsynaptic potentials.

In OFF bipolar cells, the glutamate released by the photoreceptor is excitatory, opening ligand-gated ion channels that allow the influx of cations, depolarizing the bipolar cells. In other words, OFF bipolar cells depolarize in dark and hyperpolarize in light.

In ON bipolar cells, glutamate is inhibitory. This is due to the presence of G-protein coupled receptors for glutamate.
These receptors initiate inhibitory cascades that cause the ON bipolar cell to hyperpolarize in the dark and depolarize in light.

Although the photoreceptor will always depolarize in the dark, the response of the downstream bipolar cell depends on the type of cell, determined by the type of glutamate receptor present.

Figure 6. Photoreceptors always hyperpolarize in response to light, but ON and OFF bipolar cells have opposite responses. This is because of the different glutamate receptors present in each of the bipolar cell types. On and Off Ganglion Cells by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ganglion Cells

Finally, ON and OFF bipolar cells synapse on ON-center and
OFF-center ganglion cells, respectively. Ganglion cells are the only cell type to send information out of the retina, and they are also the only cell that fires action potentials. The ganglion cells fire in all lighting conditions, but it is the relative firing rate that encodes information about light.
Figure 7. Ganglion cells fire action potentials. ON-center ganglion cells increase their firing rate when a light stimulates their receptive field. OFF-center ganglion cells decrease their firing rate in the presence of light. ON vs OFF Ganglion Cells by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive Fields

Each bipolar and ganglion cell responds to light that hits in a
specific area of the retina. This region of retina is the cell’s receptive field. Receptive fields in the retina are circular.

Size of the receptive field can vary with small receptive fields toward the center of the retina (fovea) and larger receptive fields toward the periphery. The size depends on the number of photoreceptors that synapse on a given bipolar cell and the number of bipolar cells that synapse on a given ganglion cell.

![Receptive field](image)

Figure 7. Receptive field sizes can vary depending on location of the bipolar and ganglion cells. When the photoreceptors are near the fovea, the receptive fields are smaller due to fewer photoreceptors synapsing on a single bipolar cell. Back of Retina by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Although some of the images used here will simplify the receptive field to one cell in the center and a couple in the surround, it is important to remember that photoreceptors
cover the entire surface of the retina, and the receptive field is two-dimensional.

Figure 9. Receptive fields are composed of photoreceptors in two structures. Photoreceptors in the center of the receptive field synapse directly on one bipolar cell. A ring of photoreceptors create the surround of the receptive field and synapse indirectly on the bipolar cell via horizontal cells. Retinal Surface by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Let’s use an example of an ON bipolar cell to look at the structure of receptive fields in the retina. The bipolar cell receptive field is divided into two regions. The center of the receptive field is a result of direct innervation of the bipolar cell from the photoreceptors. If a light spot covers this center portion, the bipolar cell would respond as discussed above – light hits the photoreceptor, it hyperpolarizes, decreasing glutamate release. Less glutamate leads to less inhibition of the ON bipolar cell, and it depolarizes.
Figure 10. A light spot located in the center of a receptive field of an ON bipolar cell will cause the photoreceptor to hyperpolarize and the ON bipolar cell to depolarize. Light in Center by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

There is also a surround portion of the receptive field that has the opposite effect of the center. If a light spot covers this surround portion, the ON bipolar cell would respond by hyperpolarizing. This is because the light is hitting photoreceptors that are indirectly connected to the bipolar cell. Horizontal cells are responsible for the communication between the
photoreceptors and the bipolar cell, and they depolarize the center photoreceptor.

Figure 11. A light spot located in the surround of the receptive field for an ON bipolar cell will cause the surround photoreceptor to hyperpolarize, leading to the horizontal cell to also hyperpolarize. This response would cause the center photoreceptor to depolarize, leading to the ON bipolar cell to hyperpolarize. Light in Surround by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The OFF bipolar cells and both types of ganglion cells follow these same principles and have center-surround receptive fields.
Lateral Inhibition

Like the somatosensory system, the center-surround structure of the receptive field, which is a result of the horizontal cells, is critical for lateral inhibition to occur. Lateral inhibition is the ability of the sensory systems to enhance borders or edges of stimuli. In the retina, the photoreceptors that are in the surround of one bipolar cell would also be in the center of a different bipolar cell.
Figure 12. Receptive fields overlap across the retina. A photoreceptor located in the center of one receptive field may also be in the surround of adjacent receptive fields. Adjacent Photoreceptors by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

If light shines on photoreceptor 2, and no horizontal cells were present, then photoreceptor 2 and bipolar cell 4 would show responses, but cells 1 and 3 would not.
Figure 13. Without horizontal cells, a light spot in the surround (of receptive field of cell 3) does not alter the cellular response of that bipolar cell. Light in Surround No HC by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

However, when horizontal cells are added back into the system, then the horizontal cell can cause photoreceptor 1 to depolarize, which leads to bipolar cell 3 to hyperpolarize. Comparing these two scenarios, it is important to notice that the difference in membrane potential between the two bipolar cells is larger when horizontal cells are present. This will lead to a stronger difference in light perception between those two regions of the retina.
Figure 14. When horizontal cells are present, a light spot in the surround (of receptive field of cell 3) can result in a hyperpolarization of that bipolar cell. Light in Surround with HC by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Before learning the pathway that visual information takes from the retina to the cortex, it is necessary to understand how the retina views the full visual field. The full visual field includes everything we can see without moving our head.
Figure 1. The two eyes together can view the entire visual field, which is all the space we can see without moving our head. Full Visual Field by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The full visual field can be divided in a few ways. Each eye is capable of seeing a portion of, but not the entire, visual field.
The full visual field can also be divided into the right and left hemifields. The hemifields range from the most peripheral point to the center point, splitting the full visual field into two equal regions. Both eyes are involved in viewing each hemifield. The nasal retina of the left eye and the temporal retina of the right eye view the left hemifield. The nasal retina of the right eye and the temporal retina of the left eye view the right hemifield.
Figure 3. The full visual field can be divided into left and right hemifields. Both eyes contribute to viewing these regions. Visual Hemifields by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Finally, the full visual field can be separated into monocular regions, or the space that is viewed by only one eye, and binocular regions, or the space that is viewed by both eyes.
Pathway

Visual information from each eye leaves the retina via the ganglion cell axons, creating the optic nerve. Prior to entering the brain, axons from the nasal portion of each retina cross the midline at the optic chiasm. Since the axons from the nasal retina cross to the opposite side of the nervous system but the temporal retina axons do not, this leads to the brain processing input from the contralateral hemifield. Therefore, the right side of the brain receives visual information from the left hemifield and vice versa.
Figure 5. Information from each eye is carried from the retina by the optic nerve. Information perceived by neurons in the nasal retina crosses the midline at the optic chiasm. Information from each contralateral visual hemifield then travels to the brain. Pathway from Retina by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
The optic tract enters the brain and ascends to synapse in the lateral geniculate nucleus of the thalamus. From there, axons project out to the primary visual cortex, also called the striate cortex.

Figure 6. The optic tract enters the brain and ascends to the thalamus. Information is then sent to the primary visual cortex. CNS Pathway by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive Fields

As information moves from the retina to the cortex, receptive
fields become larger and more complex. Receptive fields in the thalamus continue to be circular in shape. However, once information reaches the primary visual cortex, these circular receptive fields combine to create receptive fields that are activated by lines.

Figure 7. Circular receptive fields located in the thalamus combine to form straight receptive fields of different orientation in the visual cortex. CNS Receptive Fields by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

These cortical neurons respond best to a line in a specific orientation. The firing rate will be highest when responding to the “preferred” orientation.
Figure 8. Neurons in the primary visual cortex show increased firing rates in response to a preferred line orientation. CNS Receptive Field Responses by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Processing After the Striate Cortex

Sensory system processing of input does not end upon reaching the primary sensory cortex. Information gets sent from these regions throughout the brain. The characteristics of sensory information becomes more complex as this post-primary sensory cortex processing occurs.

In the visual system, there are two broad streams of information that leave the striate cortex. Information that travels from the primary visual cortex down through the inferior temporal lobe is responsible for determining object recognition, or what an object is. Differentiating between an apple and a person occurs in this stream. Information that
travels from the striate cortex up through the parietal lobe is responsible for motion or spatial components of vision.

Figure 9. Information continues to be processed after reaching the primary visual cortex. The dorsal stream travels to the parietal cortex and is important for spatial components of vision. The ventral stream travels to the temporal lobe and is important for object recognition. Visual Streams by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Overview

Being able to sense chemicals in the environment through taste and olfaction can help an organism find food, avoid poisons, and attract mates. Humans can perceive five basic tastes: salty, sour, bitter, sweet, and umami. Bitter taste often indicates a dangerous substance like a poison, sweet taste often signifies a high energy food, and umami taste often indicates a high protein food.

Tongue Anatomy

The surface of the tongue is covered in small, visible bumps called papillae. Taste buds are located within the papillae, and each taste bud is made up of taste receptor cells, along with supporting cells and basal cells, which will eventually turn into taste receptors cells. The taste cells have a lifespan of approximately two weeks, and the basal cells replace dying taste cells. The taste cells have microvilli that open into the
taste pore where chemicals from the food can interact with receptors on the taste cells. Although taste cells are not technically neurons, they synapse on afferent axons that send taste perception information to the brain.

Figure 1. The visible bumps on the surface of the tongues are papillae that house taste buds. Taste buds are made up of taste cells and basal cells. Tongue Anatomy by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The entire tongue is capable of perceiving all five tastes, meaning there are taste receptors for each taste present across the surface. However, some regions of the tongue are still more sensitive to specific tastes over others. The tip of the tongue is most sensitive to sweet, salt, and umami tastes. The sides are most sensitive to sour, and the back of the tongue to bitter tastes.
Figure 2. Although all tastes can be perceived across the entire tongue, sensitivity levels vary for each taste. Taste Regions by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Taste Transduction

Salt

Salt taste is mediated by the presence of amelioride-sensitive sodium channels. These receptors are usually open, and when foods are ingested with high salt concentrations, sodium flows into the cell causing a depolarization. This change in membrane potential opens voltage-gated sodium and calcium channels. The increased calcium influx causes the release of serotonin-filled vesicles. The serotonin acts on the afferent taste axon causing depolarization and action potentials.
Sour

Foods taste sour because of their acidity, and when acids are present in water, they produce hydrogen ions (protons). The exact mechanism for sour taste transduction have yet to be worked out, but it is believed that protons enter the cell through an ion channel, and then block potassium channels. The decreased efflux of potassium, along with the presence of...
the protons, depolarizes the cell causing voltage-gated sodium and calcium channels to open. Like salt taste transduction, the intracellular calcium causes release of serotonin into the synapse.

Figure 4. When sour foods are ingested, the protons from the acid enter the cell, depolarizing it, leading to release of serotonin onto the afferent taste axon. Sour Taste by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

**Bitter**

Bitter, sweet, and umami compounds all activate taste receptor cells via G-protein coupled receptors. The receptors
are dimers, meaning two proteins working together. The bitter receptors consist of dimers from the T2R family of receptor proteins, of which there are over 25. Each taste cell can express most or all of the different receptor types, and the dimers can combine in different combinations. The many receptor types and dimer combinations allows for the detection of numerous different molecules, which is important when wanting to avoid dangerous substances like poisons and toxins.

Activation of the G-protein receptor uses a second messenger system to open ion channels, allowing the influx of sodium, and to release calcium from intracellular stores. These ion changes depolarize the cell and cause ATP-specific channels to open, allowing ATP to enter the synapse and act on the afferent taste axon.
Figure 5. Bitter foods activate G-protein receptors, which cause second messenger actions that open sodium ion channels and release calcium from intracellular stores, leading to eventual efflux of ATP into the synapse. Bitter Taste by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sweet

Sweet and umami receptors are comprised of dimers from the T1R family of receptor proteins. Sweet receptors are dimers of the T1R2 and T1R3 proteins. Both proteins need to be present and functioning for activation of a sweet taste cell. Like bitter cells, activation of the G-protein receptor uses a
second messenger system to increase the influx of sodium and to release calcium from intracellular stores. These ion changes depolarize the cell and cause ATP-specific channels to open, allowing ATP to enter the synapse and act on the afferent taste axon.

Figure 6. Sweet foods activate G-protein receptors, which cause second messenger actions that open sodium ion channels and release calcium from intracellular stores, leading to eventual efflux of ATP into the synapse. Sweet Taste by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Umami receptors are comprised of the T1R3 protein, like the sweet receptor, but it is paired with the T1R1 protein. Once the G-protein coupled receptor is activated, the transduction pathway is the same as bitter and sweet taste cells.

Figure 7. High protein foods activate G-protein receptors, which cause second messenger actions that open sodium ion channels and release calcium from intracellular stores, leading to eventual efflux of ATP into the synapse. Umami Taste by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Taste Receptor Coding

Of the five tastes, only two neurotransmitters are used to communicate information to the central nervous system, so how does our brain know what tastes to perceive? The answer is how the information is encoded. The majority of taste cells use a labeled line coding method, which means that each cell and the related afferent taste axon only responds to one type of taste. For example, bitter cells only express bitter receptors and are only activated by bitter molecules. These bitter taste cells activate bitter sensory neurons and bitter regions of the taste cortex. A small portion of taste cells do use population coding as well, meaning more than one tastant can activate the cell, and perception is based on a combination of multiple cells each with a different response. Most information, however, is encoded via labeled line at the level of the taste cell.
Figure 8. Labeled lined coding occurs when one sensation (in this case, a specific taste) leads to activation of the sensory cell. Most taste cells in the tongue use this type of coding. Population coding results from broader tuned activation where multiple sensations can activate a sensory cell. Taste Coding by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways
Type your key takeaways here.

- Taste cells express specific taste receptors and are located in taste buds within the papillae.
- Salt and sour taste cells rely on ion channels to depolarize the cell and release serotonin.
- Bitter, sweet, and umami taste cells rely on G-protein coupled receptors and second messengers that open ATP channels.
- At the level of the taste receptor cells, taste is perceived by using labeled line coding.
TASTE: CENTRAL PROCESSING

Throat Anatomy

Although taste receptor cells are most prevalent on the tongue, there are other regions of the mouth and throat, including the palate, pharynx, and epiglottis, that also play a role in taste perception. The olfactory system is tightly linked to our sense of taste as well, and information from both chemical sensory systems combine in the central nervous system to give us a full range of flavors.
Taste Pathway

The tongue is innervated by three cranial nerves. The front two-thirds of the tongue is innervated by cranial nerve VII. The back third is innervated by cranial nerve IX. Finally, the epiglottis and pharynx are innervated by cranial nerve X. All three cranial nerves enter the brainstem at the medulla and synapse in the nucleus of the solitary tract. From there, information is sent to the ventral posterior medial nucleus of the thalamus. Thalamic neurons send projections to the gustatory cortex. The gustatory cortex is located deep in the lateral fissure in a region called the insula. Information processing taste stays primarily on the ipsilateral side of the
nervous system. Projections within the brain also exist between the taste regions and the hypothalamus and amygdala.

Figure 2. Taste information from the tongue travels through cranial nerves VII, IX, and X to the nucleus of the solitary tract in the medulla. Neurons in the brainstem project to the ventral posterior medial nucleus of the thalamus and then on to the gustatory cortex. Taste Pathway by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Flavor

How do 5 basic tastes turn into the myriad complex taste sensations we experience when eating food? Olfaction plays an important role in the perception of flavor, as do vision and touch. Taste information combines with information from these other sensory systems in the orbitofrontal cortex located in the frontal lobe. This region is believed to be important for
the pleasant and rewarding aspects of food. Additionally, as taste is processed in higher-order regions of the CNS, information is combined using population coding mechanisms.

Key Takeaways

- Multiple regions in the mouth and throat play a role in processing of taste
- Three cranial nerves innervate the tongue and throat
- The cranial nerves synapse in the nucleus of the solitary tract in the medulla. Information then travels to the ventral posterior medial nucleus of the thalamus and then to the gustatory cortex
- To perceive complex flavors, information from other sensory systems is combined with taste information in the orbitofrontal cortex
SPINAL CONTROL OF MOVEMENT

Overview

The motor system controls all of our skeletal muscle movement. There are multiple levels of control. Within the spinal cord, simple reflexes can function without higher input from the brain. Slightly more complex spinal control occurs when central pattern generators function during repetitive movements like walking. The motor and premotor cortices in the brain are responsible for the planning and execution of voluntary movements. And finally, the basal ganglia and cerebellum help with coordination.

We will begin exploring the simplest level of control – spinal reflexes.
Alpha Motor Neurons

Muscle fibers are innovated by special neurons called alpha motor neurons. These neurons have their cell bodies in the central nervous system in the ventral horn of the spinal cord. Their axons travel via peripheral spinal nerves to the muscles.
Figure 2. Alpha motor neurons are located in the ventral horn of spinal cord. Alpha Motor Neuron Location by Casey Henley is licensed under a Creative Commons Attribution
One alpha motor neuron can innervate multiple fibers within one muscle; the fibers associated with one alpha motor neuron is called a motor unit. The group of motor neurons that are associated with all the fibers of one muscle is called a motor pool.

Figure 3. Motor neurons can innervate more than one muscle fiber within a muscle. The motor neuron and the fibers it innervates are a motor unit. All of the motor neurons associated with one muscle are called a motor pool. Motor Unit vs Pool by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Neuromuscular Junction

The neuromuscular junction is one of the largest synapses in the body and one of the most well-studied because of its peripheral location. Acetylcholine is the neurotransmitter released at the neuromuscular junction, and it acts upon ligand-gated, non-selective cation channels called nicotinic acetylcholine receptors. These channels allow the influx of sodium ions into the muscle cell. In a healthy system, an action potential in the motor neurons always causes an action potential in the muscle cell. The action potential leads to contraction of the muscle fiber. Acetylcholinesterase, an enzyme that breaks down acetylcholine and terminates its action, is present in the synaptic cleft of the neuromuscular junction.
Figure 4. The neuromuscular junction is the synapse between a motor neuron and a muscle fiber. Acetylcholine is released and acts on nicotinic acetylcholine receptors located in the postjunctional folds of the muscle fiber. Neurotransmitter action is terminated by breakdown by acetylcholinesterase. Neuromuscular Junction by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Organization

Like the sensory systems, the motor system is also organized in a topographic fashion. Within the spinal cord, alpha motor neurons that innervate the arms and legs are located in the lateral portion of the ventral horn, whereas alpha motor
neurons that innervate muscles in the trunk are located in the medial portion.

Figure 5. The ventral horn is organized in a topographic manner, with proximal muscles (like those in the trunk) located more medially than distal muscles (like the arms or legs). Additionally, motor neurons are organized by function with extensor motor neurons located together and flexor neurons located together. SC Topography by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sensation

Proprioception is the ability to know where your body is in space, and relies on the presence of sensory receptors located within the muscles. These specialized structures are called muscle spindles, and they monitor muscle fiber stretch. Information is relayed to the nervous system via Ia sensory axons, which are large, myelinated fibers.
Figure 6. Type Ia sensory fibers wrap around the fibers within the muscle spindle. When the muscle stretches, these sensory neurons are activated. Muscle Spindle by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Reflexes

Stretch (Myotatic) Reflex

The stretch reflex, also called the myotatic, patellar, or knee-jerk reflex, occurs in response to activation of the muscle spindle stretch receptors. The stretch reflex is a common
occurrence at a doctor’s visit when the doctors taps your knee with a little hammer. This usually results in the lower leg kicking up slightly. The synaptic communication for this reflex takes place completely within the spinal cord and requires no input from the brain.

The knee is tapped on the tendon that connects to the quadriceps muscle. The tendon extends enough to stretch the quadriceps muscle, activating the stretch receptors. Sensory information travels to the dorsal horn of the spinal cord where it synapses on alpha motor neurons that innervate the quadriceps. Activation of the motor neurons contracts the quadriceps, extending the lower leg. This is called monosynaptic communication because there is only one synapse between the sensory input and the motor output.
Figure 7. When the knee is tapped, the extensor muscle is stretched. This activated the sensory fibers (blue neuron) from the muscle spindles, which synapse on and activate motor neurons (yellow neuron) that constrict the extensor muscle. The stretch reflex is a monosynaptic reflex. Stretch Reflex Extensor by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The sensory neurons also synapse on interneurons within the spinal cord that are inhibitory. These inhibitory interneurons then synapse on alpha motor neurons that innervate the hamstring, the antagonistic muscle to the quadriceps. When these motor neurons are inhibited, the hamstring muscle
relaxes, allowing the contraction of the quadriceps to occur with more ease.

Figure 8. In addition to the monosynaptic extensor reflex, the sensory information from the muscle spindle (blue neuron) also activates inhibitory interneurons (black neuron) in the spinal cord. These interneurons then inhibit the motor neurons (orange neuron) that innervate the flexor muscle. Stretch Reflex Flexor by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Withdrawal (Flexor) Reflex

A similar process can be seen in the withdrawal reflex. In this case, instead of an extension, the muscles lead to muscle
flexion in response to a painful stimulus. If, for example, you step on something painful, the reflex will be to lift up the injured foot. The sensory information that initiates this reflex is activation of pain receptors, or nociceptors. Like with the stretch reflex, the sensory information enters the spinal cord at the dorsal horn. Unlike the stretch reflex, the withdrawal reflex is a polysynaptic reflex, meaning interneurons are present between the sensory neurons and the motor neurons. Excitatory interneurons communicate with the alpha motor neurons of the flexor muscle, whereas inhibitory interneurons communicate with the alpha motor neurons of the extensor muscle. The behavioral response is flexing of the leg upward (the opposite action of the stretch reflex).
Figure 9. Pain information is sent from the periphery to the spinal cord (blue neuron). The axons synapse on interneurons within the spinal cord. Excitatory interneurons (green neuron) activate motor neurons (orange neuron) that constrict the flexor muscle. Inhibitory interneurons (black neuron) inhibit the motor neurons, leading to relaxation of the flexor muscle (red neuron).
neuron) inhibit motor neurons (yellow neuron) that innervate the extensor muscle. The leg lifts in response. Withdrawal Reflex by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Crossed-Extensor Reflex

Running in parallel to the withdrawal reflex is the crossed-extensor reflex. If you step on something sharp and lift up that leg, your other leg needs to be able to support your weight shift, or you would fall down. This is accomplished by interneurons that cross the midline of the spinal cord and communicate with motor neurons on the contralateral side of the body. The painful sensory information that initiated the withdrawal reflex also initiates the crossed-extensor reflex. In addition to the ipsilateral interneurons seen above, the sensory axons also synapse on excitatory interneurons that cross the midline. These interneurons then synapse on excitatory interneurons that activate the alpha motor neurons of the extensor muscle and inhibitory interneurons that inhibit the alpha motor neurons of the flexor muscle (the opposite configuration to the withdrawal reflex). This leads to the leg extending, providing a stable base for the weight shift.
Figure 10. If the leg lifts due to the withdrawal reflex, the opposite leg must stabilize via contraction of extensor muscles to balance the body. This is accomplished by spinal interneurons that cross the midline and communicate the sensory information to the contralateral side of spinal cord.
Inhibitor interneurons cause relaxation of the flexor muscles and excitatory interneurons cause constriction of the extensor muscles. Crossed-Extensor Reflex by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Central Pattern Generators

Locomotion

Locomotion is one example of a basic, rhythmic movement that requires coordination of a number of muscle groups to work properly (other examples include swimming, flying, respiration, swallowing).

Activity of extensor and flexor muscles in both legs must be coordinated to allow smooth locomotion without falling. These rhythmical movements are controlled at the level of the
spinal cord by circuits called central pattern generators. The spinal cord has circuitry that, in the case of walking, moves the legs in opposite patterns. When one leg is lifting up to move forward, the other leg is stable, touching the ground.

Figure 12. While walking, there must be coordinated, reciprocal activation of the extensor and flexor muscles of each leg; as an extensor is contracted (gray bar) the flexor must relax. Additionally, the muscle activation of one leg must be the opposite of the other leg, so the right extensor and the left flexor are activated at the same time. Walking Cycle Muscle Activation by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Spinal Circuitry

The control of this system probably has multiple levels. Neurons themselves may have pacemaker properties that allow for a continuous cycle of depolarization and repolarization. These neurons are then located within multi-cell circuits involving a collection of excitatory and inhibitor interneurons that results in reciprocal inhibition of opposing muscles and opposing sides of the body.
Figure 13. Central pattern generators are likely controlled by interneuron circuitry in the spinal cord. The circuit would require the motor neurons on the opposite side of the spinal cord to be activated in a reciprocal fashion. CPG Circuit by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Although the spinal cord is able to control these movements on its own, there is input from both the brainstem and sensory neurons which can have an effect on modulating the pattern of neuronal activity in the spinal cord. So when an animal needs to slow down, speed up, or turn away from a danger, for example, those inputs can alter the spinal cord circuit.
Overview

There are a number of steps that must take place for voluntary movement to take place. Assessment of the surrounding environment and the body’s location in space, followed by determining what action is appropriate, and then initiating that action. We will first focus on the cortical regions involved in planning of voluntary movement.

After work, you sit down on the couch to watch one episode of your favorite show. As the end credits appear, you realize it is now time to head to your study space and start working on class. To do this, you need to leave the couch, grab your computer from the table, get your coffee from the kitchen and head to a different room. All of these voluntary movements take a great deal of processing by the brain. You must assess your surrounding environment and your body’s location in it, determine which actions must be completed,
and then actually initiate those actions. In this chapter we will focus on how the planning of voluntary movement occurs.

Cortical Anatomy

Much of the cortex is actually involved in the planning of voluntary movement. Sensory information, particularly the dorsal stream of the visual pathway and somatosensory are processed in the posterior parietal lobe. You are sitting on the couch, your laptop is over there, your coffee is on the kitchen counter, your dog is sleeping, and you’ll need to step over her – all of these pieces of information are critical to making the right motor decisions.
Connections from the post parietal lobe are then sent to both the premotor regions and the prefrontal cortex. The prefrontal cortex, which is located in the front of the brain in the frontal lobe, plays an important role in higher level cognitive functions like planning, critical thinking, and understanding the consequences of our behaviors. The premotor area and the supplemental motor area lie just anterior to the primary motor cortex. These regions help make decisions about which actions are necessary, like grabbing your computer, and which actions are not, like laying down and watching another show.
Role of Premotor Area

The premotor regions do send axons directly to lower motor neurons in the spinal cord using the same pathways as the motor cortex (see Execution of Movement chapter). However, the premotor cortex also plays an important role in the planning of movement. Two experimental designs have demonstrated this role. First, monkeys were trained to push a button when a light turned on. Prior to this light turning on, though, another trigger indicated which button out of four...
the monkey would eventually hit. So there were two triggers: the first indicated where the monkey would push and the second told the monkey to actually push it. When brain activity was measured during this study, neurons in the premotor cortex became active when the first light trigger turned on, well before any movement actually took place (Weinrich and Wise, 1928).
In another experiment, people were trained to move their fingers in a specific pattern. Cerebral blood flow was then
measured when they repeated the finger pattern and when they only imagined repeating the finger pattern. When the movement was only imagined and not actually executed, the premotor regions along with parts of the prefrontal cortex were activated (Roland, et al, 1980).

These studies show that the premotor cortex is active prior to the execution of movement, indicating that it plays an important role in the planning of movement. The posterior parietal, prefrontal, and premotor regions, though, also communicate with a subcortical region called the basal ganglia to fully construct the movement plan. The basal ganglia are covered in the next chapter.
Key Takeaways

- Sensory information is processed in the posterior parietal before being sent to motor regions of the brain
- The prefrontal cortex and premotor cortex are critical for creating a movement plan

References


Weinrich M, Wise SP. The premotor cortex of the monkey. J Neurosci. 1982 Sep;2(9):1329-45. doi:
Overview

The basal ganglia are a group of subcortical nuclei, meaning groups of neurons that lie below the cerebral cortex. The basal ganglia is comprised of the striatum, which consists of the caudate nucleus and the putamen, the globus pallidus, the subthalamic nucleus, and the substantia nigra. The basal ganglia are primarily associated with motor control, since motor disorders, such as Parkinson’s or Huntington’s diseases, stem from dysfunction of neurons within the basal ganglia. For voluntary motor behavior, the basal ganglia are involved in the initiation or suppression of behavior and can regulate movement through modulating activity in the thalamus and cortex. In addition to motor control, the basal ganglia also communicate with non-motor regions of the cerebral cortex and play a role in other behaviors such as emotional and cognitive processing.
Basal Ganglia Input

The majority of information processed by the basal ganglia enters through the striatum. The principal source of input to the basal ganglia is from the cerebral cortex. This input is glutamatergic and therefore, excitatory. The substantia nigra is also a region with critical projections to the striatum and is the main source of dopaminergic input. Dopamine plays an important role in basal ganglia function. Parkinson’s disease results when dopamine neurons in the substantia nigra degenerate and no longer send appropriate inputs to the striatum. Dopamine projections can have either excitatory or inhibitory effects in the striatum, depending on the type of metabotropic dopamine receptor the striatal neuron
expresses. Dopamine action at a neuron that expresses the D1 receptor is excitatory. Dopamine action at a neuron that expresses the D2 receptor is inhibitory.

Figure 2. Inputs to the basal ganglia enter through the striatum. Cortical projections (shown in green) release glutamate and are excitatory. Substantia nigra projections (shown in blue) release dopamine and can be either excitatory or inhibitory. Basal Ganglia Input by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

**Basal Ganglia Output**

The primary output region of the basal ganglia is the internal
segment of the globus pallidus. This region sends inhibitory GABAergic projections to nuclei in the thalamus. This inhibitory output has a tonic, constant firing rate, which allows the basal ganglia output to both increase and decrease depending on the situation. The thalamus then projects back out to the cerebral cortex.

Figure 3. Output from the basal ganglia leaves through the internal segment of the globus pallidus. Inhibitory projections (shown in red) release GABA onto the thalamus. Excitatory thalamic projections (shown in green) communicate with the cerebral cortex. Basal Ganglia Output by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Direct Pathway

There are multiple connections within the basal ganglia as well. For motor control, there are two main circuits: the direct pathway and the indirect pathway. These circuits have opposing actions when activated by cortical neurons that release glutamate. The circuits are also modulated by dopamine release by the substantia nigra into the striatum. In the case of dopamine, unlike glutamate, the direct pathway is activated, and the indirect pathway is inhibited. It is believed that the different control mechanisms allow a finely tuned balance between the direct and indirect circuits, which allows for refined control of movement.

The direct pathway is initiated by either excitatory cortical input and/or dopamine release from the substantia nigra. The neurons in the striatum involved in the direct pathway express the D1 metabotropic dopamine receptor. The activation of this receptor is excitatory. Therefore, projections from both the cortex and the substantia nigra activate the neurons in the striatum. Those neurons are inhibitory and release GABA onto the internal segment of the globus pallidus (GPi).
Activation of the Direct Pathway

As describe above, the neurons in the GPi are inhibitory, releasing GABA onto the thalamus. Activation of the GABA-ergic striatum neurons inhibit the neurons in the GPi, releasing the inhibition on the thalamus. Inhibition of an inhibitory region is called disinhibition. Therefore, the activation of the direct pathway results in increased output from the thalamus.
The indirect pathway is a little more complex. The indirect pathway is either activated by excitatory cortical input or inhibited by dopamine release from the substantia nigra. The neurons in the striatum involved in the direct pathway express the D2 metabotropic dopamine receptor. The activation of this receptor is inhibitory.

Inhibitory neurons in the striatum involved in the indirect pathway project to the external segment of the globus pallidus (GPe). GABA-ergic neurons in the GPe project to the...
subthalamic nucleus, which then sends excitatory output to the GPi.

Figure 6. The indirect pathway in the basal ganglia consists of excitatory input from the cortex or inhibitor input from the substantia nigra. The striatal neurons project to the external segment of the globus pallidus (GPe). The GPe sends inhibitory output to the subthalamic nucleus, which had excitatory projections to the GPi. Indirect Pathway Circuit by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

**Activation of the Indirect Pathway**

If the indirect pathway is activated by cortical input, the inhibitory striatal neurons are excited. This leads to inhibition of the GPe neurons, resulting in disinhibition of the excitatory neurons in the subthalamic nucleus. This
excitatory output to the Gpi increases inhibition of the thalamus, leading to decreased thalamic output to the cortex.

Figure 7. Activation of the indirect pathway leads to increased inhibitory output to the GPe. The inhibition on the GPe leads to less inhibitory input to the subthalamic nucleus, causing increased excitatory output from the subthalamic nucleus to the Gpi. Activation of the Gpi inhibits the thalamus, resulting in decreased output from the thalamus to the cortex. Indirect Pathway Activation by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Inhibition of the Indirect Pathway

If the indirect pathway is inhibited by dopamine projections from the substantia nigra, the inhibitory striatal neurons are inhibited. This leads to excitation of the GPe neurons, resulting in inhibition of the excitatory neurons in the subthalamic nucleus. This decreased excitatory output to the
Gpi decreases inhibition of the thalamus, leading to increased thalamic output to the cortex.

Figure 8. Inhibition of the indirect pathway leads to decreased inhibitory output to the GPe. The disinhibition on the GPe leads to more inhibitory input to the subthalamic nucleus, causing decreased excitatory output from the subthalamic nucleus to the Gpi. Lower activation of the Gpi decreased the inhibition on the thalamus, resulting in increased output from the thalamus to the cortex. Indirect Pathway Inhibition by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Loops through the Basal Ganglia

There are multiple circuits that pass through the basal ganglia:

1. The **motor** circuit, described above
2. The **oculomotor** circuit, which plays a role in eye movement
3. The **associative** circuit, which plays a role in executive functions like behavioral inhibition (preventing impulsive behaviors) planning and problem solving, and mediating socially appropriate behaviors

4. The **limbic** or emotional circuit, which plays a role in the processing of emotion and reward.

Although the circuits each incorporate different regions of the basal ganglia, the general loop is the same: cortical input to the striatum leads to internal processing within the basal ganglia structures. Basal ganglia output projects from the pallidum to the thalamus, which then inputs back to the cortex. It is important to recognize that the basal ganglia plays an important role in a number of functions. For example, medications that are used to treat Parkinson’s can sometimes lead to the presentation of impulse control disorders, a result of dopaminergic changes in the limbic loop through the basal ganglia.

**Key Takeaways**

- The subcortical basal ganglia nuclei receive information from the cortex and send output
to the thalamus

- Motor control through the basal ganglia occurs through both the direct and indirect pathways
- Disinhibition is when an inhibitory region is itself inhibited
- The basal ganglia are best known for their role in motor control but are also critical for emotion and behavioral inhibition
EXECUTION OF MOVEMENT

Motor cortex

The primary motor cortex lies just anterior to the primary somatosensory cortex in the precentral gyrus located in the frontal lobe.
Figure 1. The primary motor cortex is located in the frontal lobe in the precentral gyrus, which is just anterior to the central sulcus. Primary Motor Cortex by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Like the somatosensory cortex, the motor cortex is organized by a somatotopic map. However, the motor cortex does not map onto the body in such an exact way as does the somatosensory system. It is believed that upper motor neurons in the motor cortex control multiple lower motor neurons in the spinal cord that innervate multiple muscles. This results in activation of an upper motor neuron causing excitation or inhibition in different neurons at once, indicating that the primary motor cortex is responsible for movements and not simply activation of one muscle.
Stimulation of motor neurons in monkeys can lead to complex motions like bringing the hand to the mouth or moving into a defensive position (Graziano et al, 2005).

Figure 2. The map of the body that exists on the motor cortex is less specific than the somatosensory map because cortical neurons control multiple muscles at the same time. Motor Map by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Population coding

The motor cortex controls movement by using population coding mechanisms. Upper motor neurons are broadly tuned to a certain movement in a certain direction, meaning firing rate is highest when moving in one direction, but firing also occurs in when moving in nearby directions. For example, when a monkey is trained to move its hand toward the left in
response to a cue neurons “tuned” toward left movement will be active right before and during the movement. Neurons tuned to other directions will also be active, though. (Georgopoulos, et al, 1982)

This means that the firing rate of one specific neuron does not give enough information to know direction of movement. It’s the combined firing rates of an entire population of neurons that indicates direction.

![Figure 3. Motor movement is coded in the primary motor cortex. Information from one neuron is not enough to determine the direction of movement; a population of neurons must be used. Based on Georgopoulos, et al, 1982. Population Coding by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.](image)

**Descending Spinal Tracts**

There are multiple descending tracts within the spinal cord that send information from the brain to the motor neurons in the ventral horn. The lateral tracts are responsible for carrying
information about voluntary movement of the arms and legs. The ventromedial pathways are responsible for carrying information about posture and balance.

Figure 4. The descending motor tracts travel from the brain through the white matter in the spinal cord. Descending Spinal Tracts by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Lateral Tracts

Corticospinal Tract

The largest of the lateral pathways is the corticospinal tract. This pathway sends information directly from the motor and premotor cortices down to the motor neurons in the spinal cord. Cortical axons travel through the brainstem and then cross the midline at the base of the medulla. So like the somatosensory system, the right side of the cortex processes information for the left side of the body and vice versa. In the
spinal cord, the axons travel through the lateral column and synapse in the ventral horn on motor neurons that typically innervate distal muscle.

Figure 5. Motor information to the arms and legs travels from the primary motor cortex through the medulla where it decussates. The axons continue traveling through the lateral corticospinal tract and synapse on an alpha motor neuron in the ventral horn of the spinal cord. Motor pathway by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Corticobulbar Tract

Another lateral tract is the corticobulbar pathway which sends motor information to cranial nerves. This path travels
ipsilateral from the cortex through the pons and medulla where it branches off at the appropriate cranial nerve level and then innervates cranial nerve neurons bilaterally.

Figure 6. Motor information to the face travels from the primary motor cortex to the pons and medulla where it branches to synapse on cranial nerve nuclei on both sides of the brainstem.

Ventromedial Tracts

There are four ventromedial pathways that travel in the spinal cord as well and send indirect input from motor cortex.

- The vestibulospinal tract is important for head balance as we move. This tract begins in the vestibular nucleus.
- The tectospinal tract is responsible for moving the head in response to visual stimuli. This tract begins in the
superior colliculus.

- The two reticulospinal tracts play a role in managing anti-gravity reflexes needed for posture and standing. These tracts begin in the reticular formation.

Key Takeaways

- The motor cortex is located in the frontal lobe
- The motor map is not as detailed as the somatosensory homunculus
- The motor cortex uses population coding to encode direction of movement
- The lateral tracts carry information about voluntary movement of the arms and legs
- The ventromedial pathways carry information about posture and balance

References
PART V
STRESS
It is likely every reader of this chapter has experienced some form of stress, perhaps due to a big exam, a looming deadline, or an unplanned interaction with a spider.
Types of stress

Stress is often split into two categories: physical and psychological. Physical stress can be caused by trauma, illness, or injury. Blood loss, dehydration or allergic reactions are examples of physical stressors. Psychological stress has an emotional and mental component. Fear, anxiety, and grief are examples of psychological stress. The neural circuits involved in responding to the different stressors are overlapping but separate.

Stress response systems

The body has two main systems for responding to stress: the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. The autonomic nervous system response occurs very quickly because it is synaptic in nature and is responsible for the “fight or flight” response by stimulating heart rate and breathing and inhibiting digestion. The HPA axis is a hormonal response, so it is a slower response. Its downstream effects also promote energy use.
Neural Control

Hypothalamus

The hypothalamus plays a critical role in stress, activating both the autonomic and hormonal responses. The hypothalamus is a region right above the brainstem on either side of the 3rd ventricle. The hypothalamus plays an important role in managing hormone release in the body and in maintaining homeostasis. So this small structure is critical for everything from hunger, to sleep, to reproduction, to stress.

View the hypothalamus in the BrainFacts.org 3D Brain

Figure 2. The hypothalamus is located adjacent to the third ventricle shown in orange in a coronal view. Hypothalamus Coronal View by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
The hypothalamus is influenced by activity in other regions of the brain. The amygdala is located medially in the temporal lobe. The amygdala, which means “almond” in Latin, due to its shape, plays a critical role in the processing of emotions and consolidating emotional memories. It is especially active during fear learning and is important in evaluating the salience, or importance, of a situation. For instance, when we look at frightened faces, our amygdala is more activated than when we see neutral faces. Conditions such as anxiety, depression, and post-traumatic stress disorder are all linked to amygdala dysfunction. The amygdala communicates with the hypothalamus, sending information from higher cortical regions that process sensory information to the hypothalamus. The amygdala has an excitatory influence on the hypothalamus, so increased amygdala activity leads to an increased stress response.

View the amygdala in the BrainFacts.org 3D Brain
Figure 3. The amygdala is located in the deep in the anterior portion of the temporal lobe shown in yellow in a coronal view. Amygdala by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Hippocampus

Just posterior to the amygdala lies the hippocampus. The hippocampus, which means “seahorse” due to the similarity between its shape and the animal, is important in the long-term consolidation of memories, spatial navigation, and associating contextual cues with events and memories. Like the amygdala, the hippocampus communicates with the hypothalamus, but the hippocampus has an inhibitory control over the stress response.

View the hippocampus in the BrainFacts.org 3D Brain
Figure 4. The hippocampus is located in the deep in the temporal lobe shown in purple in a coronal view. Hippocampus by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Prefrontal Cortex

Finally, the prefrontal cortex, which is located in the front of the brain in the frontal lobe, plays an important role in higher level cognitive functions like planning, critical thinking, and understanding the consequences of our behaviors. The prefrontal cortex is one of the last brain regions to fully develop and may not be fully developed until an individual reaches their mid-20s. Experts think this might explain why teens are more likely than adults to participate in risky behaviors. The prefrontal cortex is also associated with the inhibition of impulsive behaviors and like the hippocampus, has inhibitory control over the hippocampus and the stress response.
Figure 5. The prefrontal cortex is located in the anterior portion of the frontal lobe. Prefrontal Cortex by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
HPA AXIS

Overview

When presented with a stressor, our brain activates the hypothalamic-pituitary-adrenal (HPA) axis, which initiates a hormonal response.

Hypothalamus

The hypothalamus, which sits below the thalamus, integrates information from many regions of the central nervous system and plays a critical role in the maintaining homeostasis in the body. The hypothalamus regulates temperature, hunger, thirst, blood volume and pressure, sleep and wakefulness, reproductive functions, and stress and fear responses. Many of these functions are managed via control of hormone release by the pituitary gland.

View the hypothalamus in the BrainFacts.org 3D Brain
Pituitary

The pituitary gland is located right below the hypothalamus. The pituitary is divided into two lobes, the anterior and the posterior pituitary. These regions are responsible for the release of different hormones and are controlled by the hypothalamus in different ways.

View the pituitary in the BrainFacts.org 3D Brain
Hormone Release

The stress response relies on anterior pituitary function. Neurons in the hypothalamus release a hormone called corticotropin-releasing hormone (CRH) into a specialized capillary system that lies between the hypothalamus and the pituitary. When this hormone reaches the pituitary gland, it causes the endocrine cells of the pituitary to start releasing
adrenocorticotropic hormone (ACTH) into the general circulation.

Figure 3. In response to stress, the hypothalamus releases corticotropin-releasing hormone (CRH) causing the pituitary to release adrenocorticotropic hormone (ACTH). CRH and ACTH Release by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The ACHTH travels to the adrenal cortex, located on top of the kidney. The adrenal cortex releases cortisol, a glucocorticoid hormone, into the blood stream. Cortisol travels throughout the body and has many effects that prepare our body for either fleeing or fighting the stressor. Promotion of energy use (for a quick escape or for defense) occurs through the release of glucose, the sugar the body uses for
energy. Additionally, systems not needed for fight or flight, like the immune system and gastrointestinal system, are inhibited.

The adrenal glands release cortisol into the bloodstream in response to activation by ACTH. HPA Axis by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Negative Feedback

Once the stress response has been initiated, and cortisol enters the circulation, the hormone itself is able to act on the hypothalamus and pituitary and tell them to stop producing CRH and ACTH. This is called a negative feedback loop.
The decreased neurohormone release will eventually stop the production of cortisol.

Figure 5. Cortisol released by the adrenal cortex inhibits the release of CRH and ACTH from the hypothalamus and pituitary, respectively, via a negative feedback loop mediated by glucocorticoid receptor activation. Cortisol Feedback by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Negative feedback is possible because neurons in the hypothalamus and pituitary express glucocorticoid receptors that are activated by cortisol. Cortisol is a steroid and is able to cross the phospholipid bilayer. Glucocorticoid receptors are located in the cytoplasm of the cell. The receptors dimerize after cortisol binds, and the dimer moves to the nucleus where
it can alter DNA transcription, inhibiting the production and release of the CRH and ACTH.

Animation 1. Cortisol can cross the phospholipid bilayer and bind to glucocorticoid receptors. The receptor dimerize, move to the nucleus, and interact with DNA, preventing the transcription of the hormones CRH and ACTH. Cortisol Action by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chronic Stress

While this cortisol response to stress is particularly important in certain situations, like moments of danger, chronic stress is an unhealthy scenario which can put people at risk for heart disease and other illnesses. Chronic stress can cause structural and functional changes within the cortical regions that play a role in control of the HPA axis due to long-lasting exposure
to cortisol. Cell loss or damage within the hippocampus and prefrontal cortex lead to decreased inhibitory control over the hypothalamus whereas dendritic growth within the amygdala lead to increased excitatory control.
SEXUAL DIFFERENTIATION

Overview

Sexual differentiation is the process by which a person develops into either a male or a female. For the purpose of this chapter, the content will be based on a male / female binary to introduce the basic concepts of reproductive development. However, it is important to recognize that in real life, chromosomal sex, physical sex, and gender exist on a continuum and cannot always be simplified into a two-structure system.

During development, the body and the brain undergo either A) feminization and de-masculinization or B) masculinization and de-feminization. In most cases, the differentiated brain will lead to behaviors that correspond appropriately to the differentiated gonads.
Figure 1. In most cases, human females have feminized and desmasculinized brains and bodies whereas human males have masculinized and defeminized brains and bodies. Gender Icons by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chromosomal Sex

In humans, DNA is organized into 46 chromosomes. One set of 23 chromosomes comes from the mother and the other set comes from the father. Twenty-two pairs are called autosomal chromosomes. These chromosome are similar in length and have the same genes present at the same location regardless of if they are received from the mother or father. However, for all genes, the allele present for each gene may be different from each parent. The last pair of chromosomes is responsible for determining if an individual becomes a male or female; these are called the sex chromosomes. In humans the sex chromosomes are named either X or Y.
Figure 2. Humans have 23 pairs of chromosomes, making 46 total. 22 pairs are called autosomal and have similar structure from each parent. The final pair are the sex chromosomes and determine if the individual is a male or female. Chromosomes by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Fertilization occurs when a sperm cell from the father fuses with an egg cell from the mother. All egg cells contain X sex chromosomes. Sperm cells contain either X or Y, which means chromosomal sex in humans is determined by the sperm. If an X sperm fertilizes an egg, the resulting fetus will be XX and a female, whereas if a Y sperm fertilizes an egg, the resulting fetus will be XY and a male.
On the Y chromosome is a gene called the sex-determining region (SRY) of the Y chromosome. The SRY gene is required for masculinization of the embryonic gonads. The SRY gene encodes for a protein called the testis-determining factor (TDF), which causes the embryonic gonads to differentiate into the testes. The testes then begin secreting both testosterone and a hormone called the Müllerian inhibiting substance (MIS). Testosterone causes Wolffian ducts to develop into the vas deferens, seminal vesicles, and epididymis. MIS causes the Müllerian ducts to degenerate.
Figure 4. The undifferentiated gonadal system is the same for both sexes until the SRY gene is activated during development. In the presence of the SRY gene, the male reproductive system develops. The gonads become the testes, the Wolffian ducts become the vas deferens, seminal vesicles, and epididymis, and the Müllerian ducts degenerate. Male Gonad Differentiation by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In females, when the SRY gene and secreted hormones are not present, the gonads differentiate into the ovaries, the Müllerian ducts develop into the fallopian tubes, uterus, and vagina, and the Wolffian ducts degenerate.
Figure 5. The undifferentiated gonadal system is the same for both sexes. If no hormones are present during the 6th to 12th week of gestation, the female reproductive system develops. The gonads become the ovaries, the Müllerian ducts become the fallopian tubes, uterus, and vagina, and the Wolffian ducts degenerate. Female Gonad Differentiation by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Hormones During Development

In addition to differentiating the reproductive duct system, the presence or absence of gonadal hormones during development also differentiates the rest of the body, including the brain. Testosterone will cause the brain, body, and behavior of the individual to be masculinized and defeminized. The quiescent ovaries do not release hormones which causes the brain, body, and behavior of the individual to be feminized and demasculinized.
Figure 6. Testosterone presence during development masculinizes and defeminizes the brain, body, and behavior. No hormone exposure during development feminizes and demasculinizes the brain, body, and behavior. Developmental Hormones by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

These hormonal effects of secreted testosterone on the brain must take place during a specific time in development, called a critical period. This early role of testosterone is called an organizational effect and results in a permanent change in the nervous system and therefore behavior. Organizational effects of hormones lead to major, generally irreversible, aspects of cell and tissue differentiation. Organizational effects take place during critical periods like prenatal development and puberty.

In adulthood, the same hormones trigger physiological or behavioral responses like inducing reproductive behavior or ovulation, but these influences, called activational effects, are reversible and short-lived. Removal of the activating hormone will cause the behavior to stop, but replacement later will cause the response to begin again because the brain has previously been organized to produce those behaviors when hormones are present.
Figure 7. Hormones can have long-lasting, organizational effects when present during critical periods such as during the prenatal period or puberty. During these critical periods, hormones will alter the structure of the nervous system, setting up cells and circuits needed to display sex-typical behaviors later in life. Those sex-typical behaviors are then activated in adulthood by the presence of gonadal hormones. Organizational versus Activational by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The role of activational hormones can be demonstrated by adult castration in male rats. Healthy males with intact testes will show sexual behavior when placed with a female rat. Castration, the removal of the testes, will cause males to stop showing sexual behavior because the activating hormone, testosterone, is no longer present. However, if the castrated males receive testosterone replacement, they will resume showing sexual behavior.
Figure 8. Removing testosterone by castrating an adult male rat will decrease the amount of sexual behavior displayed because the hormone can no longer activate those behaviors (solid orange and dotted blue lines). However, when the castrated animal is treated with testosterone, sexual behavior returns (solid orange line). Castration Effects by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
Steroid hormones like testosterone and estradiol are able to pass through the phospholipid membrane of a neuron. Some neurons express receptors for these hormones. Androgen receptors bind androgens like testosterone while estrogen receptors bind estrogens like estradiol. When a hormone binds to a receptor in the neuron, the hormone-receptor complex dimerizes and moves into the nucleus where it can bind to specific sites on the DNA and act as a transcription factor to turn on or off certain genes.

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Animation 1. Steroid hormones can cross the membrane without assistance. In the cell, they can bind to hormone
receptors, which dimerize, move to the nucleus, and act as transcription factors on the DNA. Steroid Hormone Action by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

When the testes secrete testosterone during the prenatal critical period, the effect is to masculinize and defeminize the brain, body, and behavior, and this is accomplished through the transcription of a specific set of genes. However, those genes are not always transcribed by the action of androgen receptors. When testosterone enters the cell, it does not always bind to androgen receptors. Some neurons also express proteins that can break testosterone down into its metabolites. 5-alpha reductase converts testosterone into dihydrotestosterone, or DHT, another androgen that is able to bind the androgen receptor. And aromatase can convert testosterone into estradiol, an estrogen that can bind to the estrogen receptor.

In some mammals, like rodents, this conversion of testosterone to estradiol is the main process by which neurons and the brain are masculinized. The estrogen receptors cause the transcription of masculinizing genes. Therefore, somewhat surprisingly, even though estrogen is typically thought of as a female hormone, its actions during development are responsible for much of the masculinization that occurs in the brain in some animals. It should be noted,
though, that estrogen does not appear to have these same masculinizing effects during human development.

Animation 2. After testosterone enters the cell, if it does not bind to an androgen receptor, it can be metabolized by enzymes in the cell. 5-alpha reductase converts testosterone into dihydrotestosterone. Aromatase converts testosterone into estradiol. Both DHT and estradiol can bind to receptors. During developmental critical periods, the aromatization of testosterone to estradiol activated estrogen receptors which leads to the transcription of masculinizing genes. Aromatizaion by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.
This is where you can add appendices or other back matter.