Introduction to Neuroscience

INTRODUCTION TO NEUROSCIENCE

Open Edition

VALERIE HEDGES

Michigan State University Libraries
East Lansing

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IMAGE CREDITS

Cover Image

Cover design provided by Valerie Hedges.

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INTRODUCTION

Valerie Hedges

Introduction to Neuroscience is designed for undergraduate students enrolled in a typical 2-semester sequence of introductory neuroscience courses. This book specifically targets students enrolled in Introduction to Neuroscience 1 and Introduction to Neuroscience 2 at Michigan State University and primarily contains topics covered in those courses.

This book will guide students through concepts, such as: the structure and function of nervous system cells and nervous system structures; the different sensory systems; motor systems; motivation and reward; stress; sex and the brain; emotions; nervous system disorders; learning; and memory.

This text has been remixed and revised from two different open educational resources aimed at undergraduate neuroscience students:

Foundations of Neuroscience by Casey Henley, Michigan State University

The Open Neuroscience Initiative by Austin Lim, DePaul University

In addition, new original content has been added to supplement what was provided in the above texts. The text includes many images and animations throughout and will be divided into shorter chapters that focus on a single topic. As this text is meant for undergraduate students, the writing is aimed at students that have not taken a neuroscience course before. Neuroscience terminology will be defined throughout the text through the use of the embedded Glossary terms to help with ease of reading. Each chapter will end with an interactive quiz for student self-evaluation of the content.

Find errors or have suggestions? Please email hedgesva@msu.edu

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PART I

INTRODUCTION TO NEUROSCIENCE

1.

WHAT IS NEUROSCIENCE?

What is Neuroscience?

Neuroscience is the study of the nervous system, the collection of nerve cells that interpret all sorts of information which allows the body to coordinate activity in response to the environment.

The study of neuroscience has taught us that the brain is a complicated organ with several connection routes, both between different bodily organs and within itself. Some of those connections communicate information down towards the body, such as signals that allow us to control the movements of our muscles or to change the activity of our internal organs. Other connections ascend into the brain, conveying all sorts of information from the world around us into a representation of our surroundings. Still, other routes communicate between brain areas, such as when the sudden detection of a threat passes through our visual system and turns into a "get ready" signal that then prepares the rest of our body for conflict. Because of this complex system of communication, the nervous system can be thought of as a series of highways and roads that connect different cities (organs).

Resources

- Scientist links to learn more
- Glossary Terms
- Key Takeaways
- Test Yourself

The nervous system conveys all of these different types of information using a combination of electrical and chemical signals. The main active cellular units of the nervous system, the **neurons**, are highly sensitive to changes in their environment. A wide variety of chemicals called **neurotransmitters** are responsible for passing information between neurons.

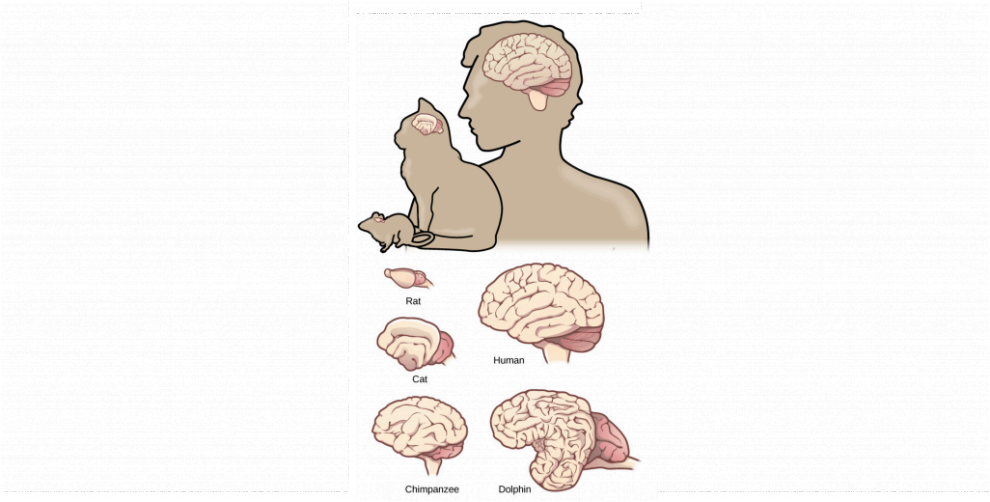

Figure 1.1. Brain size comparison between different vertebrate mammals. Brain images are shown for a rat, cat, chimpanzee, human, and dolphin. There are similarities in the layout of the structure of the brain across all species.

Neuroscience is an integrative field of study

Realistically, our modern understanding of "neuroscience" is a combination of several academic disciplines, all using their strengths to understand some aspect of the nervous system. Because of this integrative nature, it is possible to study neuroscience from many different perspectives, each of them more fitting for answering different types of questions. These "angles" of analysis are described below.

Biology

At the root of the study is biology. Whenever you are studying living processes, such as learning, visual perception, or consciousness, you dip into the realm of biology. The broad field of biology can be subdivided into smaller, more precise categories. Molecular neurobiologists study proteins and gene regulation, cellular neurobiologists examine how networks of neurons communicate with one another, and cognitive neuroscientists study the underlying causes of behaviors. Understanding neuroscience involves genetics, such as the autosomal dominant neurodegenerative condition Huntington's disease. Other biological sub-disciplines, such as ecology and evolution, are also considered in neuroscience as well, such as the parasite Toxoplasma, which changes an animal's response to fearful stimuli, allowing the organism to reproduce as it moves through different species in the food web.

Psychology

Psychology provided the earliest explanations about the brain and ideas about the origin of the mind. Some questions in this field branched off from philosophy as people began thinking about the "mind–body problem", the discussion that centered around the question of whether a function as complex as consciousness could result from the activity of a clump of cells. Psychologists also wondered whether parts of the brain in isolation have different properties than when those parts are working together. This property, called emergence, is the idea that the whole is greater than the sum of its parts. Psychologists examine neuroscience from a top-down view, aiming questions at understanding the whole organism before looking at smaller components of the organism (compare this with biological approaches, often a bottom-up view that starts at the level of cells or molecules).

Chemistry

Chemistry is a strong influencer of nervous system function—just ask anyone who forgot their morning cup of coffee! We use a variety of endogenous (originating from within the body) chemicals that act as signaling molecules, allowing communication between cells. These chemicals exist in many different structures, which determine their function; some are acidic while others are basic, some are polar, others are fat-soluble, and some are even gases. The nervous system is also highly sensitive to influence by exogenous chemicals (meaning they originate from outside the body), such as caffeine and cocaine.

Physics

Many principles of physics can be observed through the functioning of neurons. For example, neurons maintain a negative electrical charge, usually measured on the scale of tens of millivolts (a millivolt is a thousandth of a volt.) The main way for neurons to send signals depends on a temporary change in this voltage; this signal is called an **action potential**. This change in voltage is brought on by the movement of charged ions across the cell membrane, and they closely follow the rules of magnetism: opposite charges attract while like charges repel.

Mathematical Modeling

The field of computational neuroscience has grown from the use of mathematical modeling to describe or predict some aspect of the nervous system. If our current estimates are correct, we have around 86 billion neurons in the brain, a number so large that it is difficult to

conceptualize. It would be nearly impossible to understand that many components of a system without taking advantage of the sheer mathematical strength of a computer.

Healthcare Providers

Healthcare providers, like neurologists and psychiatrists, work from a different angle. They coordinate closely with researchers to apply scientific knowledge from the field or laboratory to treat patients, thus using biological principles as therapies. For example, neurologist Dr. Oliver Sacks used his knowledge of the dopamine neurotransmitter system to treat patients with a paralysis-like condition in the 1960s, leading to the development of levadopa treatment for **Parkinson's disease**. Other healthcare providers use imaging strategies like a CT scan to assess the extent of a head injury or the location of a brain tumor, while an **EEG** can be helpful for the diagnosis of **epilepsy**.

Engineers

Engineers help develop the tools needed to understand questions in neuroscience, such as the patch clamp rig or electron microscope, highly specialized pieces of lab equipment. They also work closely with healthcare providers to translate science into therapy, such as the deep brain stimulator devices for the treatment of conditions such as **Parkinson's disease**. Collectively, all the people who participate in neuroscience in some way are united by their interest in the workings of the body. Because of the overwhelming complexity of the nervous system, there are many questions still unanswered. The continual appearance of new questions in neuroscience keeps us wondering, inspires curiosity, and promises a multitude of fascinating career paths for centuries to come.

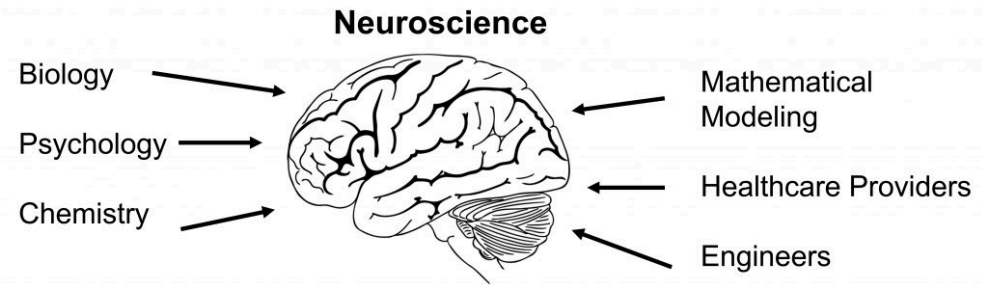

Figure 1.2 Areas of study that contribute to the field of Neuroscience. Many fields contribute to our understanding of modern neuroscience including biology, psychology, chemistry, mathematical modeling, healthcare providers, and engineers.

How do we learn about neuroscience?

Experimental design

The gold standard in science is the use of **experimental design**. In an experiment, the scientist uses a stepwise process of developing a research question and hypothesis, then answering that question by performing tests. The main goal of an experiment is to establish a causal relationship between one factor that is being changed, the independent variable, and the factor that is influenced, the dependent variable. A well-designed experiment has variables that are carefully controlled, which minimizes the influence of extraneous variables, often called confounding variables. The influence of confounding variables can be eliminated by comparing the experimental group with a control group, a group that is as similar as possible in every way except for the manipulation of the independent variable. Importantly, subjects or patients are generally assigned to the experimental or control group at random.

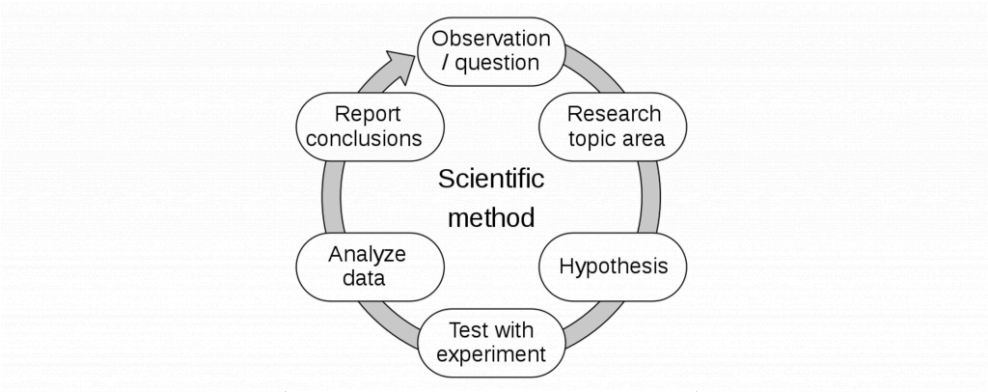

Figure 1.3 The Scientific Method. The Scientific Method starts with the development of a research question or observation that will lead to a research topic area and hypothesis. The hypothesis is tested through experimentation and analysis. The results of the experiment are then communicated via a report, which can further support additional observations or questions.

Case Studies

Another strategy is the **case study**, a highly detailed description of a single patient and their condition. A case study documents the details regarding a specific deficit or enhancement and is an opportunity to examine individuals with very rare conditions, which are useful for informing about the functions of different brain structures. Like a quasi-experimental study, case studies only show correlation, not causation. It is difficult to generalize the findings from a case study to the population at large.

Perhaps the most famous case study in all of neuroscience is the 1848 story of the railroad worker Phineas Gage. Gage was a construction foreman working on the railroad when an unfortunate explosive workplace accident caused a iron rod to be driven through his left frontal lobe, largely destroying it. Remarkably, Gage survived this accident and lived another 12 years. However, Gage's

acquaintances described subsequent changes in his personality, teaching us that one of the functions of this area of the brain is regulating our inhibitions.

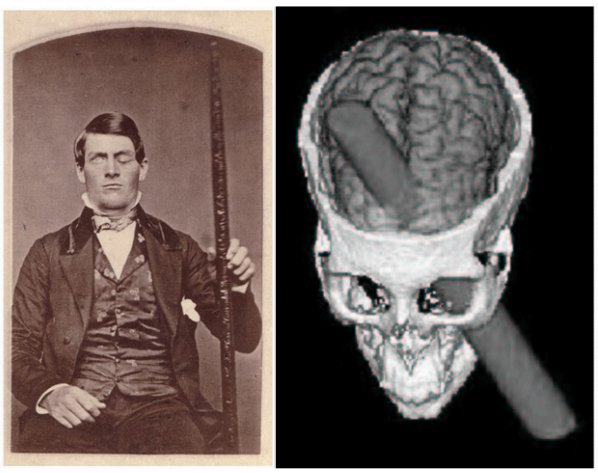

Figure 1.4 Image of Phineas Gage and his site of injury. The figure on the left is an image of Phineas Gage holding the iron rod that caused his injury. The image on the right shows a Magnetic Resonance Image rendering of the location of the rod in the injury. The rod entered below the left eye and damaged much of the left frontal cortex.

Case studies can be helpful for the development of hypotheses that can later be tested experimentally. For example, consider another famous case study of Patient HM, the man who had his left and right hippocampus surgically removed and couldn't create certain types of memory. A research question based on this case study might be: "Is the hippocampus needed for the creation of navigational memory?" Then, an experimental study could be performed in rodents, where we surgically remove the hippocampus (experimental group) or a different part of the brain (control group) and see how well the rodents perform on a memory task.

The Use of Animals in Research

Though there are many ways that we can directly study humans through experimentation or case studies, it is often impossible to test every question in humans. Instead of always studying humans,

scientists often use nonhuman model organisms, the most common organisms being the worm *C. elegans*, fruit flies (*Drosophila melanogaster*), zebrafish (*Danio rerio*), song birds, mice, rats, and macaque monkeys.

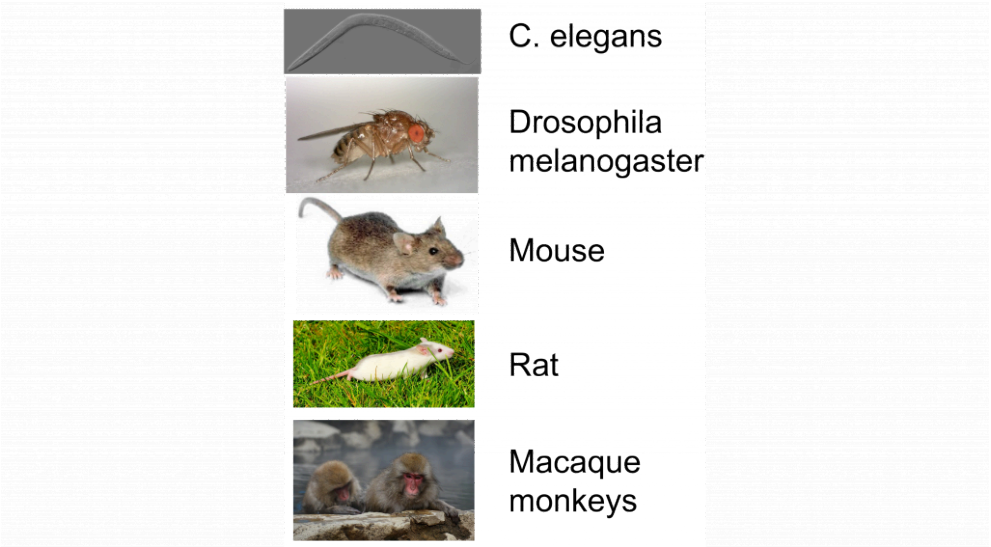

Figure 1.5 Experimental Animal Models. Images of C. elegans (worms), Drosophila melanogaster (fruit flies), mice, rats, and Macaque monkeys.

The closer we move towards the human, the more similarities the model organism shares with us. Of the commonly used model organisms, macaque monkeys are the non-humans that are most similar to humans. We share 93% of our genetic material with macaques, but we still have different metabolic and physiological processes, and our behaviors are much different from theirs. Ethical constraints prevent us from performing experiments that may cause physical or psychological harm if performed in humans. We would never conduct a test on humans to assess what concentration of neurotoxin leads to brain damage (these experiments aren't done very frequently in nonhumans anyway). Invertebrates, such as worms and fruit flies are not as heavily regulated by ethics oversight committees, allowing scientists to conduct a wider set of experiments on these animals.

Our moral responsibilities toward animal subjects are that:

1. Animals should only be used in worthwhile experiments.
2. All steps are taken to minimize pain and distress.
3. All possible alternatives to animal research are considered.

Research facilities at colleges and universities are monitored by an Institutional Care and Use

Committee (IACUC). The IACUC consists of fulltime veterinarians, scientists, and community members. They must follow federal laws when approving animal research.

Experimental Preparations

Performing an experiment in an intact, living organism, whether human or nonhuman, is described as an **in vivo** (Latin meaning "within life") preparation. The main strength of this strategy is that the data collected here are more predictive of the human condition, which is one of the main goals of biomedical research. However, the in vivo preparation has challenges, because thousands of variables within a living system are uncontrolled or still unknown. There are also very strict ethical limitations on the nature of experiments that can be done in vivo.

On the other hand, an **in vitro** (Latin meaning "within glass") preparation is an experiment performed on cultured cells or isolated molecules of DNA, RNA, or protein. These preparations have the opposite strengths and weaknesses of in vivo preparations. They allow for extremely good control over variables, but the results are less reliable in translating to a therapy. The regulations on these experiments are much more lax compared to in vivo experiments; most of the regulatory guidelines are to protect the experimenter rather than the patient or the experimental subject.

Falling in between these two preparations is an **ex vivo** experiment. In this kind of experiment, a section of the living organism is taken, such as a slice of brain, a tissue biopsy, or a detached frog leg. The strengths and limitations of these experiments are somewhere in between that of the other two preparations.

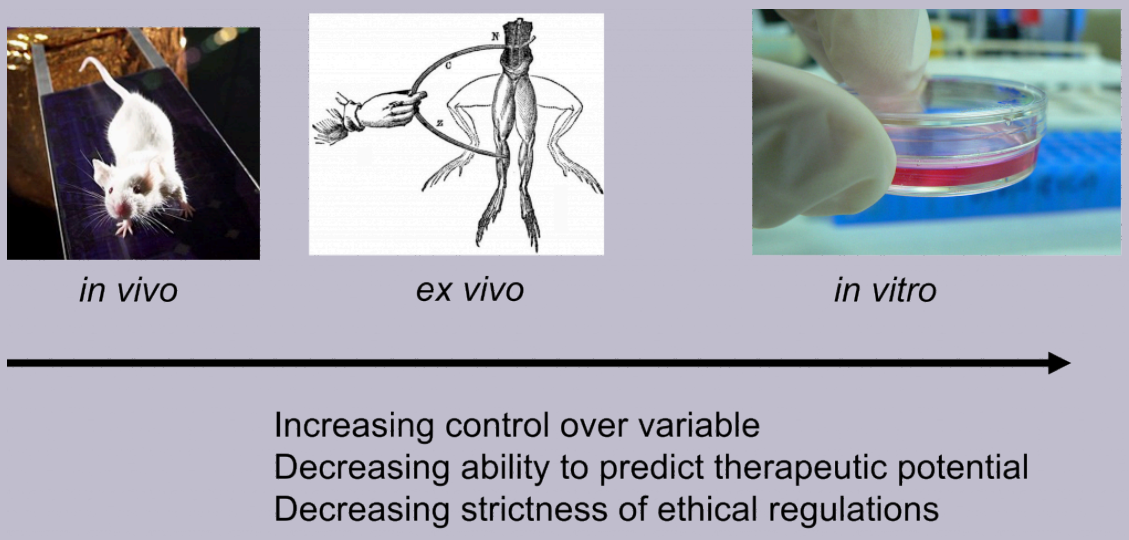

Figure 1.6 Experimental Preparations. Details of the in vivo, ex vivo, and in vitro preparations can be found in the text. The in vivo preparation has the least control over variables, but increased ability to predict therapeutic potential and increased strictness of ethical regulations. The ex vivo preparation has more control over variables, and decreasing ability to predict therapeutic potential and strictness of ethical regulations. The in vitro preparation has the most control over variables but the least ability to predict therapeutic potential and the least strict ethical regulations.

What neuroscience is not

As complex as the brain is, naturally misconceptions make their way into popular culture. It's valuable to address these myths about neuroscience and explain the evidence that refutes these statements .

Myth 1: "We only use 10% of our brain."

This wildly inaccurate statistic has been the foundation for several fictional movies, TV shows, and books. The truth is that we use every part of the brain, and most of our brain is active most of the time—just not at the same time. Neurologist V.S. Ramachandran uses a great analogy to describe the fallacy of this myth: does a traffic light only use 33% of its lights? A properly functioning traffic light

will use all three lights at very precise times. The activity of the brain is closely regulated by multiple mechanisms which prevent unusual electrical activity. In fact, if too many cells were active at the wrong times, just like a traffic light showing both green and red, chaos ensues—one cause of seizures is excessive neural activity.

Myth 2: "Forming memories causes new neurons to be born."

Another misconception is the idea that each new cell in our brain represents a new memory. While we are far from understanding the process of exactly how memories are formed in the brain, we do have a few clues. Most likely, memories are stored at the sites of close contact between neurons, called synapses. Changes in ways neurons connect and communicate with one another is likely the mechanism behind how memories are formed and stored, rather than the creation of new neurons. Even though the process of cell reproduction is halted in the majority of adult neurons, we are still capable of new neuronal growth, a process called **neurogenesis**. A few brain areas in particular, like the hippocampus (used in learning and memory functions and the olfactory epithelium (used for smelling), do exhibit frequent birth and death of new neurons.

Myth 3: "The brain cannot repair itself."

If neurons aren't being replaced in adulthood, then how do people spontaneously recover from neurological injuries like a **stroke**? One of the most amazing features of the brain is the phenomenon of **plasticity**, the ability to change over time. Even if critical brain areas are damaged, it is theorized that the brain learns how to "rewire itself", essentially figuring out how to carry out these functions without using the damaged connections. Unfortunately, there are some conditions that are neurodegenerative, meaning that their symptoms get progressively worse over time. Many of these disorders, like **Parkinson's disease** and **Alzheimer's disease**, currently do not have any simple cures or treatments that don't carry risks and side effects. For people with these conditions, there is not strong evidence that the brain can recover from the destruction caused by these diseases.

Myth 4: "If you are analytical, you are left brain

dominant, but if you are creative, you are right brain dominant."

A common misconception is that the two hemispheres of the brain are responsible for wildly different functions. The truth is that nearly every function that the left half of the brain can do, the right half can do just as well, and vice versa. Sensory information, voluntary control of the muscles, memories, and many other behaviors can be performed equally well by both the left and right halves of the brain. A major exception to the "left vs. right" component is the processing and production of language. For some reason unknown to scientists, these functions are heavily lateralized in the left hemisphere for most people.

Fascinatingly, we do have one strange quirk about signaling between the brain and the rest of the body: signaling pathways from the left brain crosses over to communicate with the right half of the body, and vice versa. This contralateral organization is an unintended consequence of evolution, and is one of the major distinguishing features of the vertebrate brain.

Neuroscience is ever-changing

One of the most exciting and satisfying aspects of modern science is the rapidity of new discoveries in the field. New findings are often communicated by publishing academic studies in scientific journals. More neuroscience studies were published between 2015 and 2020 than in the previous seventy years! But, advancements in neuroscience haven't always moved so quickly.

Trepanation was a surgical intervention that involved drilling a hole into an individual's skull. It is believed to be one of the oldest surgical procedures according to archaeological evidence. Interestingly, skulls that show evidence of trepanation have been dated to 6500 BCE and show evidence of healing, indicating that the patient survived the surgery.

Figure 1.7 Trepanated Skull. This image shows an example of trepanation, or drilling holes in the skull of individuals as a form of treatment. The growth of the skull around the site of surgery suggests healing and that this procedure was performed while the individual was still alive.

Localizationism

For hundreds of years, physicians attempted to correlate behaviors with changes in the brain. In the mid 1800s, the physician **Paul Broca** contributed to **localization** theory by concluding that specific areas of the brain were responsible for carrying out specific functions. This idea was supported by **ablation** studies that demonstrated that when different brain structures were ablated, or lesioned, there were specific associated functional losses. Further, electrically exciting specific brain structures resulted in eliciting specific behaviors.

Most likely, some behaviors are more localized than others, but still rely on signals from across many other brain areas. As with most fields of biology, absolutes are rare in neuroscience.

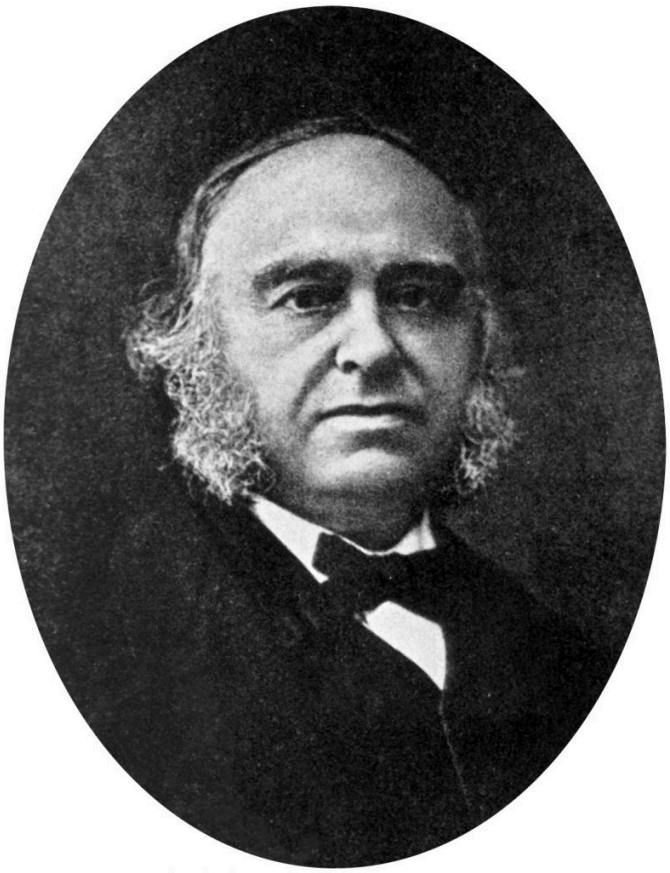

Figure 1.8. Image of Paul Broca.

Plasticity

The real strength of our brain is its flexibility: brains are capable of changing and adapting to a wide variety of circumstances. Blind people use their visual areas of the brain while echolocating, **stroke** survivors can regain lost motor functions using the unaffected brain circuits, and babies can effortlessly learn two languages simultaneously in a bilingual household.

Plasticity is based on the idea that not only is the brain capable change, but that our experiences change the structure and function of our nervous system.

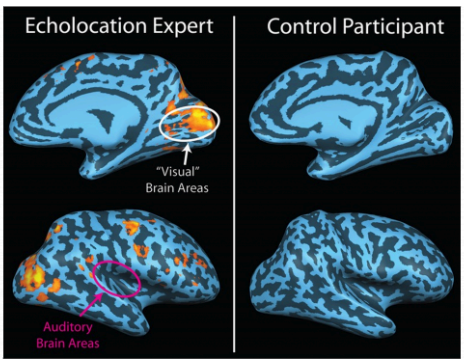

Figure 1.9 Example of Brain Plasticity. Brain images are shown of two different individuals, a blind individual that is an echolocation expert and a control participant. The blind echolocation expert shows an increase in activity within areas of the brain that typically respond to visual information, but no activation in areas of the brain that respond to auditory information. The brain is plastic and has allowed for the blind individual to use areas of the brain that typically process sight to instead process echolocation information.

Key Takeaways

- Neuroscience is the study of the nervous system and is an integrative field of study that incorporates biology, psychology, chemistry, physics, mathematical modeling, and health care providers.
- The study of neuroscience is accomplished through experimental studies, case studies, and the use of experimental animal models.
- There are many popular myths concerning neuroscience and it is important to analyze data that refutes these myths.
- Though the field of neuroscience is relatively young and ever-changing, humans have been interested in the brain and its function for centuries.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/intronеuroscience1/?p=407#h5p-23

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PART II

CELLS OF THE NERVOUS SYSTEM STRUCTURE & FUNCTION

2.

CELLS OF THE NERVOUS SYSTEM: THE NEURON

There are 2 major cell types within the nervous system: **Neurons** and **Neuroglia**. Neurons are cells that transmit electrical information. Neuroglia are supporting cells of the nervous system.

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.

Resources

- Scientist Links to Learn More
- Glossary Terms
- Key Takeaways
- Test Yourself

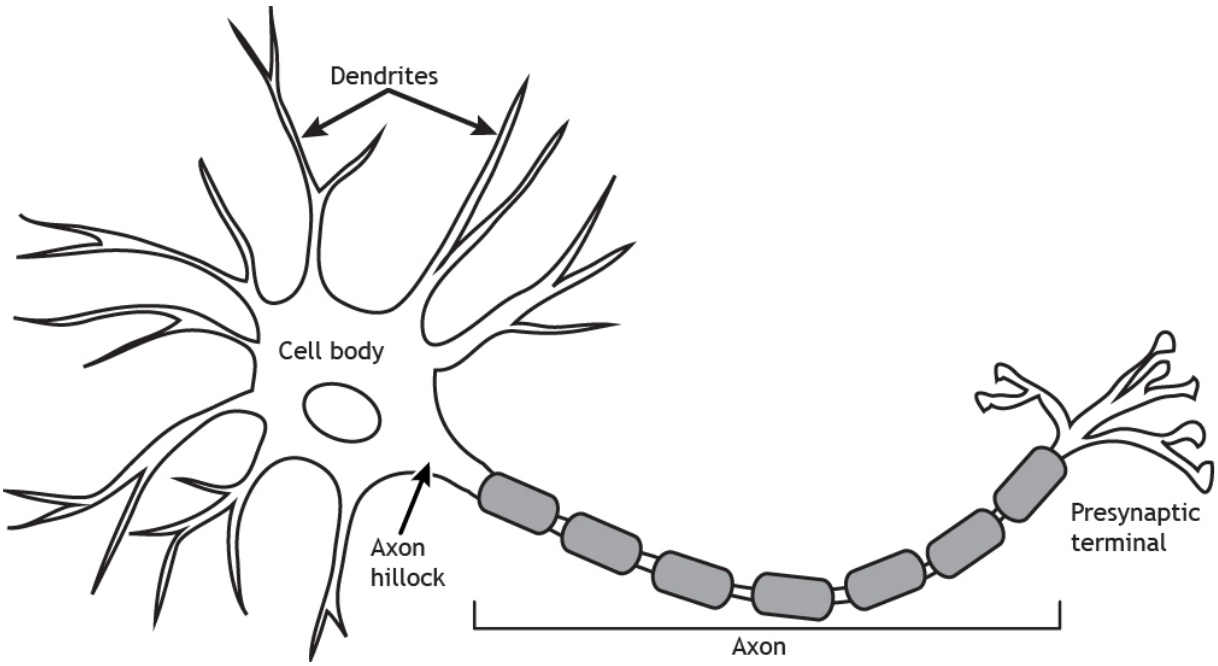

Figure 2.1. A typical neuron. Dendrites branch out from the cell body, where the nucleus is located. The axon hillock is located where the cell body transitions into the axon. The axon begins at the axon hillock and ends at the presynaptic terminal, which can branch into multiple terminals. 'Neuron' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Although neurons do have a variety of adaptations that make them unique from other types of cells in the body, they are still cells. Therefore, they contain all of the basic features of a typical mammalian cell.

For example, they are made up of an aqueous cytoplasm bounded by a cell membrane. This cell membrane, also called a plasma membrane or lipid membrane, consists of a sheet of several individual molecules called phospholipids, which consist of two hydrophobic (water-fearing) tails and a hydrophilic (water-loving) end. These phospholipids arrange themselves into a bilayer, with the hydrophobic tails touching each other and the hydrophilic sides facing the cytoplasm and the extracellular space, which are both mostly water. Because of the chemical properties of the cell membrane, it is very effective at keeping ions and charged molecules separated, while allowing small molecules like water and oxygen across the cell.

Neurons also have all the organelles that you would see in other cell types, like a nucleus and mitochondria. The number of neurons in the adult human brain, according to our current best

estimate, is close to 86 billion. This number was calculated using a revolutionary technique, the isotropic fractionator or "brain soup", developed by Brazilian neuroanatomist Suzana Herculano-Houzel. To put this number in context, we have about 37 trillion cells in the whole body, so neurons in the brain make up about 0.2% of all cells in the body. Below are some unique characteristics that neurons have in common.

1. **Neurons are electroactive**, which means that they are charged cells that can change their charge.
2. **Neurons are specialized for rapid communication.**

   Many cells are capable of sending and receiving chemical signals across long distances and time scales, but neurons are able to communicate with a combination of electrical and chemical signals in a matter of milliseconds. Additionally, the shape of neurons and the organization of the neurons on a microscopic level make them effective for sending signals in a very specific direction.
3. **Neurons are "forever" cells.**

   We are constantly replacing non-neuronal cells. For example, the cells in our bones replace themselves frequently at a rate of about 10% each year. Our body makes new skin cells to replace the dying skin cells on the surface so that we have a "new" skin every month. The cells along the inside of our stomachs, exposed to very harsh acidic conditions, get replaced about every week. About 100 million new red blood cells are created every minute! On the other hand, the mature nervous system generally does not undergo much neurogenesis: the creation of new neurons.

   The neurons that we have after development are the ones that we will keep until we die and this permanence of neuronal count makes them different from almost every other cell of the body. However, the idea of adult neurogenesis is a topic of debate among neuroscientists since some areas, like the olfactory system and the hippocampus, display new nerve cell production.
4. **...But, neurons can change.**

   Even though new neurons are not created in most areas of the brain, neurons still have the capability to change in their structure and function. Some of these changes, such as physical changes to the structures of the input sites of the neurons, are believed to last for a lifetime.

   We use the word *plasticity* to describe the ability for the brain to alter its morphology. This term is derived from the Greek *plastikos*, meaning "capable of being shaped or molded"—think of plastic surgery, where a person changes their physical appearance.

   Also, neurons do have the capacity to repair themselves to some extent. Neurons of the Peripheral Nervous System may get injured or completely destroyed as a result of trauma to the

body. Afterwards, those injured neurons can regrow to connect once again with their original partner. This regrowth seems to depend on a few chemical signals that the body produces, such as nerve growth factor and brain derived neurotrophic factor. However, this process is often very slow, and does not always successfully restore the nervous system to the way it was pre-injury.

Dendrites

The main function of neurons is to use changes in electrical properties in order to communicate with connected cells. This communication usually moves in one direction, and we will use this pathway as an outline for discussing the anatomical structures of the neurons.

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.

We believe that spines are one of the most important sites where the nervous system is able to change. For example, neurons change shape after exposure to various environmental conditions, such as stress or exposure to drugs. Tiny changes to the surface of the neuron at the level of dendritic spines is an example of **plasticity**.

Dendritic plasticity is thought to underlie the reason that we can learn new facts or maintain memories about our childhood over long periods of time. Some set of tiny, submicroscopic changes to the morphology of dendritic spines may represent a single complex memory that you form. A neuron does not need spines for receiving information or for plasticity to take place. Many cells lack spines but are still capable of permanently changing. The input site may be anywhere along the dendrite, or even at the cell body—the "center" of the neuron.

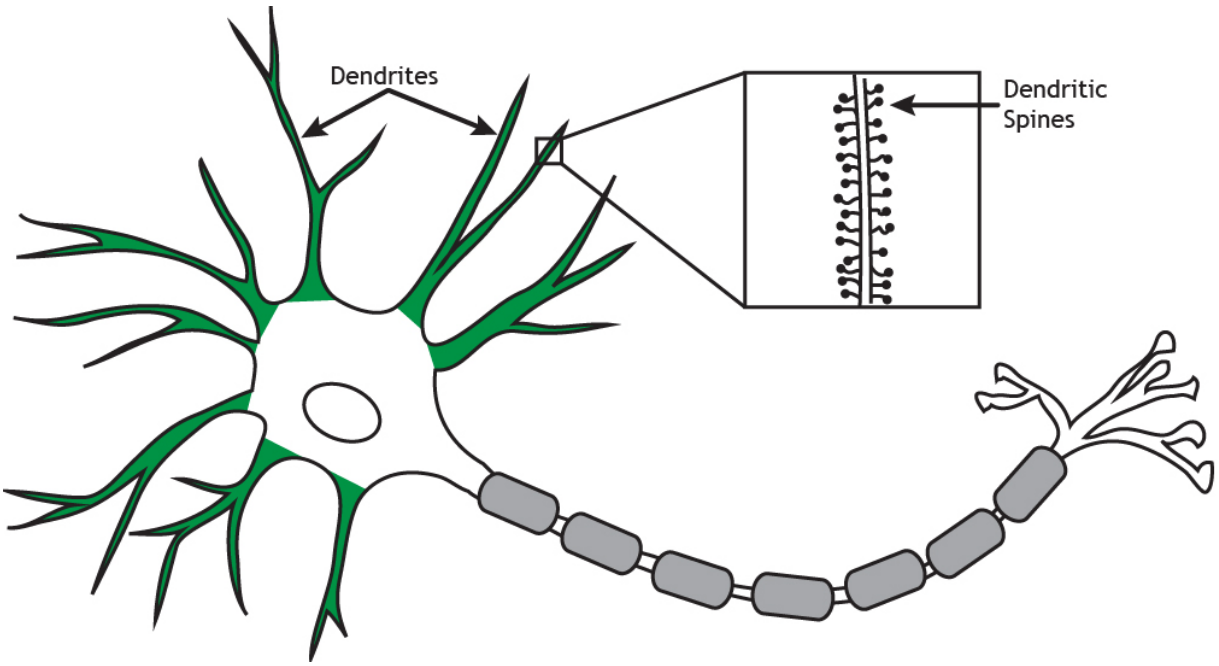

Figure 2.2. Dendrites branch out from the soma. Their function is to receive information from other neurons. Some dendrites have small protrusions called spines that are important for communicating with other neurons. 'Dendrites' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Cell Body

Information that arrives through the many dendrites of a neuron eventually filters into the cell body, or the **soma**, of the neuron. The cell body (shown below in green) contains the nucleus and cellular organelles, including the 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.

The cell body is responsible for deciding whether to pass a signal onto the next cell. The cell membrane of the soma performs a complex set of "cellular arithmetic" that weighs all of the incoming signals: excitatory, inhibitory, and modulatory signals. After all of the calculations have been performed, the membrane decides to send a signal, either a "yes" or "no" output, which travels down the axon.

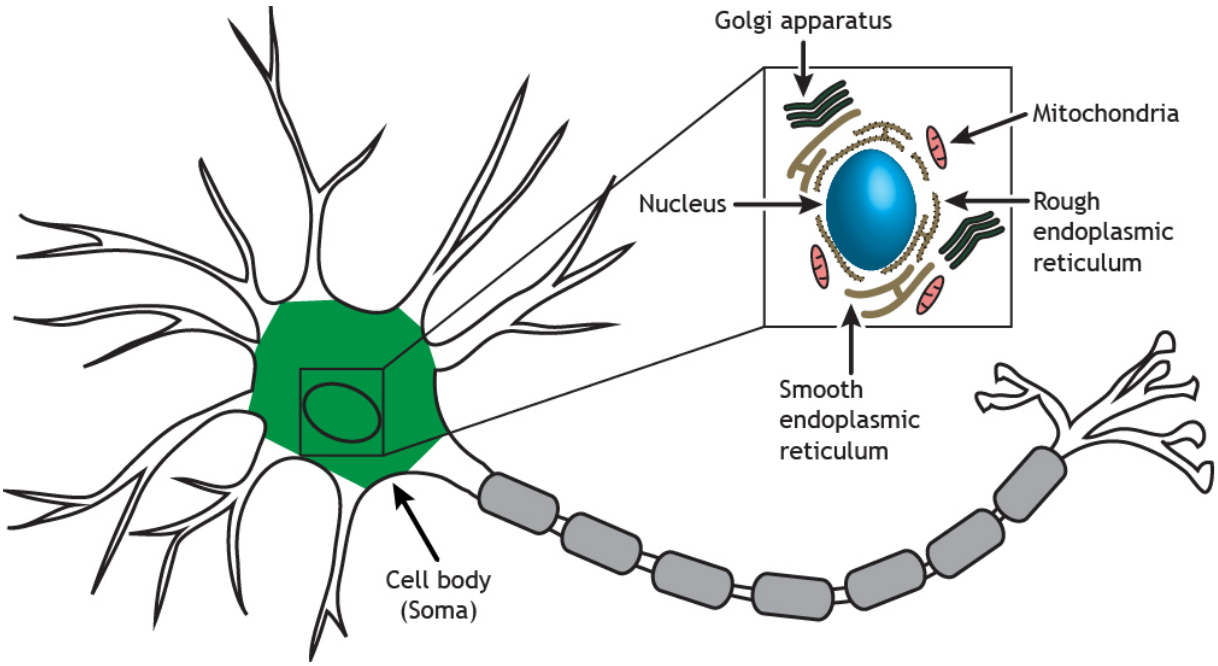

Figure 2.3. The cell body, or soma, of the neuron contains the nucleus and organelles that are commonly found in other cell types and are important for basic cellular functions. These organelles include mitochondria, endoplasmic reticulum, and Golgi apparatus. 'Soma' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axon

The **axon** is the main output extension of the neuron. 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.

Several axons can bundle and travel together; these are **nerves**. Axons can be very long; the longest axon in the human body is part of the sciatic nerve that runs from the posterior end of the spinal cord down the leg to control the muscles of the big toe.

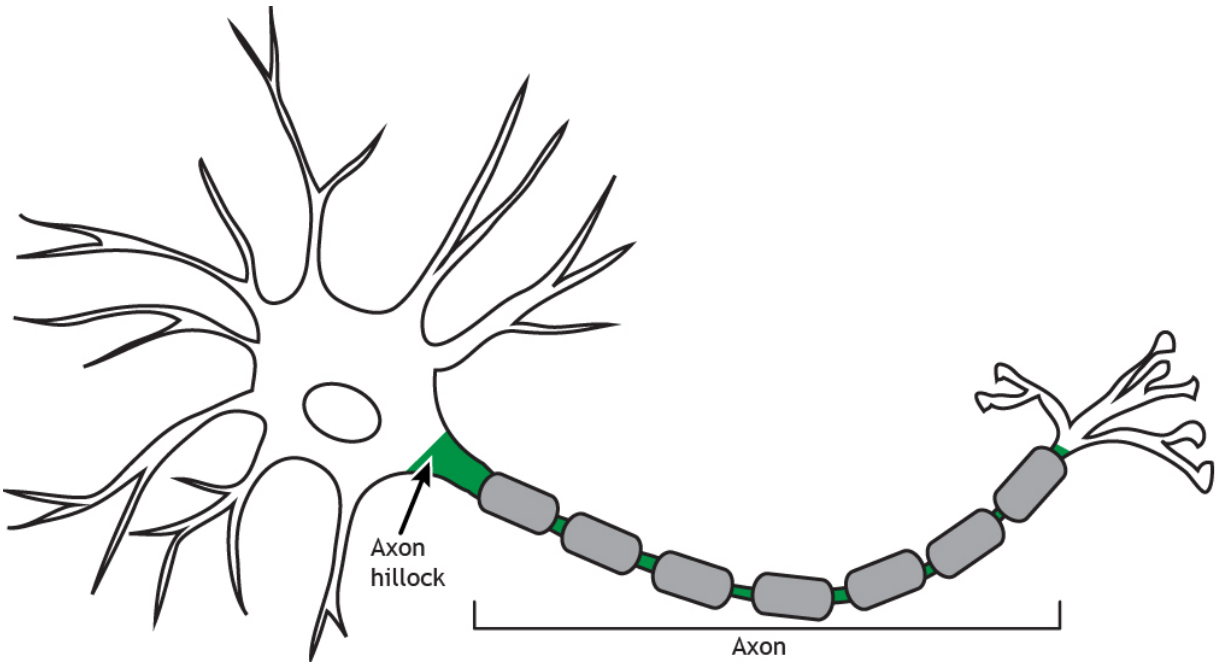

Figure 2.4. The axon is a long single projection that begins at the axon hillock, the region between the cell body and the axon. The axon terminates at the presynaptic terminal. 'Axon' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International 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.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=29#video-29-1

Animation 2.1. 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.

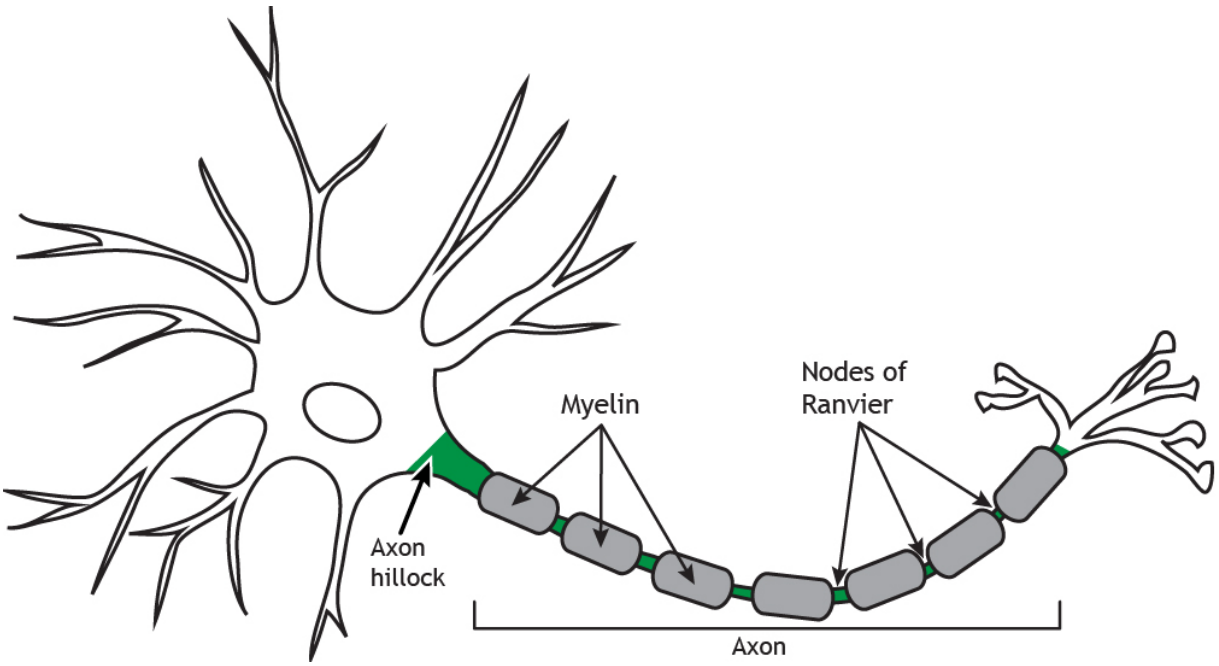

Figure 2.5. Myelin wraps around and insulates the axon. The spaces between the myelin sheath, where the axon is uncovered, are call the Nodes of Ranvier. 'Myelin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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.

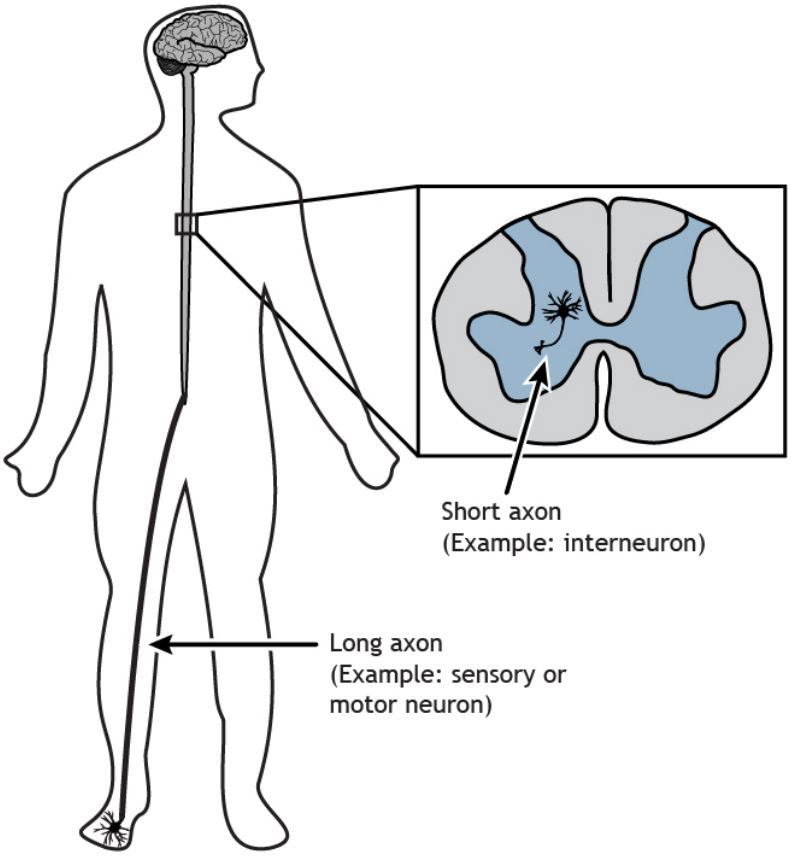

Figure 2.6. Axons vary in length. Spinal interneurons, neurons that fully exist within the spinal cord, can have short axons, whereas sensory or motor neurons, which need to reach from the spinal cord to the appropriate body region, for example the toe, have long axons. 'Axon Length' by Casey Henley 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.

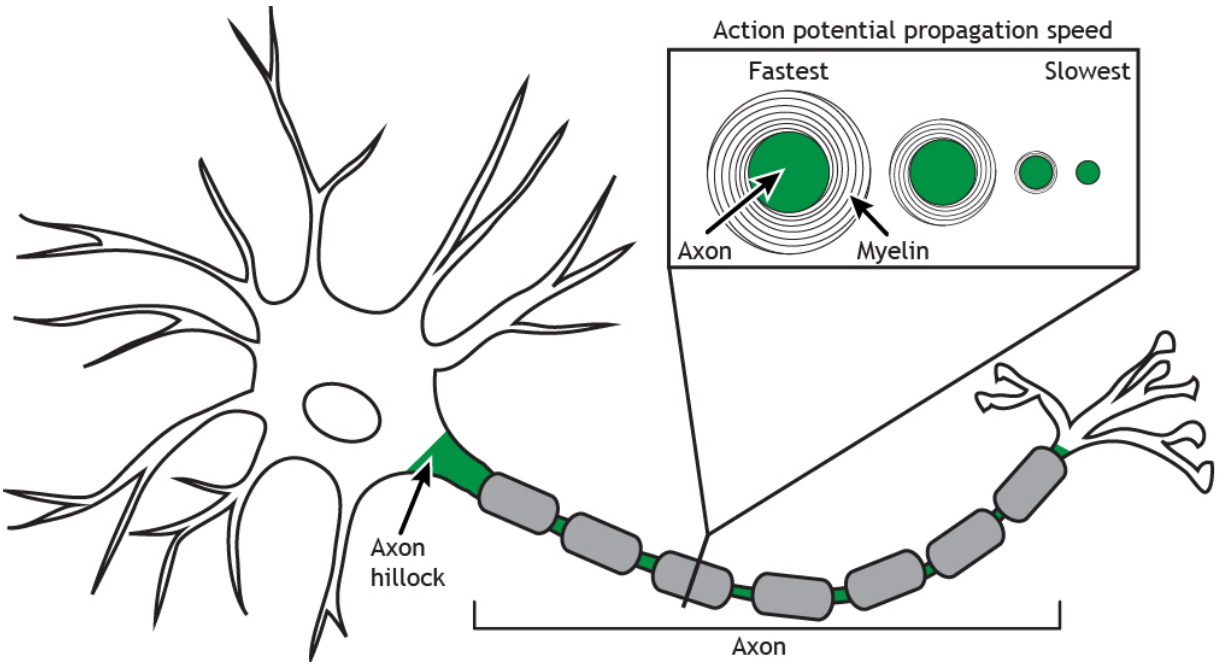

Figure 2.7. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. 'Axon Diameter' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axoplasmic Transport

Axoplasmic transport refers to the movement of material within the axon. 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.

Microtubules run the length of the axon and provide the cytoskeleton tracks necessary for the transportation of materials. Proteins aid in axoplasmic transport. **Kinesin** is a motor protein that uses ATP and is used in anterograde transport of materials. **Dynein** is another motor protein that also uses ATP, but is used in retrograde transport of materials.

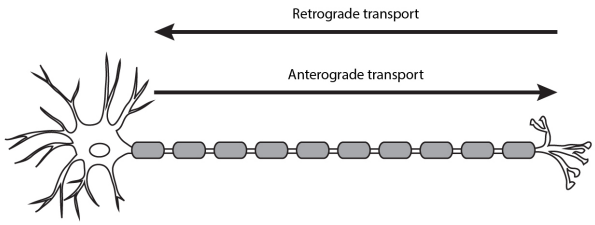

Figure 2.8. Cellular components need to be able to move throughout the cell to have proper functioning. Anterograde transport moves components from the cell body toward the terminal. Retrograde transport moves components from the terminal toward the cell body. 'Axonal Transport' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The Synapse

The **synapse** is the physical distance that separates two neurons.

Electrical Synapse

Electrical synapses physically share cytoplasm. An electrical synapse may be less than 5 nanometers apart. Cells connected by electrical synapses share cytoplasm, but have two separate cell membranes.

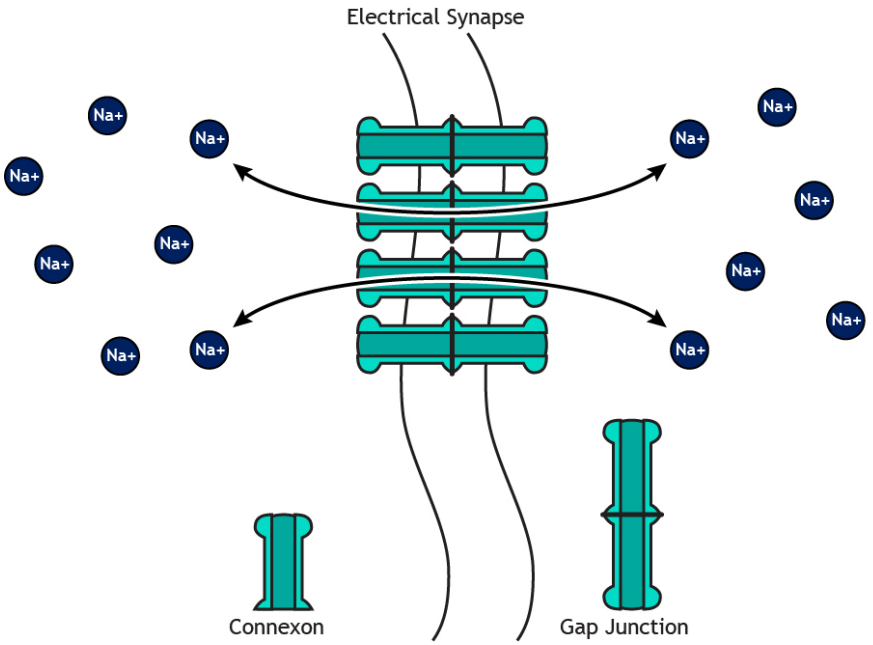

Figure 2.9. Since an electrical synapse is a direct, physical connection between the cytoplasm of two neurons, ions are able to flow in either direction across the gap junction. 'Bidirectional Electrical Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chemical Synapse

Chemical synapses use neurotransmitters to communicate. Chemical synapses can vary depending on the nature of the synapse. A chemical synapse is a larger distance, about 15–40 nm across. Adjacent neurons connected by chemical synapses do not share cytoplasm.

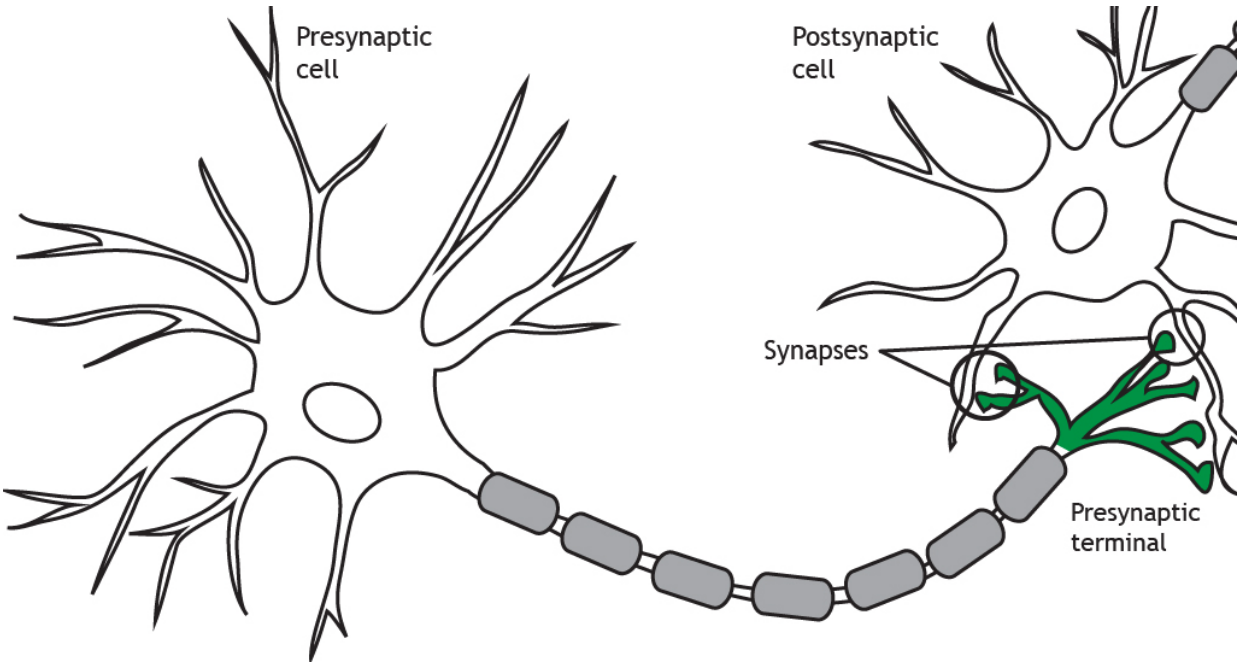

Figure 2.10. Synapses are found between two adjacent cells. In this image, the axon terminals (presynaptic terminals) are synapsing on the dendrites of another neuron (postsynaptic cell). "Presynaptic Terminal' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Presynaptic versus Postsynaptic

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.

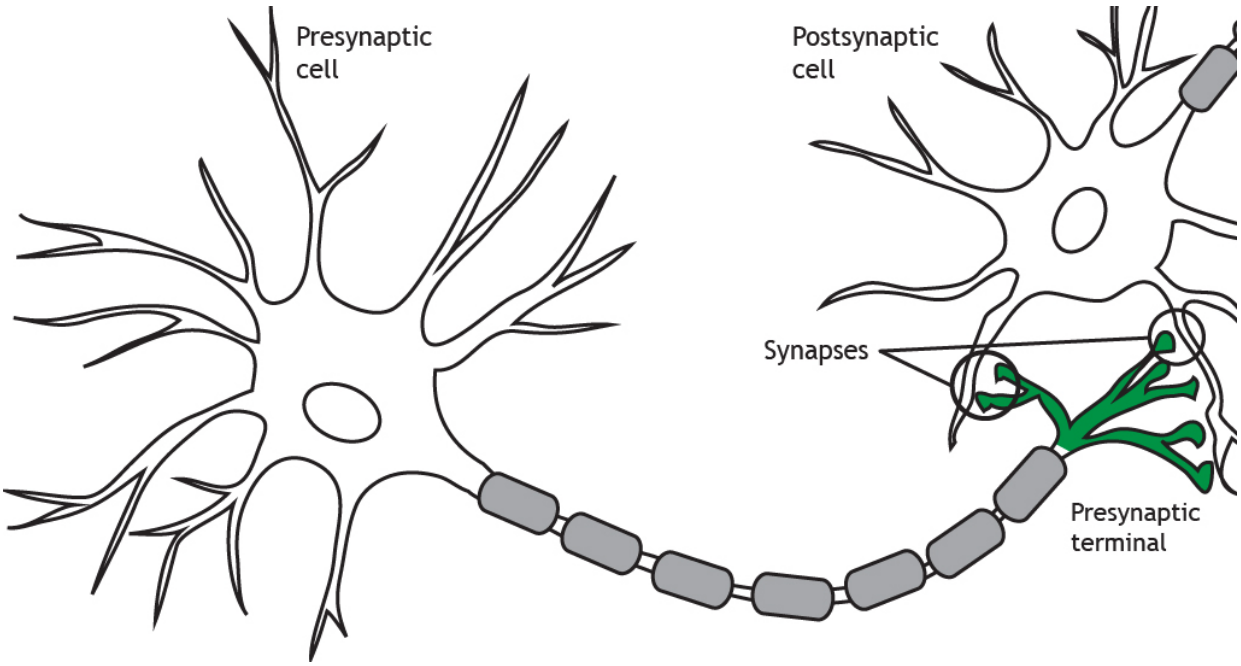

Figure 2.11. The presynaptic terminal forms synaptic contacts with a postsynaptic cell. 'Presynaptic Terminal' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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**.

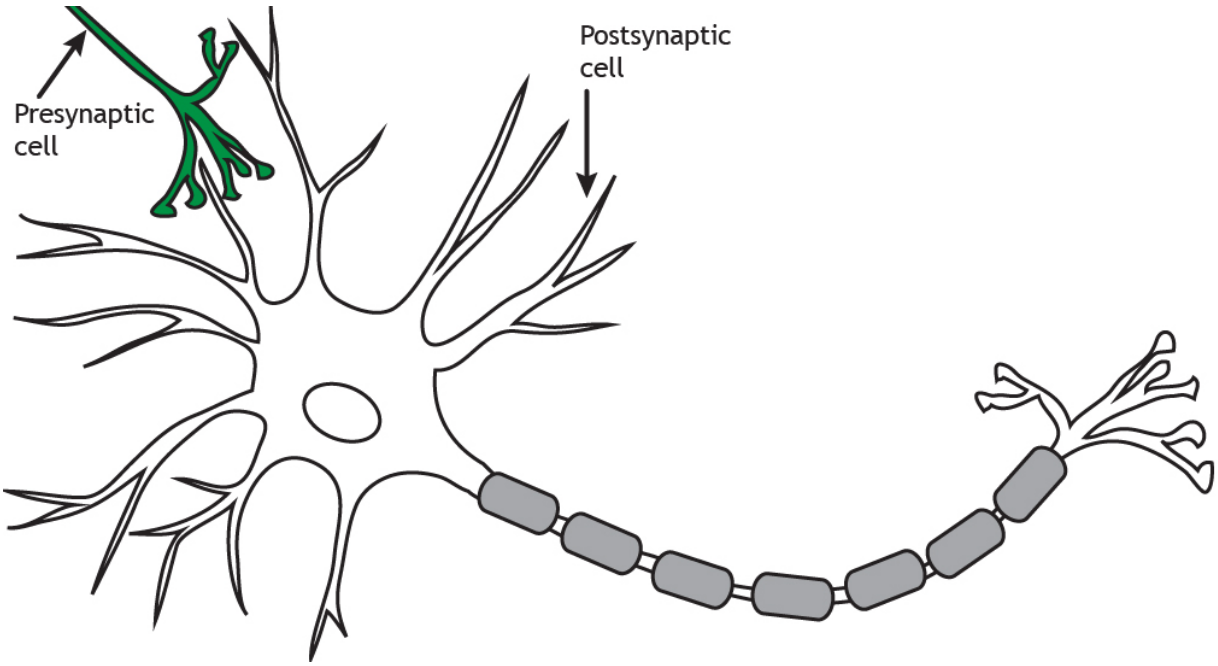

Figure 2.12. The presynaptic cell is the neuron that releases neurotransmitters into the synapse to act upon the postsynaptic cell. 'Postsynaptic Cell' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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.

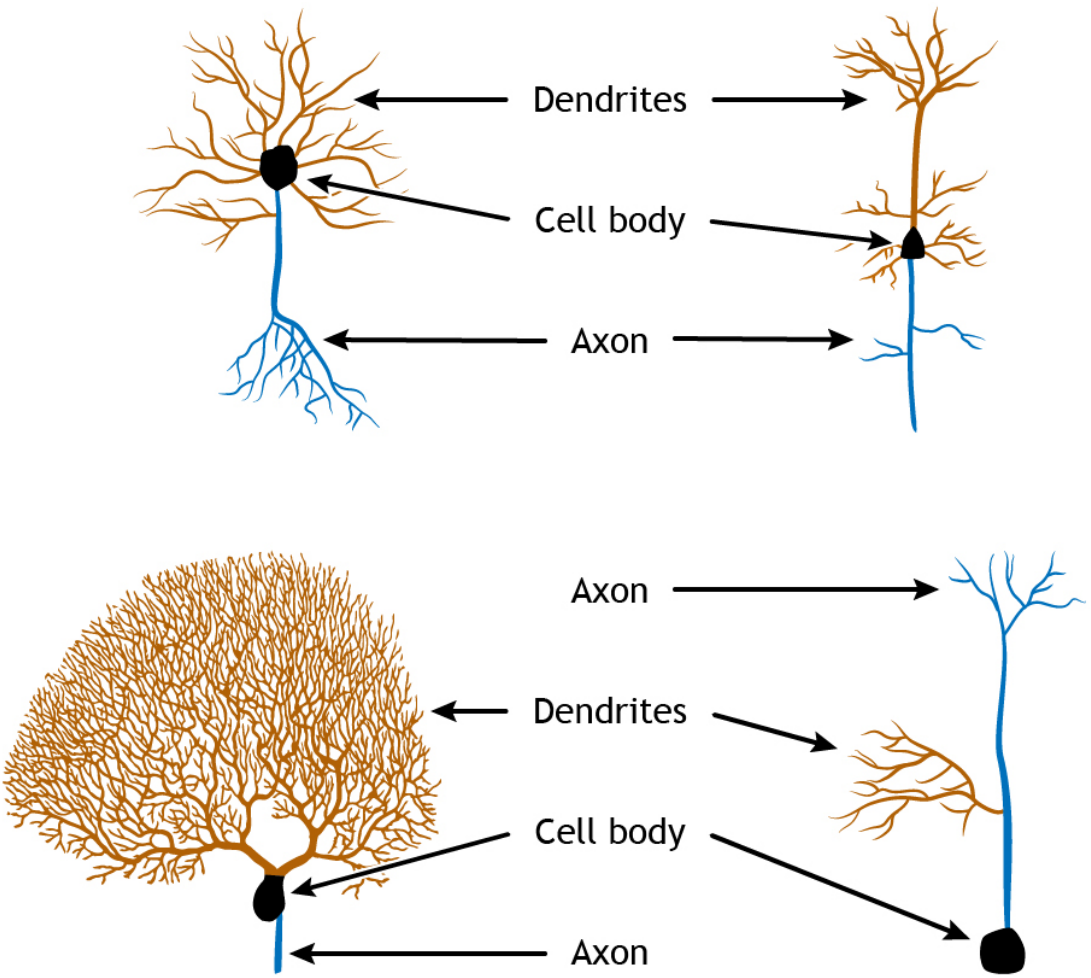

Figure 2.13. Neuron structure is variable, but the main components of cell body (shown in black), dendrites (shown in brown), and axon (shown in blue) are common among all neurons. 'Neuron Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- 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!

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3.

CELLS OF THE NERVOUS SYSTEM: GLIA

Although most of neuroscience is concerned with understanding the functions of neurons, there are other cells in the nervous system that are just as interesting. These cells are grouped together under the umbrella classification of **glia**. Historically, when these non-neuronal cells were visualized under the microscope, the **histologists** and anatomists had no idea about their function. They were seen all around the neurons, so the assumption was that these cells were structural elements, a sort of living glue, that held the nervous system together. Today, we know that these glia serve a variety of functions; unfortunately, the misnomer "glia"—derived from the Latin word for "glue"—is still used to describe these non-neuronal components of the nervous system.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Astrocytes

Astrocytes are named for their characteristic star-shaped morphology. One of the main functions of astrocytes in the brain is to help maintain the **blood-brain barrier**. At the end of the extensions of the astrocyte are protrusions called "endfeet". These endfeet are often wrapped around the endothelial cells that surround the blood vessels. The endfeet release important biological compounds that allow the endothelial cells to remain healthy as they function in maintaining the blood-brain barrier. Astrocytes are also very closely associated with **synapses**.

Astrocytes also synthesize and produce a variety of **trophic factors**, which are helper molecular signals that serve several different functions. For one, trophic factors signal to neurons that the neuron

should continue to live, or that specific synapses should be maintained. They help guide the neurons as they reach out, forming synapses where appropriate.

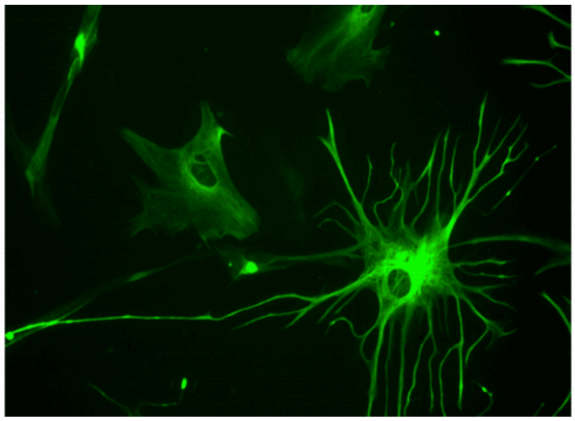

Figure 3.1 Astrocyte. A green fluorescent marker has been used to stain astrocytes within brain tissue. The astrocytes has star-like projections off the cell body.

Oligodendrocytes

The main function of the oligodendrocytes is to add a layer of **myelin** around the axons of nearby neurons in the **central nervous system**. A single oligodendrocyte is able to myelinate up to 50 segments of axons. As cells that produce myelin, they are responsible for increasing the conduction speed of nearby neurons as they send signals. Oligodendrocytes only exist in the **central nervous system**.

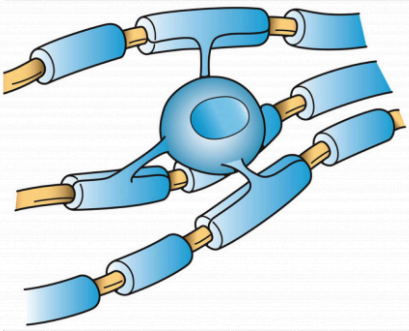

Figure 3.2 Image of an oligodendrocyte. A single oligodendrocyte shown in blue covers axons from multiple neuron axons with myelin sheath.

Schwann Cells

Schwann cells can only be found in the **peripheral nervous system**. The main action of Schwann

cells is to provide a section of **myelin** sheath for peripheral nervous system neurons, and in this way, they function similarly to the oligodendrocytes. Schwann cells produce only a single section of myelin, compared to oligodendrocytes, which myelinate multiple sections. Schwann cells also function in the regeneration of injured axons. When nerves in the peripheral nervous system are damaged after trauma, Schwann cells rapidly mobilize to the site of injury.

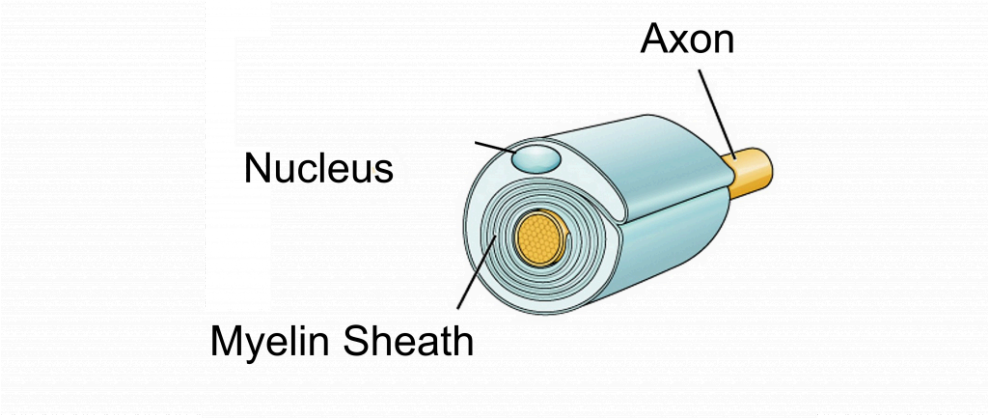

Figure 3.3 Schwann Cell. The Schwann cell is shown in blue. A single Schwann cell wraps myelin around a neuron axon, shown in yellow. Multiple Schwann cells are needed to myelinate one neuron axon.

Microglia

Microglia are a bit different from the other glial cell populations. For one, microglia are more immune cells rather than neural. They act as cellular scavengers that travel throughout the brain and spinal cord. It is estimated that microglia make up 10-15% of all cells in the brain.

As immune cells, microglia identify and destroy clumps of proteins, dead/dying cells, or foreign pathogens that enter into the brain. After an injury to the **central nervous system**, like a traumatic blow to the head, microglia rapidly react to the area of the insult.

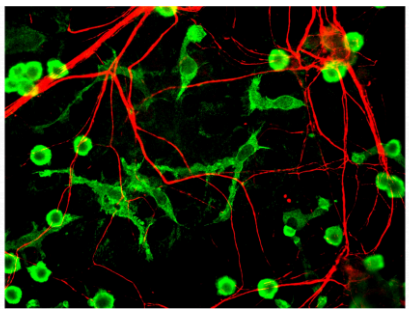

Figure 3.4 Photograph of microglia and neurons. In this microscope photograph, microglia are stained with a green fluorescent stain and neurons are stained with a red fluorescent stain. Microglia are much smaller than neurons.

Ependymal Cells

Along the inside of the **ventricles** are a lining of glia called ependymal cells. These ependymal cells are **columnar** with small fingerlike extensions called **cilia** that extend into the ventricles and into the central canal that runs down the inside of the spinal cord. The cilia have motor properties that allow for them to rhythmically beat to create a current in the surrounding fluid.

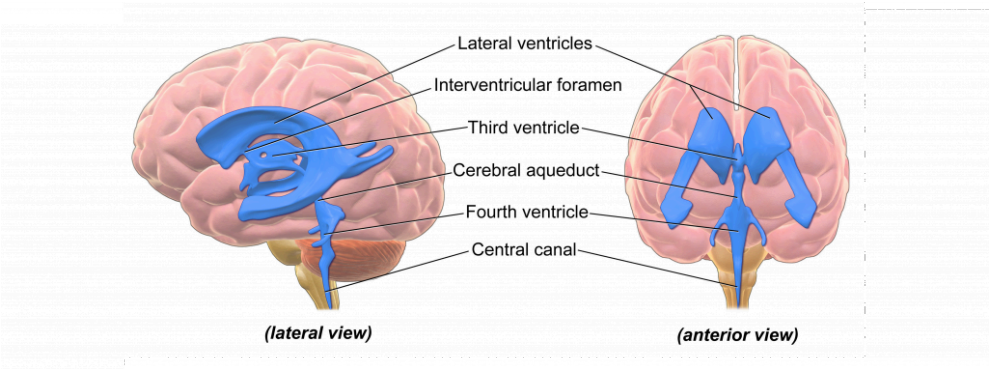

Figure 3.5 Image of brain ventricles. The brain ventricles (shown in blue) are hollow areas within the brain that are interconnected and filled with cerebrospinal fluid. The ventricles are connected to the central canal of the spinal cord. The ventricles are show in a lateral view (left) and anterior view (right).

Ependymal cells produce **cerebral spinal fluid** (CSF). In total, the body can make about half a liter of CSF each day (a little more than two cups.) The ependymal cells are part of a structure called the choroid plexus, the network of blood vessels and cells that form a boundary between the blood and the CSF.

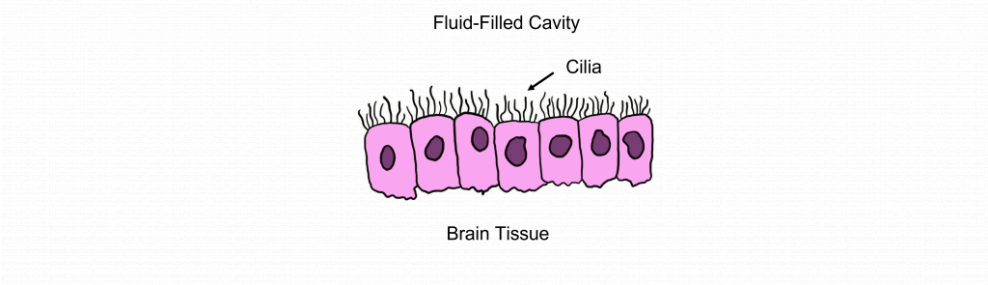

Figure 3.6. Ependymal Cells. Ependymal cells are ciliated columnar cells that line the ventricles and other fluid-filled spaces of the central nervous system. The rhythmic beating of the cilia create movement of the surrounding cerebral spinal fluid. 'Ependymal Cells' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- There are multiple different types of glia cells that each have their own functions

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4.

VISUALIZING CELLS OF THE NERVOUS SYSTEM

Resources

- Scientist Links to Learn More
- Glossary Terms
- Key Takeaways
- Test Yourself

For the majority of human history, the only way we were able to study the structure of the brain was with crude, butcher-like methods. Wait for a person to die, saw a giant hole in the top of the skull, take the brain out, and slice it into pieces to see if there was some correlation between the way the brain looks and the way they died. With these methods, only major changes in gross anatomy could be observed, such as those resulting from severe birth defects or trauma.

Brain analysis methods were enhanced by the scientific adoption of light microscopy. Naturalists in the mid 1600s such as Antonie van Leeuwenhoek, Jan Swammerdam, and Robert Hooke began looking at biological substances up close, and the brain proved to be a complex and interesting sample of tissue.

Visualizing Cells: Cell Staining

Staining is an imaging method that is often used in conjunction with microscopy. Thin slices of brain tissue are exposed to various chemical processes. The chemicals that are used for staining have different affinities for parts of cells.

For staining to work, the tissue needs to be subjected to a series of chemical processes. First, the tissue needs to be fixed. **Fixation** is a chemical process that is accomplished by exposing the tissue to a chemical like paraformaldehyde. The most effective way to expose every part of the body to

fixative is to "hijack" the endogenous circulatory system by flushing fixative through the arteries, a process called **perfusion**. Chemically, fixatives cause adjacent proteins to become covalently bonded (crosslinked), a process which causes the proteins to become unchangeable; they become "fixed" in time. These fixatives are very harsh chemicals, and usually kill microorganisms and inactivate the endogenous enzymes that normally degrade biological tissue. (As a side note, fixatives are particularly nasty carcinogens that can permeate easily through latex gloves.)

After fixation, devices such as a microtome or cryostat are used to slice the brain into sections as thin as 10 microns. Stains do not always reliably pass all the way through thick sections of tissue, such as an intact brain. With thin slices, chemical stains are able to permeate through the depth of the tissue.

Next, stains are used to color the cells of the nervous system. This process is used because it is good for identifying the location of specific proteins at a subcellular level.

Nissl-Staining (Cresyl Violet Staining)

A stain is needed to distinguish individual cells in nervous tissue.

Nissl stain (Cresyl Violet Stain) was discovered by Franz Nissl. It stains nucleic acids such as RNA and DNA. Thus, the stain is only localized to neuronal cell bodies, where RNA and DNA are found. This staining method is useful for studying neuronal arrangement and how densely neurons are packed in specific brain structures.

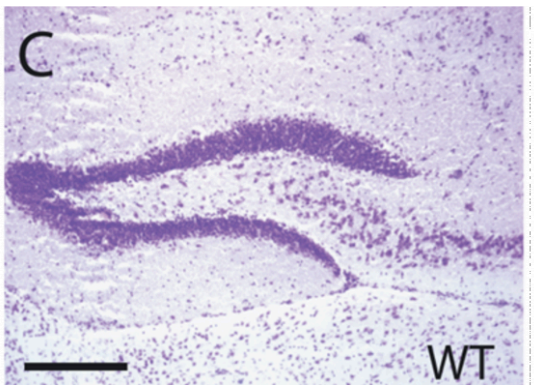

Figure 4.1 Nissl Staining (Cresyl Violet Staining). This microscope photograph shows neuronal cell bodies stained purple within mouse brain tissue in a structure called the hippocampus. The Nissl stain allows researchers to determine cellular density.

Golgi Staining

A major advancement in the study of neuronal morphology came about in the late 1800s. The Italian anatomist and biologist Camillo Golgi identified a shortcoming with the cellular analysis techniques of the time: structures in the central nervous sytem were impossible to distinguish from one another. The cells in the brain were so densely packed together, that it became difficult to identify which cellular material belonged to which cell.

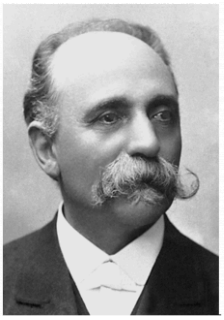

Figure 4.2 Photograph image of Camillo Golgi, the developer of the Golgi-staining technique.

Golgi came up with a new technique using a silver compound that caused the silver to precipitate inside the cell membranes. However, not every cell took up the silver. Instead, only a small fraction of neurons, maybe 1% or even less, were completely stained in black, which stood out remarkably well against the light yellow background of the surrounding tissue. This reaction, initially called the "black reaction", is now known as a "**Golgi stain**". (Despite being more than a hundred years old, we currently don't know the mechanism by which the silver stain is taken up into the neurons, or what determines why certain cells take the stain and others don't.)

Because of the great contrast between cell and background, every single part of the neuron was completely filled, allowing Golgi to do drawings of the morphology of this nervous tissue. Based on his staining results, Golgi supported the idea that the parts of the nervous system are all one very large, physically connected network. This idea was known as the **Reticular Theory**.

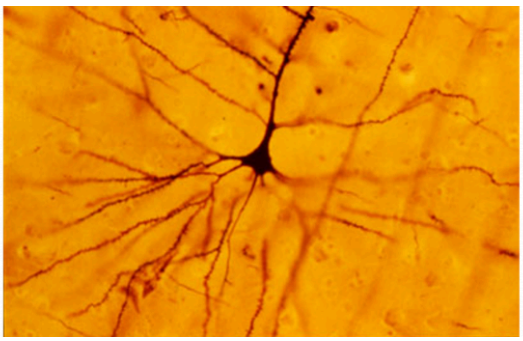

Figure 4.3 Golgi-stained pyramidal neuron. In this microscope photograph, the black/dark stain is staining a single neuron and its projections. The Golgi stain allows for visualization of dendrites and the neuron axon.

Santiago Ramon y Cajal

About 10 years later, the Spanish neuroanatomist Santiago Ramon y Cajal repeated some of Golgi's staining experiments with other sections of nervous tissue. Looking at similar darkly-filled neurons, Cajal arrived at a different conclusion: the nervous system is not a giant net, but rather a series of individual units that are separated from one another physically. This idea came to be known as the **Neuron Doctrine**.

Figure 4.4. Photograph of Santiago Ramon y Cajal.

Both Golgi and Cajal were awarded the shared Nobel Prize in Physiology or Medicine in 1906 for their accomplishments in helping to understand "the structure of the nervous system". Even though

Cajal's **Neuron Doctrine** was adopted widely by scientists, the elucidation of this organization would not have been made possible without Golgi's development of the silver stain. The sharing of this prestigious award was ironic because of the many disagreements between the two scientists.

Cajal's Neuron Doctrine was eventually given more support with the aid of modern techniques, like electron microscopy, that are capable of physically seeing the distance between two neurons. The Neuron Doctrine represents our current understanding of how the nervous system is organized.

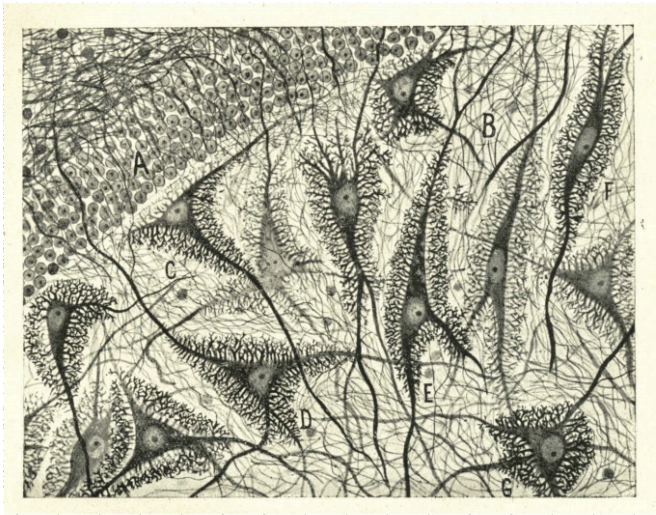

Figure 4.5. Example of Santiago Ramon y Cajal drawing. This is an example of one of the many intricate hand drawings done by Santiago Ramon y Cajal while he looked through a microscope at nervous system tissue.

Key Takeaways

- Nissl stains stain neuronal cell bodies
- Golgi stains stain entire neurons and allows for visualization of cell structures (dendrites and axons)
- Neurons are discreet cells and are not interconnected together together into a network

Test Yourself!

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5.

ION MOVEMENT

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

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 cell membrane that separates the inside of the cell from the outside is a very effective boundary. It is described as being selectively permeable, which means that some molecules are able to travel across the membrane easily, other molecules have an intermediate ability to cross, and other molecules are completely incapable of passing. Generally, gases and molecules of water are able to pass through the cell membrane easily. Large molecules like glucose, and charged molecules like ions or amino acids, are unable to pass across the membrane.

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.

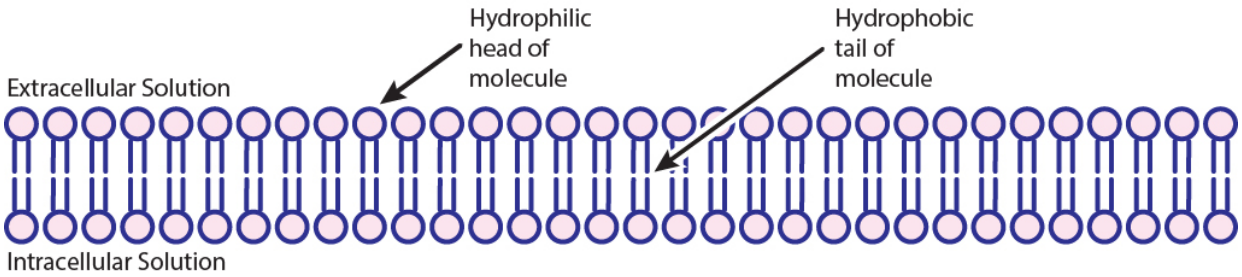

Figure 5.1. The neuronal membrane is composed of two layers of phospholipid molecules that form a barrier to water and water-soluble molecules due to the organization of the hydrophilic heads and hydrophobic ends of the molecules. 'Phospholipid Bilayer' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Ion Channels Allow Ion Movement

Most cells of the body, including neurons, have specialized transmembrane proteins embedded in the cell membrane. These transmembrane proteins are huge protein complexes that span the entirety of the membrane, with an outer side and an inner side. In the middle of the protein is a pore, which is essentially a "tunnel" that allows molecules and ions to pass across the cell membrane. These proteins are called **ion channels**. These channels are passive since they do not use any cellular energy to move ions. Rather, they simply provide easy passage for ions. It may be useful to think of an ion channel as a "cellular door". **Ion channels** are embedded throughout the neuronal membrane.

Channels can be opened and closed in a number of different ways. We can categorize ion channels into four major classes based on their opening and closing conditions.

1. **Leak channels** are persistently open. You can think of these leak channels as revolving doors that are never locked. Neurons usually have several leak channels.
2. **Voltage-gated ion channels** open in response to a change in membrane potential.
3. **Ligand-gated ion channels** open in response to chemical (ligand) binding, such as neurotransmitters.
4. **The fourth class of ion channels is a catch-all category that includes a wide variety of channels that are used by the sensory systems.** They open and close in response to unique stimuli depending on what they are able to sense. For example, some open and close depending when they are moved physically, such as a distortion or stretch (**mechanoreceptors**). We have these in the hair cells of our ears, in our skin, and in our muscles. **Photoreceptors** in our eyes

have ion channels that close in response to being hit by photons of light, and this activity is necessary for us to be able to see in both brightly and dimly lit environments.

One important feature of ion channels is their ability to distinguish ions based on their chemical properties. For example, some channels are selective for Na+, while preventing the passage of all other ions. Each ion channel has special molecular characteristics that allow certain types of ions to pass through the pore while excluding other ions. Channels can be specific to one ion or allow the flow of multiple ions.

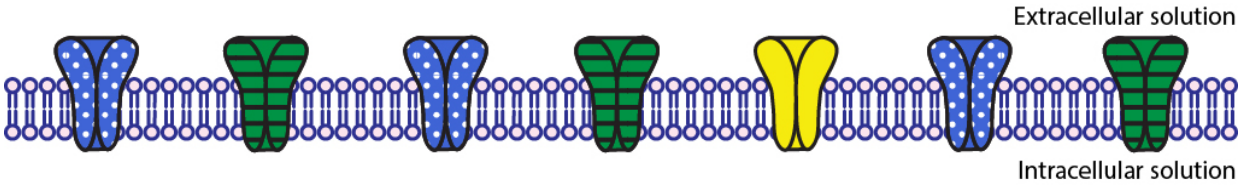

Figure 5.2. The phospholipid bilayer with embedded ion channels. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Membrane with Channels' by Casey Henley is licensed under a Creative 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.

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Animation 5.1. 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

Gradients Drive Ion Movement

Ions move in predictable ways. Concentration (chemical) and electrical gradients drive ion movement. The **chemical gradient** refers to the natural process by which a high concentration of a substance, given enough time, will eventually diffuse to a lower concentration and settle evenly over the space. 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. The **electrical gradient** refers to the electrical forces acting on charged molecules, "pulling" opposite charges together while also "pushing" like charges away from one another—just like the polarity of magnets. 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.

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Animation 5.2. 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.

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Animation 5.3. 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 licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View static image of animation.

Important Ions for Neurons

Sodium, potassium, and chloride ions are found in different concentrations across the neuron cell membrane. The location of these ions across the cell membrane and their concentration gradients are important for the function of the neuron. Sodium (Na+) ions are more concentrated in the extracellular fluid and less concentrated within the intracellular fluid. Whereas potassium (K+) ions are more concentrated within the intracellular fluid and less concentrated in the extracellular fluid.

Table 5.1. Concentrations of sodium, potassium, and chloride inside and outside of the cell.

Ion	Inside concentration (mM)	Outside concentration (mM)
Sodium (Na+)	15	145
Potassium (K+)	125	5
Chloride (Cl-)	13	150

Key Takeaways

- 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)

Test Yourself!

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6.

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 (also called the ground electrode) is placed in the extracellular solution. The recording electrode is inserted into the **cell body** of the neuron.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

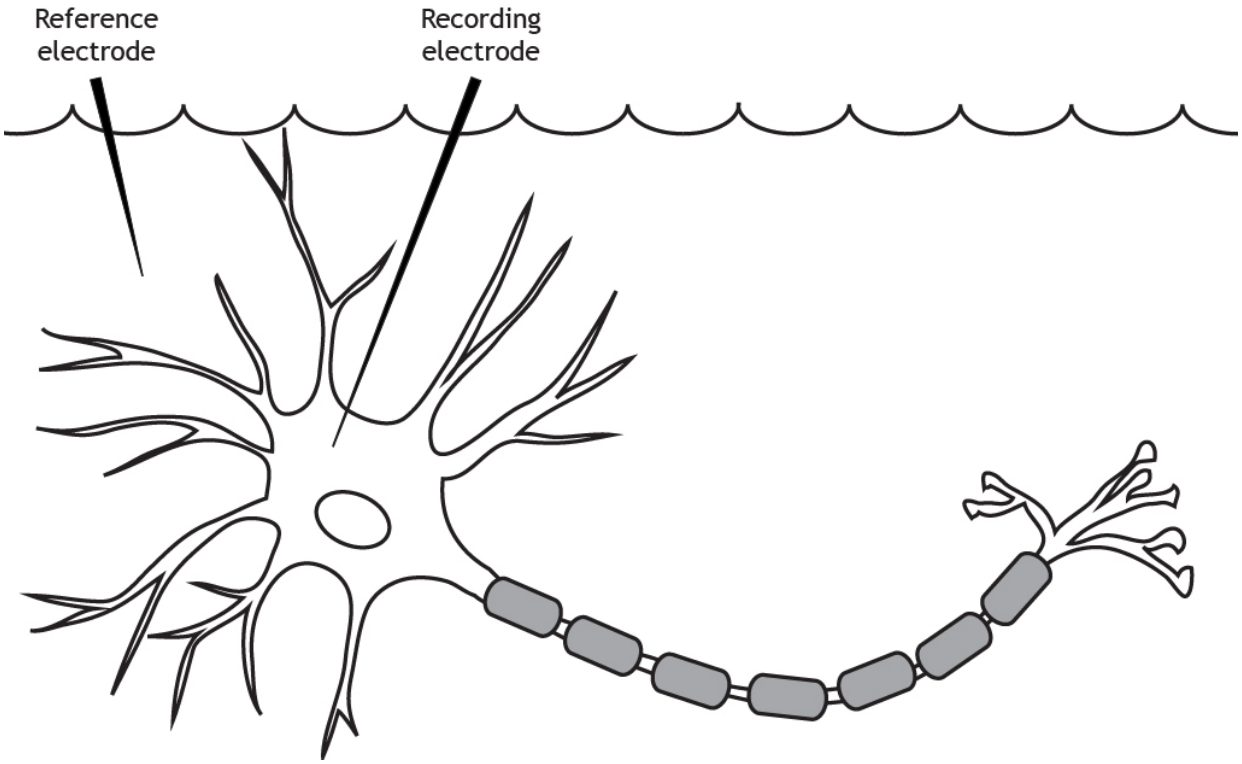

Figure 6.1. The membrane potential is measured using a reference electrode placed in the extracellular solution and a recording electrode placed in the cell soma. The membrane potential is the difference in voltage between these two regions. 'Measuring Membrane Potential' by Casey Henley is licensed 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. The membrane potential is measured as the difference in charge between the outside of the cell and the inside of the cell. 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, or gets more negative than it was at rest, that is a **hyperpolarization** because the membrane is becoming more polarized. This is also referred to as an increase in membrane potential.

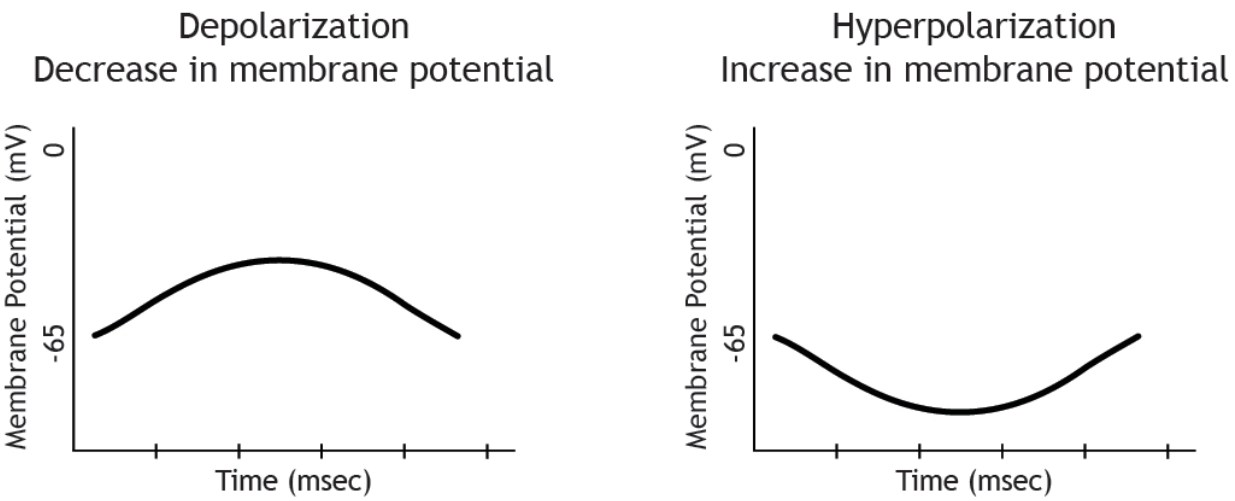

Figure 6.2. A decrease in membrane potential is a change that moves the cell's membrane potential toward 0, or depolarizes the membrane. An increase in membrane potential is a change that moves the cell's membrane potential away from 0 or hyperpolarizes the membrane. 'Membrane Potential Terms' by Casey 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.

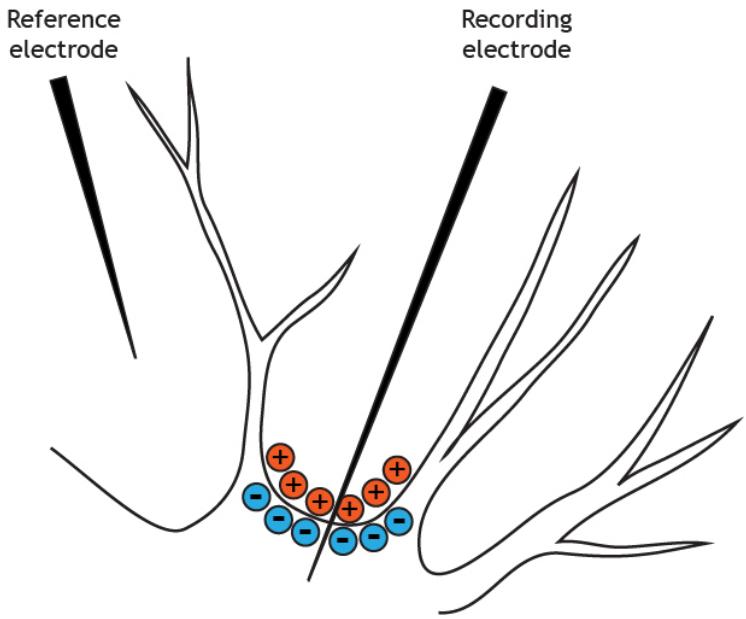

Figure 6.3. The inside of the neuron has a more negative charge than the outside of the neuron. 'Membrane Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

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.

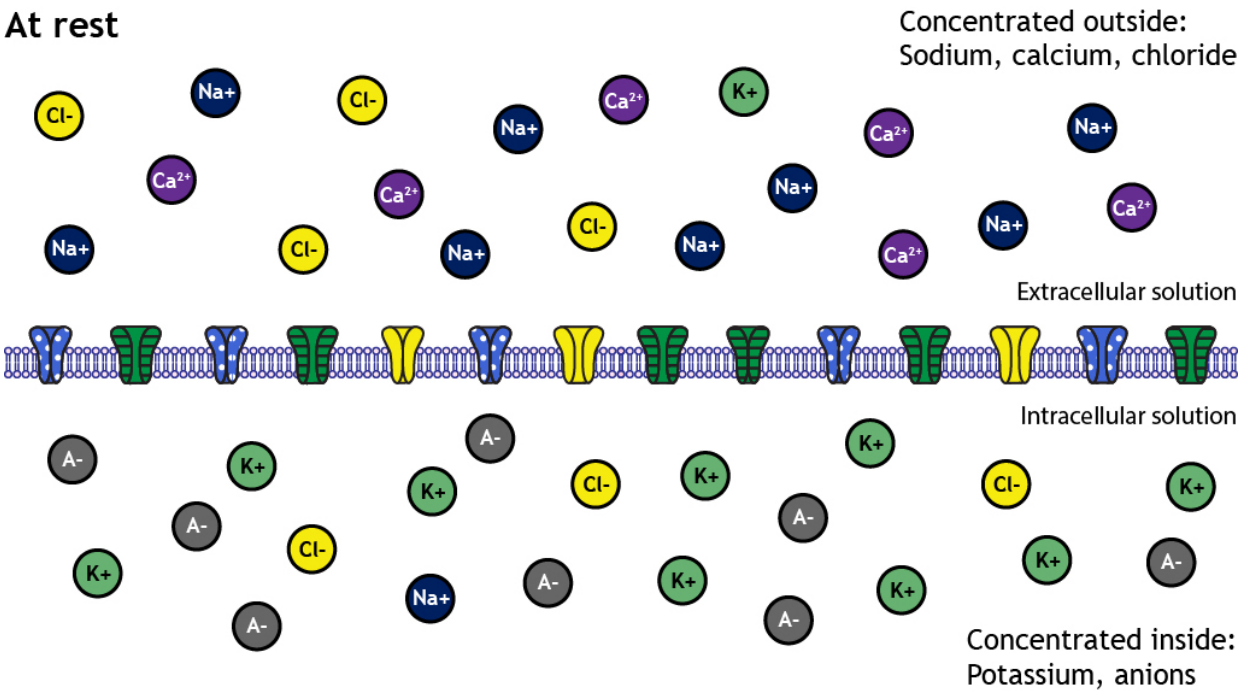

Figure 6.4. For a typical neuron at rest, sodium, chloride, and calcium are concentrated outside the cell, whereas potassium and other anions are concentrated inside. This ion distribution leads to a negative resting membrane potential. The dotted, blue channels represent sodium leak channels; the striped, 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.

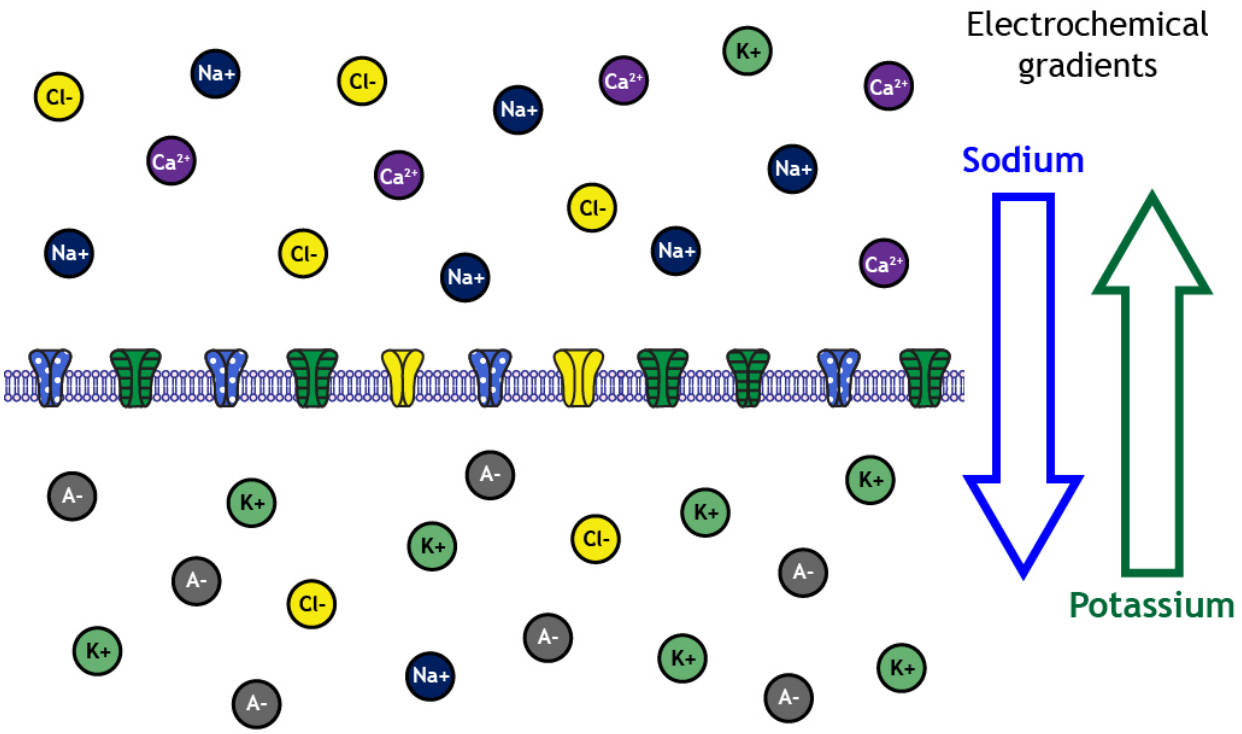

Figure 6.5. The distribution of ions on either side of the membrane lead to electrochemical gradients for sodium and potassium that drive ion flow in different directions. If the membrane is permeable to sodium, ions will flow inward. If the membrane is permeable to potassium, ions will flow outward. 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:

Example: Driving Forces on Sodium Ions

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** of an ion, which is approximately +60 mV for sodium.

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Animation 6.1. 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

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**:

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

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

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

An Example: Sodium's Equilibrium Potential

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

For Sodium:

z = 1

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

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

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

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.

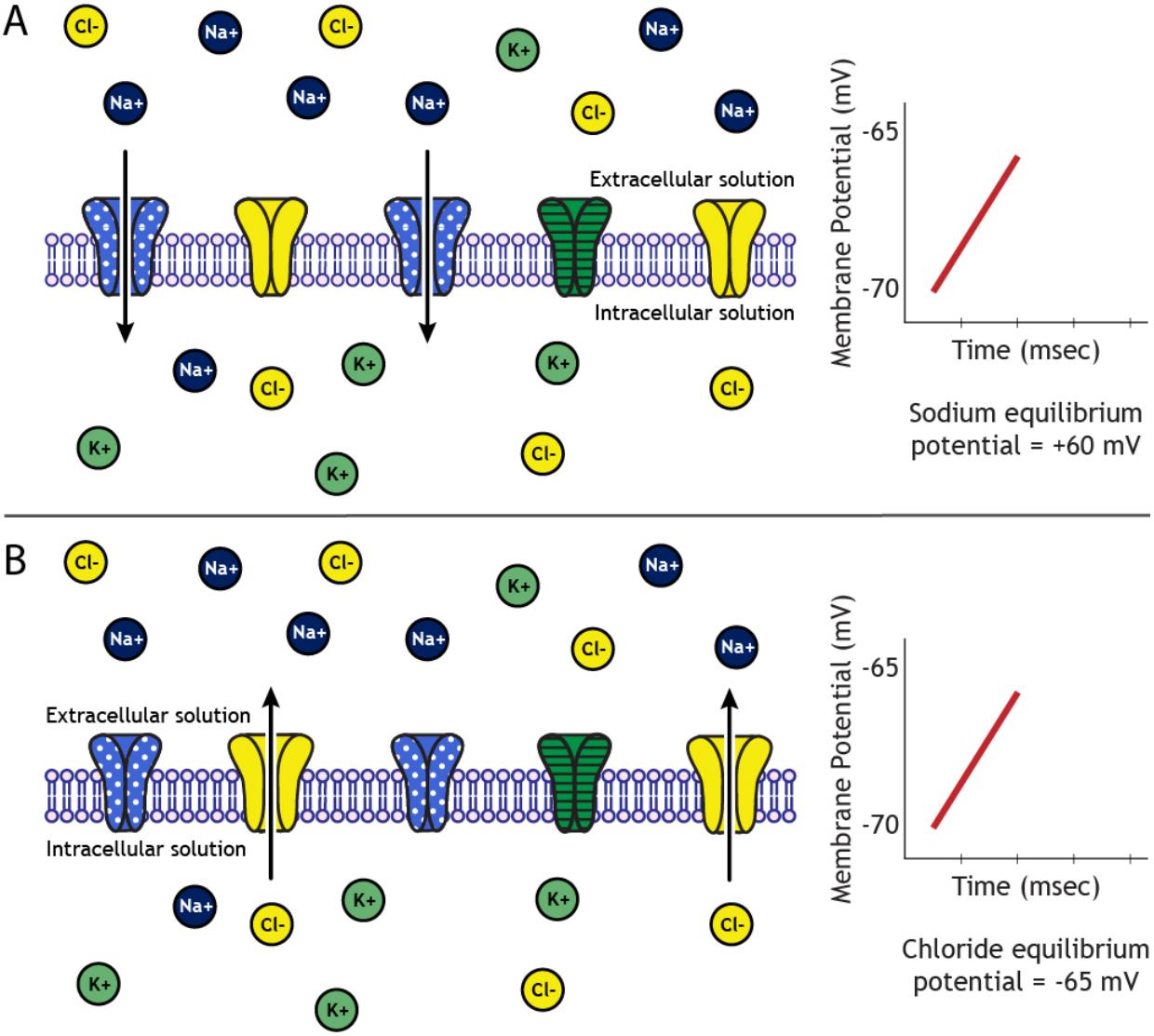

Figure 6.6. A) If a cell is at rest at -70 mV, sodium ions will flow into the cell to move the cell's membrane potential toward sodium's equilibrium potential of +60 mV. B) At the same resting membrane potential, chloride would flow out of the cell, taking away its negative charge, making the inside 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.

Concentration and Equilibrium Potential Values

We will use the following ion concentrations and equilibrium potentials:

Table 6.1. Typical ion concentrations inside and outside of the Neuron and the equilibrium potential for each ion.

Ion	Inside concentration (mM)	Outside concentration (mM)	Equilibrium Potential
Sodium (Na+)	15	145	+60 mV
Potassium (K+)	125	5	-85 mV
Chloride (Cl-)	13	150	-65 mV

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!

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7.

THE MEMBRANE AT REST

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. The resting membrane potential of a typical neuron is around -65mV to -70mV, though it can vary.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

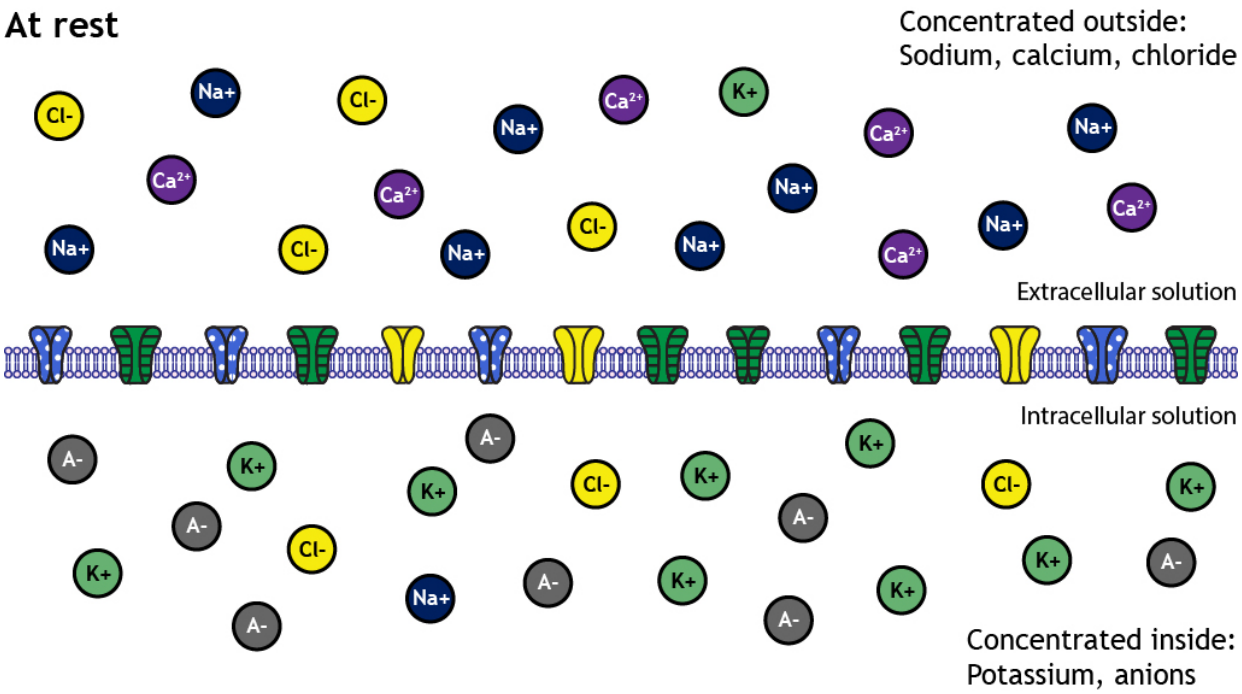

Figure 7.1. For a typical neuron at rest, sodium, chloride, and calcium are concentrated outside the cell, whereas potassium and other anions are concentrated inside. This ion distribution leads to a negative resting membrane potential. The dotted, blue channels represent sodium leak channels; the striped, 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.

Why is the Resting Membrane Potential -65 mV?

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.

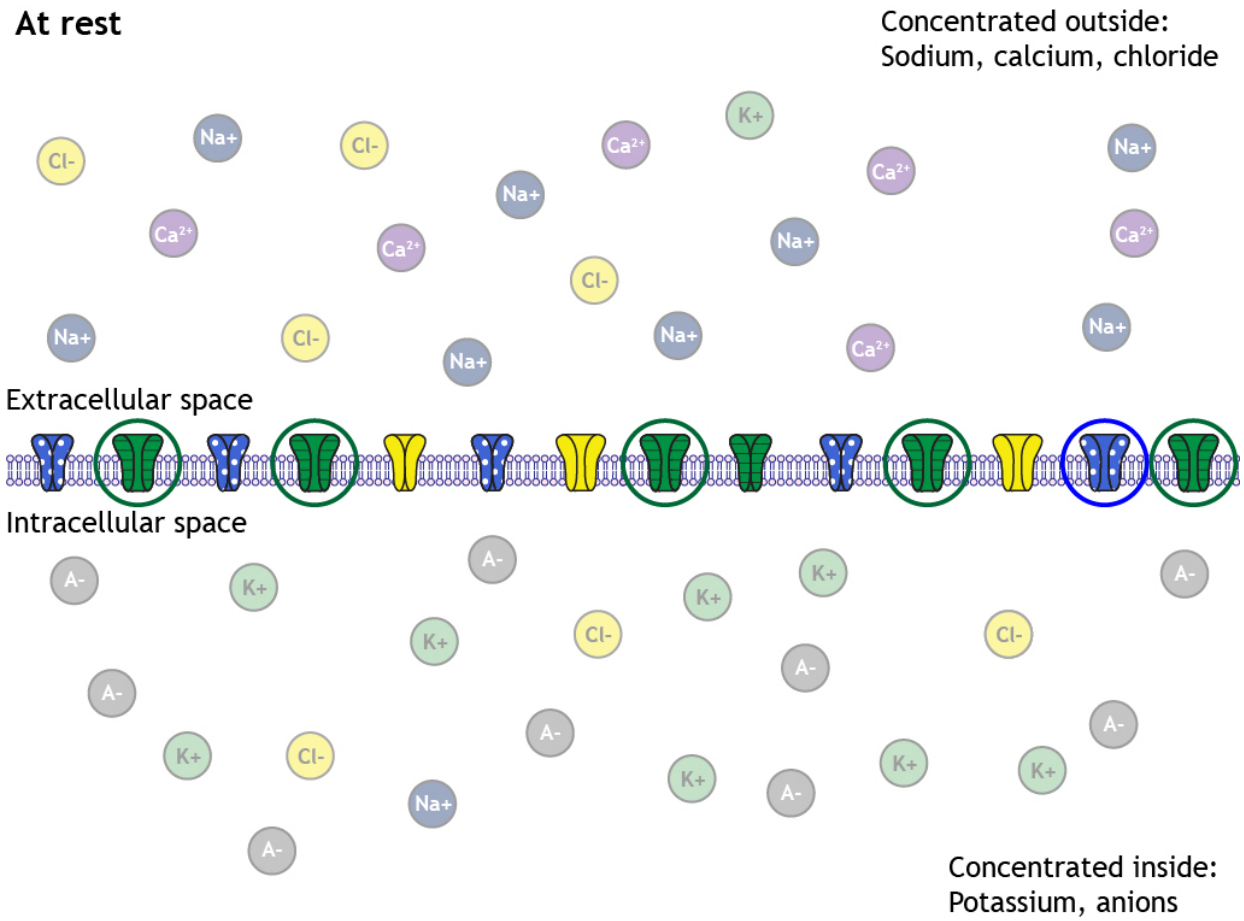

Figure 7.2. At rest, the distribution of ions across the membrane varies for different ions. Additionally, at rest, more potassium non-gated ion channels (emphasized by green circles) are open than sodium channels (emphasized by the blue circle). The dotted, blue channels represent sodium leak channels; 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.

1. Potassium Can Cross Membrane at Rest through Leak Channels

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.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=44#video-44-1

Animation 7.1. 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.

Resting Membrane Potential Value

The resting membrane potential of a neuron is typically around -65mV to -70mV (but can vary quite a bit). 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 open non-gated potassium channels were the only structural ion flow element present in the cell membrane, the membrane potential would eventually reach potassium's equilibrium potential. However, the membrane has other open non-gated ion channels as well. Although, there are fewer of these channels compared to the potassium channels. The permeability of chloride is about half 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.

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Animation 7.2. The membrane at rest is most permeable to potassium and this leads to potassium efflux. However, the membrane is also permeable to chloride and sodium, so the flow of these ions keeps 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.

2. Intracellular Anions

There are negatively charged anions trapped within the cell that contribute to the negative intracellular charge when compared to the extracellular charge.

3. Activity of the Sodium/Potassium Pump

It is critical the ion gradients that exist across the membrane be maintained for proper neuronal function.

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. The pump is removing three positively

charged ions from inside the cell and adding two positively charged ions. This leaves the inside of the cell always more negative than the outside of the cell.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=44#video-44-3*

Animation 7.3. 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

Importantly, **membrane potential** is affected by all of the ions that exist around the membrane. 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

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

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

P_{ion} is the relative permeability of each ion

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

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

Example: The Neuron at Rest

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

[table id=2 /]

$$V_m = 61 * \log \frac{1[5] + 0.04[145] + 0.4[13]}{1[125] + 0.04[15] + 0.4[150]} = -65mV$$

Potassium Levels Must be Regulated within the Brain

Clearly, potassium levels must be tightly regulated due to the permeability of potassium for the neuronal membrane. Due to the importance of maintaining appropriate potassium levels, the brain has a specialized structure called the **Blood Brain Barrier** that helps to maintain proper extracellular potassium in the brain by limiting the amount of potassium that can move from capillaries into the brain. Without the blood brain barrier, eating foods that are high in potassium, like a banana, could completely halt the function of your brain!

Typically, capillaries are very leaky vessels, allowing a variety of different nutrients and waste products to pass between the capillaries and the body tissues. The capillaries in the brain, however, are surrounded by astrocytes (a type of glia that we learned about in Chapter 3). The addition of the astrocytes makes it more difficult for substances to pass between the blood and the brain tissue.

In addition to blocking the movement of potassium from the blood to the brain tissue, astrocytes also have potassium pumps in the astrocyte membranes that actively pump potassium out of the extracellular fluid and into the astrocytes to help regulate extracellular potassium levels. This is called potassium buffering.

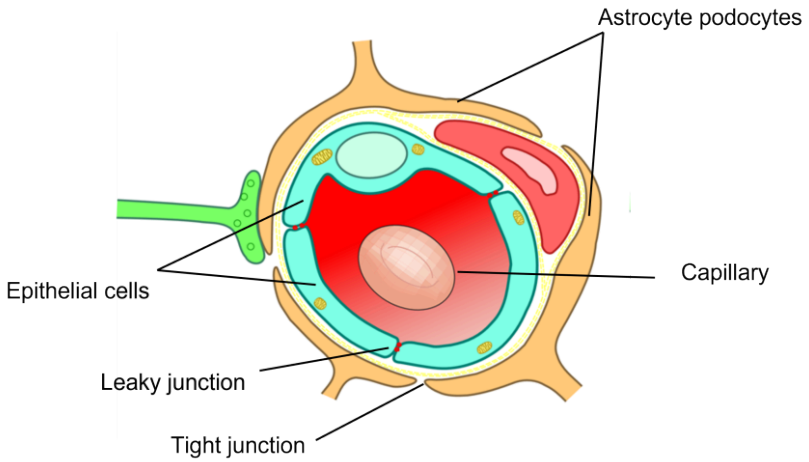

Figure 7.3. Blood Brain Barrier. Capillary vessels are typically lined with epithelial cells wtih leaky junctions between adjacent cells that allow for transfer of substances between circulation and the body tissues. Within the brain, astrocyte podocytes (feet) surround the capillaries, forming tight junctions that provide another barrier to the movement of substances between circulation and neural tissues. This blood brain barrier restricts the movement of many different things to help keep the solution surrounding the brain cells fairly consistent, which is especially important in maintaining potassium concentration.

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
- The membrane potential can be calculated by knowing the concentrations of each ion inside and outside the cell membrane and the permeabilities of each ion

Test Yourself!

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8.

ELECTRICAL ACTIVITY IN NEURONS

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

The membrane potential will always fall into one of the following categories:

1. Resting membrane potential
2. Graded Potentials (postsynaptic potentials)
3. Action potentials

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 through **action potentials** 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 (Graded Potentials)

Postsynaptic potentials (also called graded 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.

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Animation 8.1. 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.

Depolarization: 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.

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Animation 8.2. 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.

Hyperpolarization: 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, the electrochemical gradients drive chloride to flow into the cell when chloride channels open. 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 make this ion flow **inhibitory**. Therefore, an IPSP is an inhibitory change in the membrane potential of a postsynaptic neuron.

An IPSP can also be caused by the opening of potassium channels. The equilibrium potential of potassium is -80 mV, so if the neuron is at rest at -60mV, the electrochemical gradients drive potassium out of the cell when potassium channels open. As positively charged potassium ions leave the cell, this causes the cell's membrane potential to **hyperpolarize**. This demonstrates the importance of the equilibrium potential in driving ion movement.

Like an EPSP, an IPSP is also typically brief, and the membrane potential will return to rest if no additional stimulation occurs.

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Animation 8.3. 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; 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 8.4. 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 potassium or chloride channels is typically inhibitory.

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Animation 8.5. If the cell is at rest at chloride's equilibrium potential, chloride will leave the cell when a stimulus opens the chloride channels, 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 8.6. 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-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

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 a single excitatory input occurs.

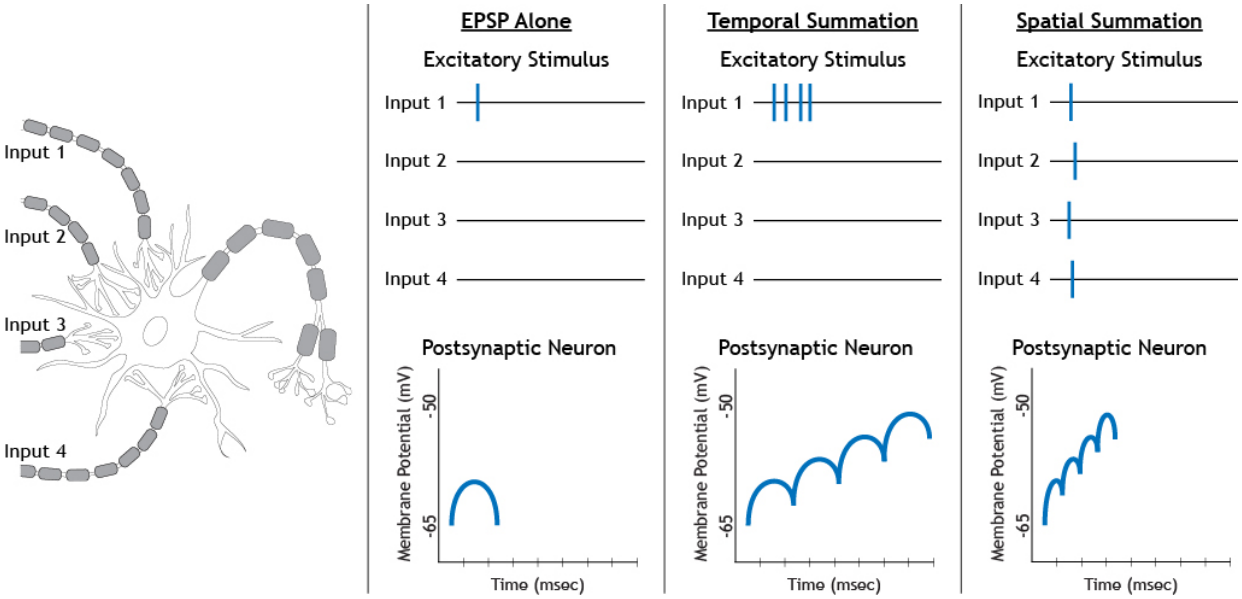

Figure 8.1 EPSPs can summate via temporal or spatial summation. Temporal summation occurs when a presynaptic neuron, Input 1 in the figure, stimulates the postsynaptic neuron multiple times in a row. Spatial summation occurs when more than one presynaptic neuron (inputs 1 through 4 in the figure) each 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.

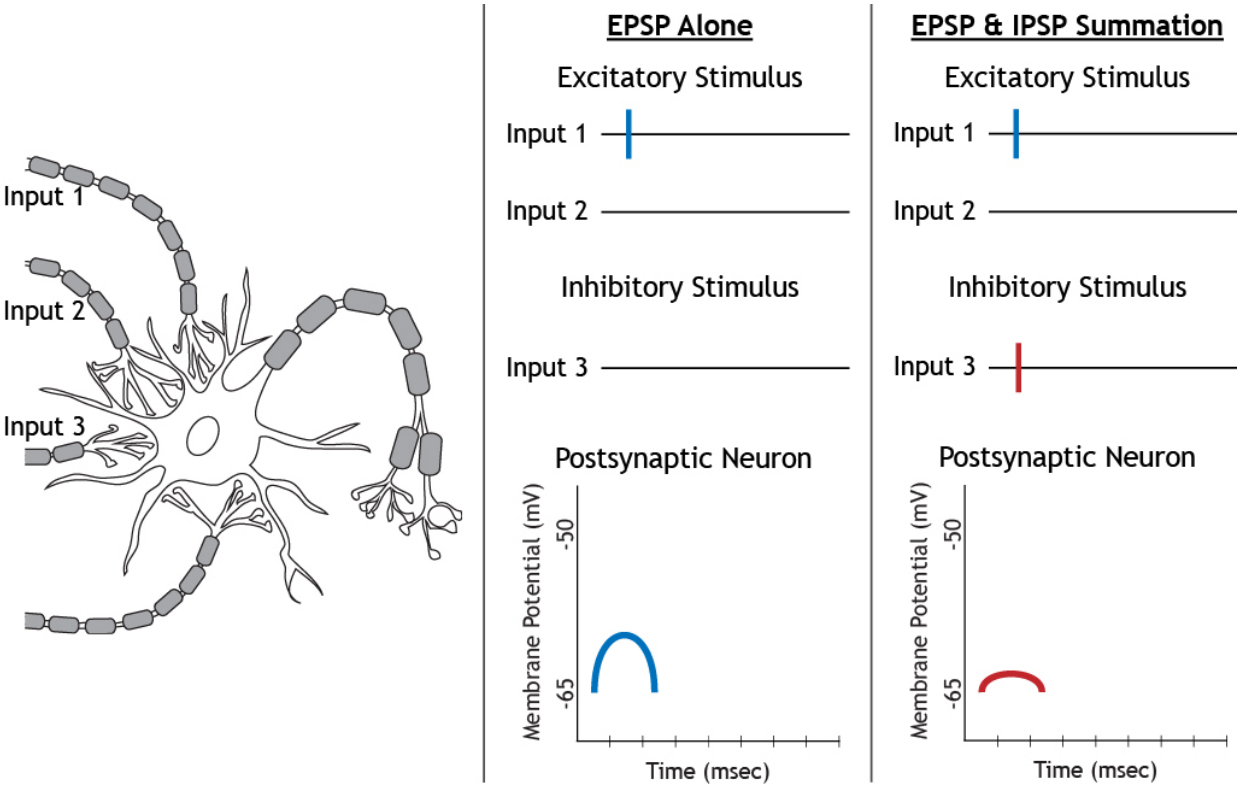

Figure 8.2. If an inhibitory input (input 3 in the figure) stimulates the postsynaptic neuron at the same time as an excitatory input (input 1 in the figure), the result is a decrease in the amount of depolarization or the complete prevention of depolarization depending on the strength of the inhibitory 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).

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Animation 8.7. 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.

Key Takeaways

- 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

Test Yourself!

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9.

ACTION POTENTIALS

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

As covered in previous chapters, 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.

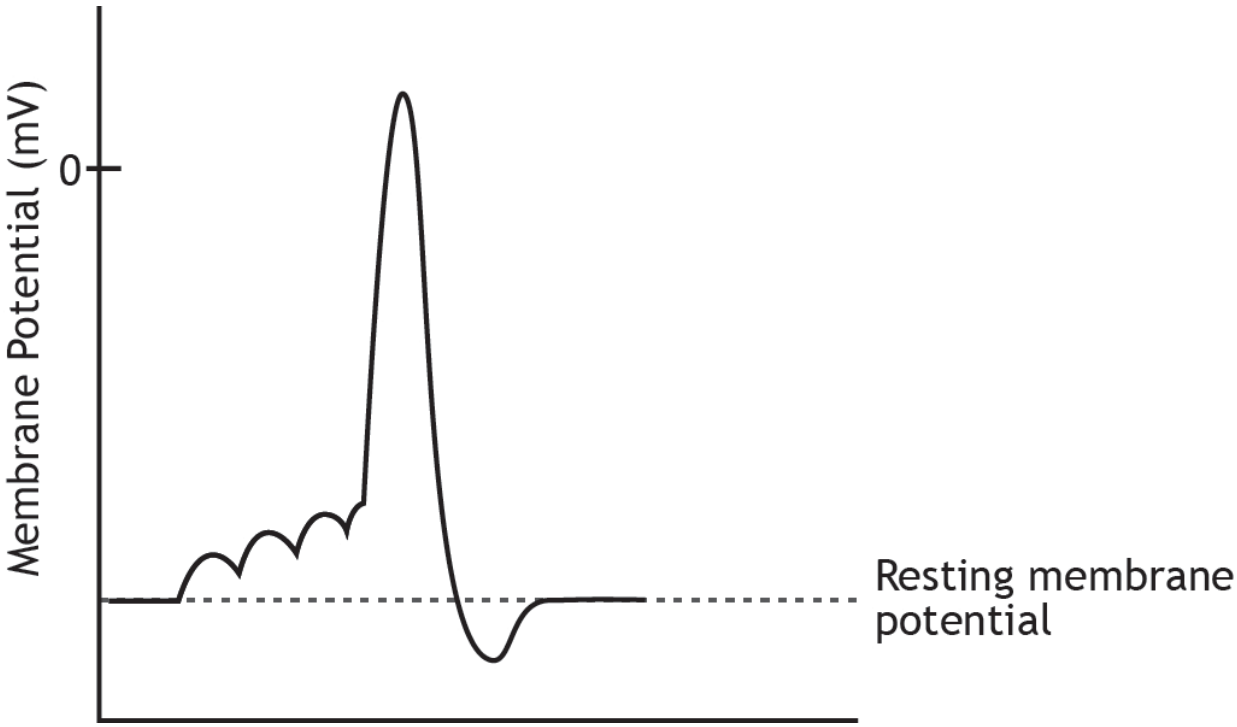

Figure 9.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will begin at a negative resting membrane potential, will rapidly become positive, and then rapidly return to rest during an action potential. 'Action Potential' by Casey 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 the release of chemical neurotransmitters that communicate with a postsynaptic neuron.

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Animation 9.1. 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 is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

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.

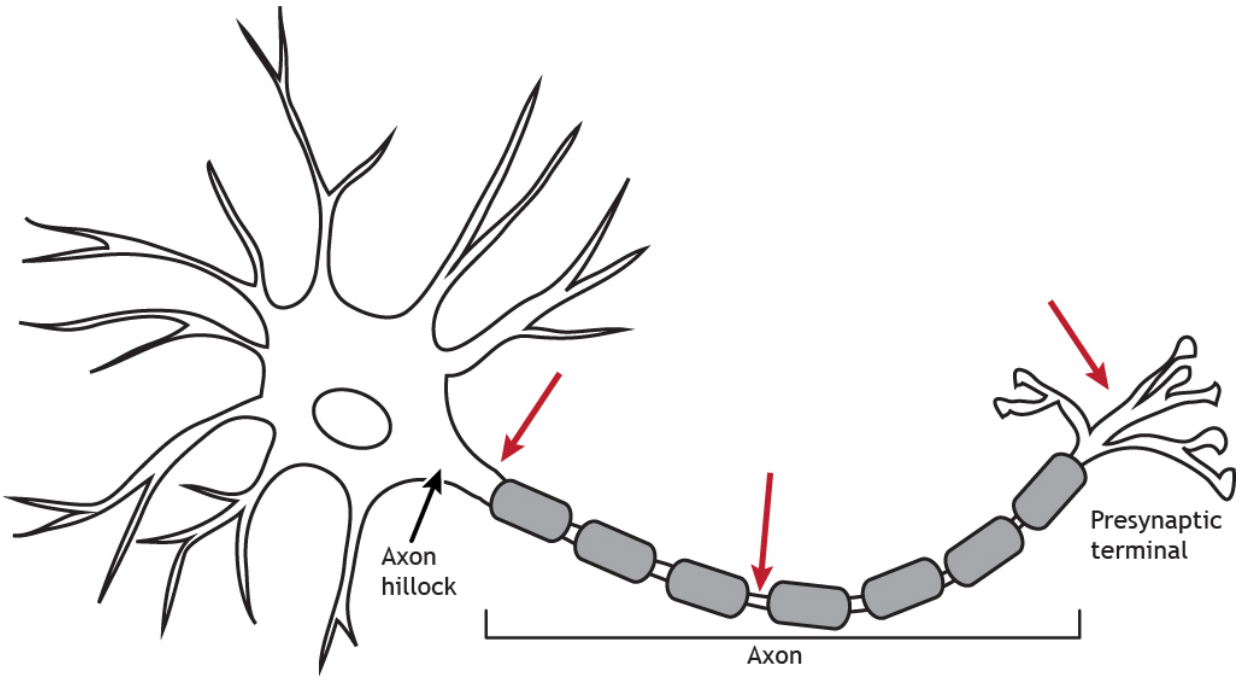

Figure 9.2. Voltage-gated channels critical for the propagation of the action potential are located at the axon hillock, down the axon at the Nodes of Ranvier, and in the presynaptic terminal. 'Voltage-Gated Channel Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial 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 **EPSP**s summate together.

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Animation 9.2. 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.

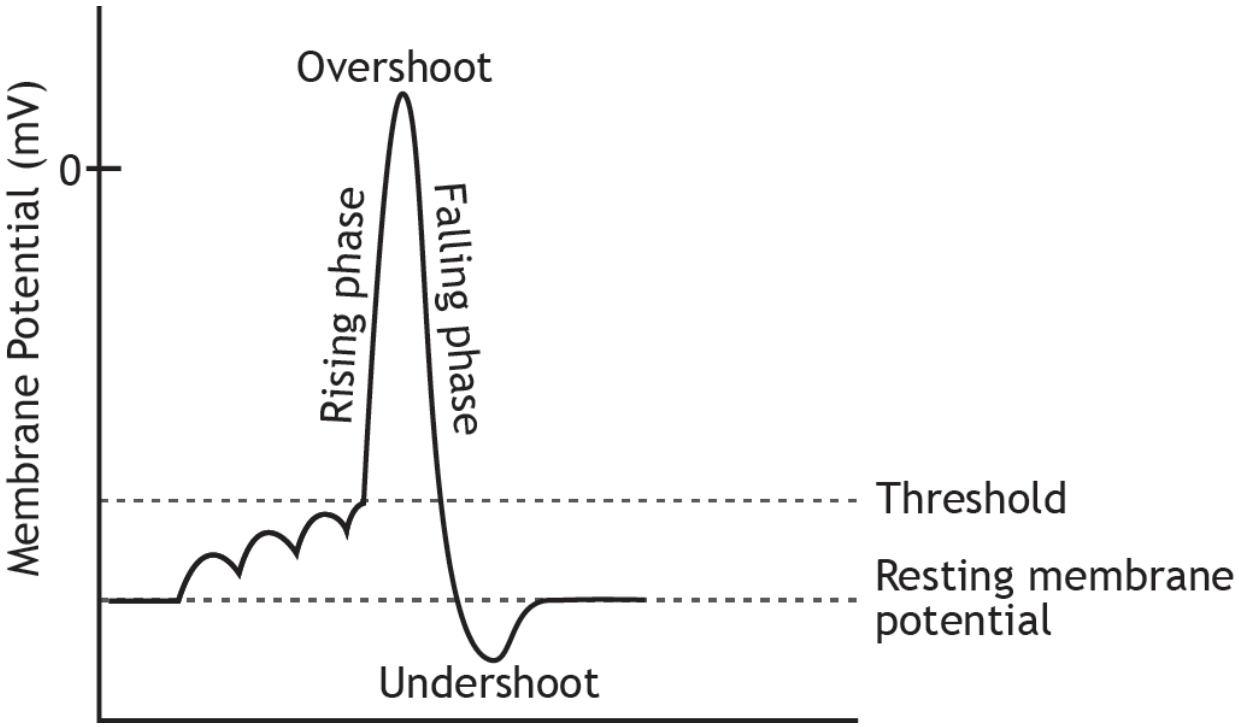

Figure 9.3. EPSPs that summate to reach threshold initiate the action potential. The depolarizing rising phase moves the membrane potential from threshold to above 0 mV. The overshoot is the peak of the action potential where the membrane potential is positive. The falling phase repolarizes the membrane potential, and the undershoot takes the membrane potential more negative than the resting membrane potential. After the undershoot, the membrane potential returns to rest. 'Action Potential Phases' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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, opening immediately. The electrochemical gradients drive sodium into the cell causing the depolarization.

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Animation 9.3. 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, which returns the cell's membrane potential 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.

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Animation 9.4. 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 chloride channels. 'Falling 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.

Undershoot

As the membrane potential returns to resting level, the sodium channels will de-inactivate, returning to the closed position, ready to be opened again by another voltage change. 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.

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Animation 9.5. 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 9.6. 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 licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Refractory Periods

The Absolute Refractory Period

Each neuron does have a maximum firing rate. 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. 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 during the undershoot, voltage-gated potassium channels are still open. During the undershoot, 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.

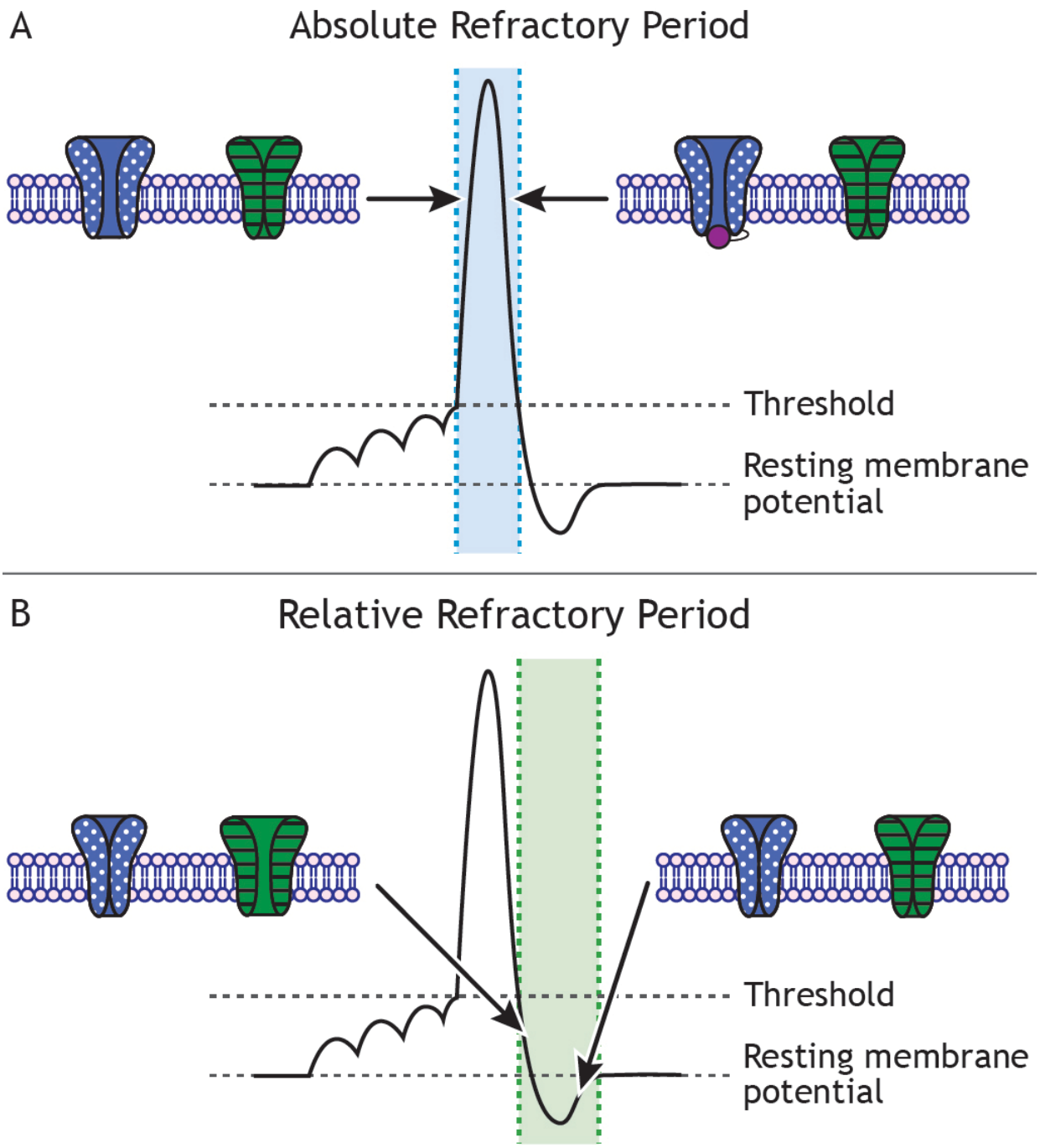

Figure 9.4. The maximum firing rate of a neuron is determined by the refractory periods. A) During the absolute refractory period, no additional action potentials can be fired because the voltage-gated sodium channels are either already open (rising phase) or inactivated (falling phase). In these states, 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 open voltage-gated potassium channels cause a hyperpolarization of the membrane. After the potassium

channels close, it takes a short period of time for the membrane potential to return to rest. 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.

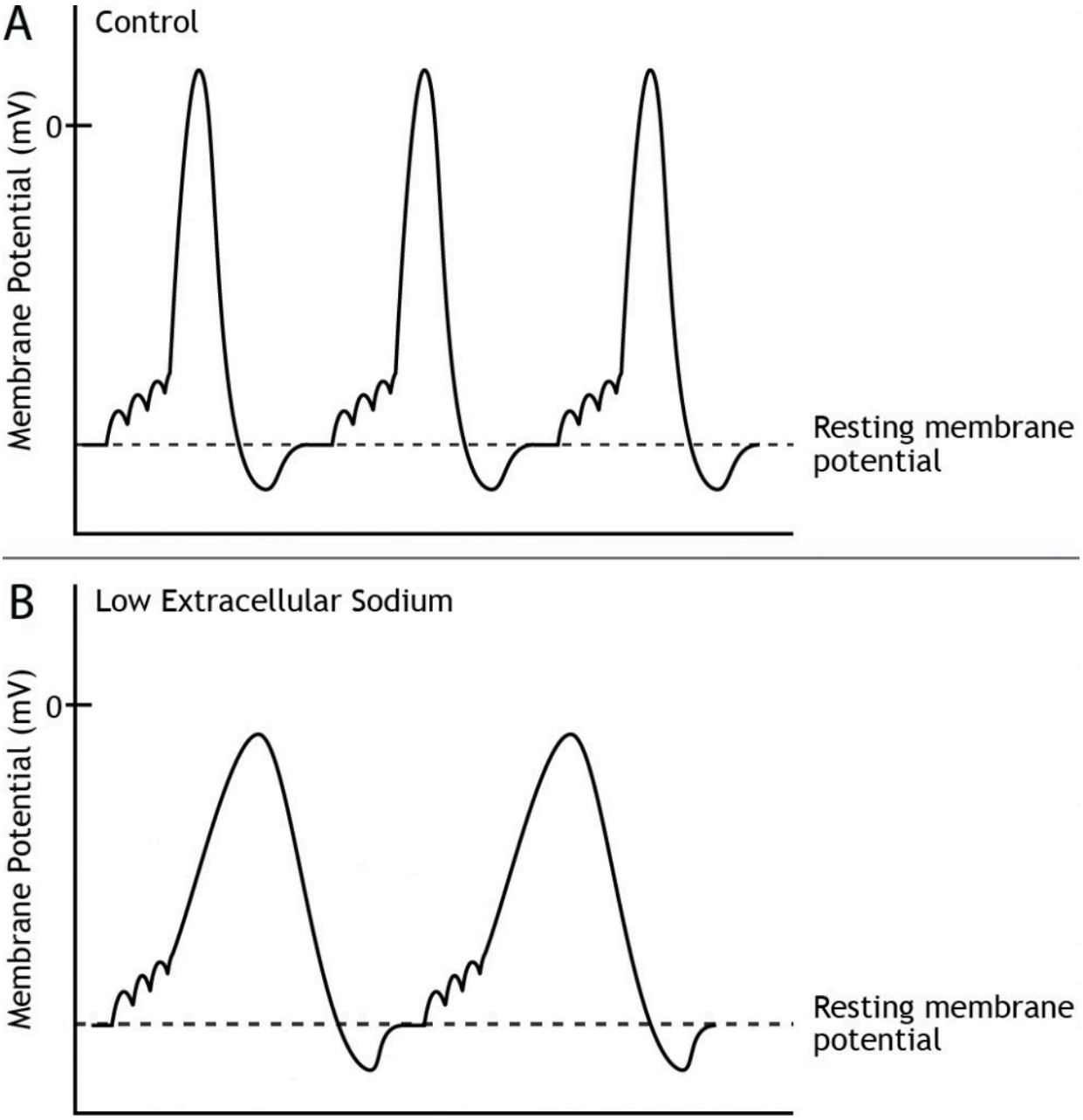

Figure 9.5. A) A neuron kept under the same conditions will display action potentials of similar height and length. B) However, if cellular conditions change, so will the action potential characteristics. If extracellular sodium levels are decreased compared to control levels, the action potential will 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.

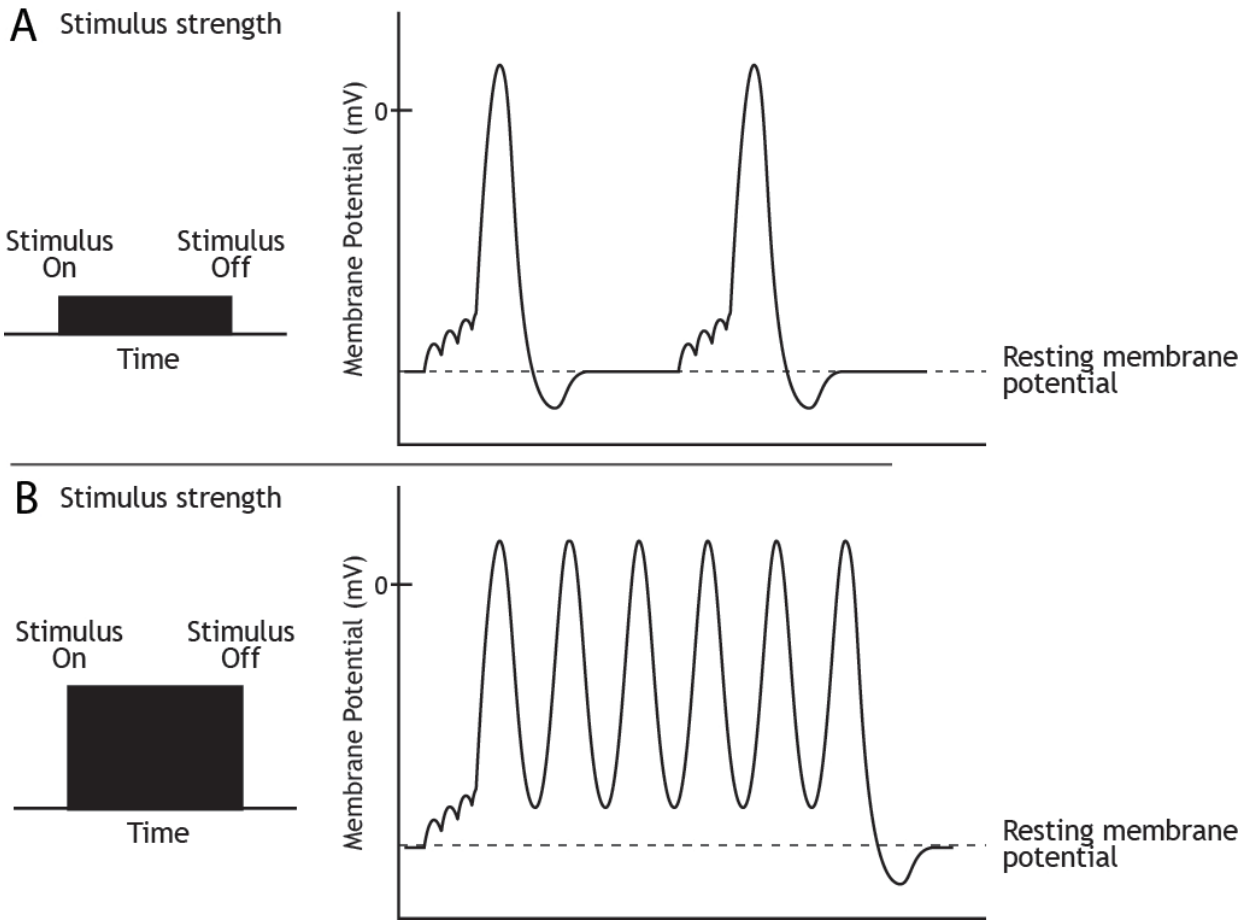

Figure 9.6. Information about the strength of a stimulus is encoded by the rate of action potential firing. A) A weak stimulus results in few action potentials being fired. B) A strong stimulus results in many action potentials firing in a row. 'Stimulus Strength' by Casey Henley is licensed under a 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 axon segments to threshold.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=57#video-57-7*

Animation 9.7. 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, 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.

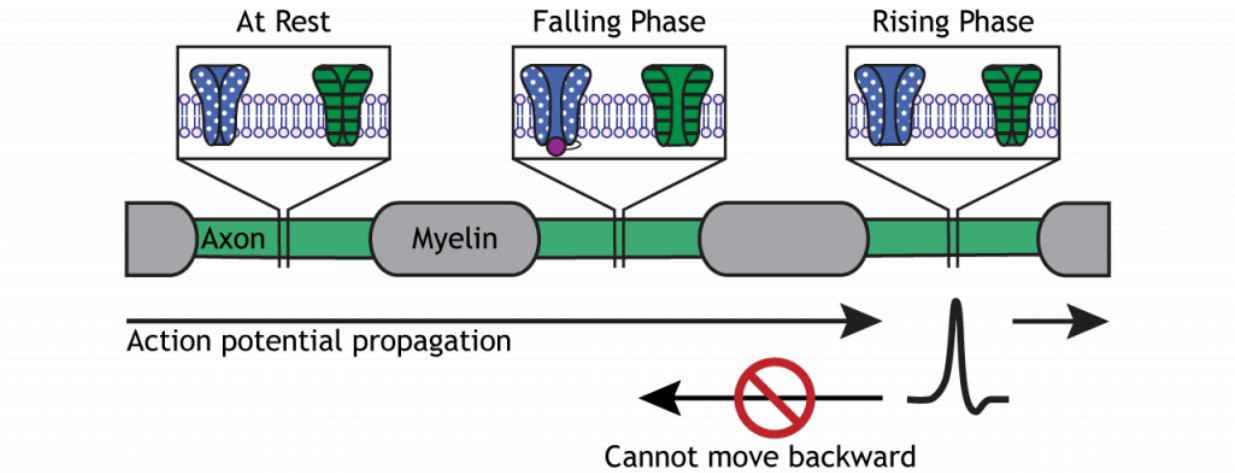

Figure 9.7. Action potentials only travel in one direction. The inactivated sodium channels prevent the action potential from moving backward down the axon. Blue dotted channels: sodium channels; green striped channels: potassium channels. The dotted, blue channels represent voltage-gated sodium channels; 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 additional 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.

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Animation 9.8. 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, 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 to cause the regeneration of the action potential in the next axon segment.

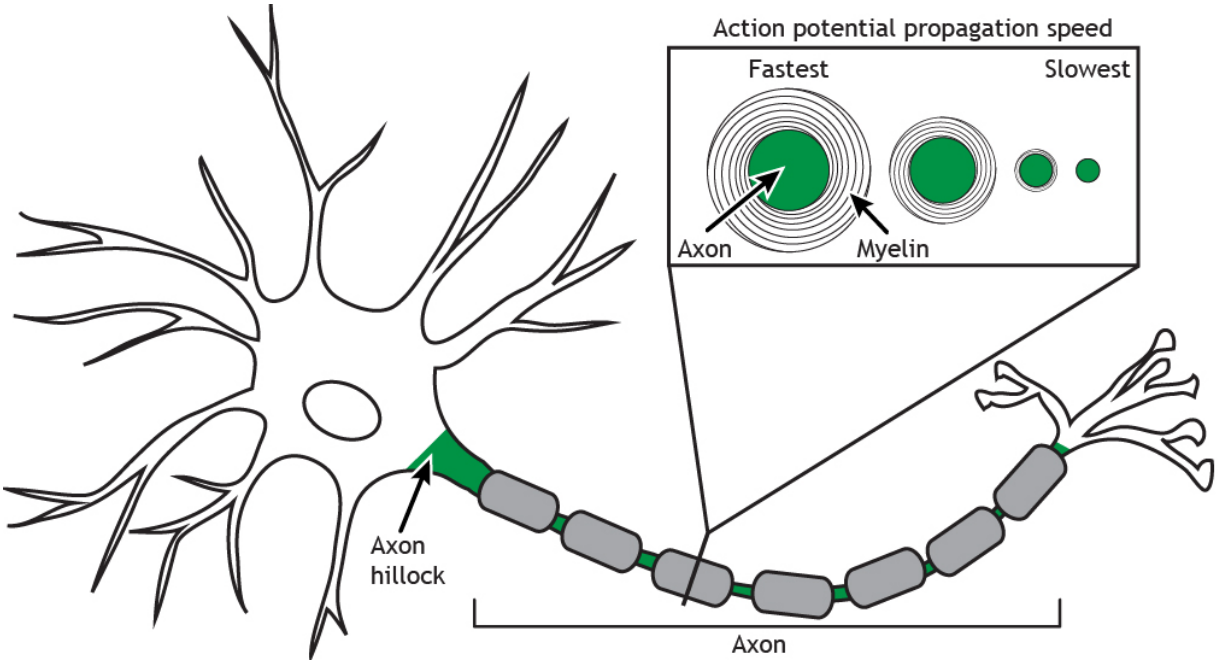

Figure 9.8. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. 'Axon Diameter' by Casey Henley 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!

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10.

VOLTAGE CLAMP

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

In the previous chapter, we covered ion flow and membrane potential changes that occur in the neuron during the action potential. 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.

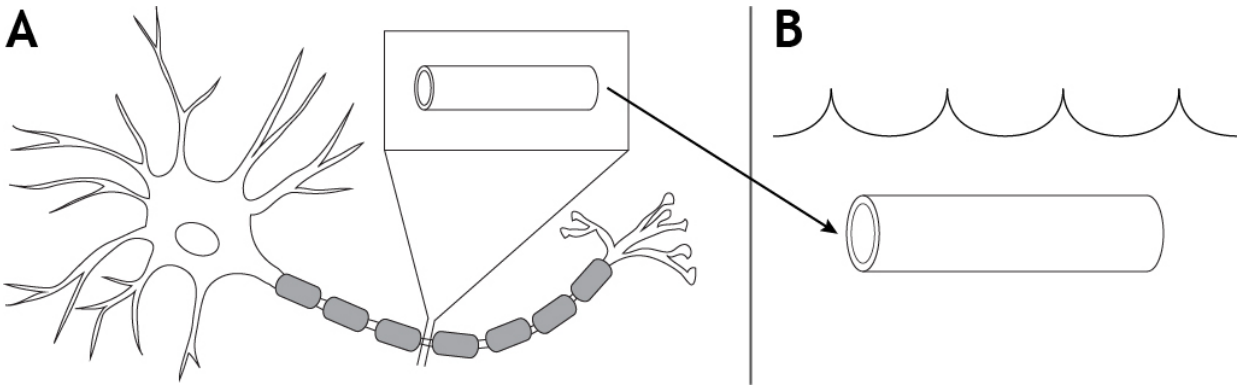

Figure 10.1. To conduct a voltage clamp experiment, a portion of the axon is removed from the neuron. The axon is placed in a special solution that is similar to physiological extracellular solution. 'In Vitro Axon' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (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 (or ground electrode) is placed into the extracellular solution. The voltage difference between these two electrodes is the membrane potential of the axon.

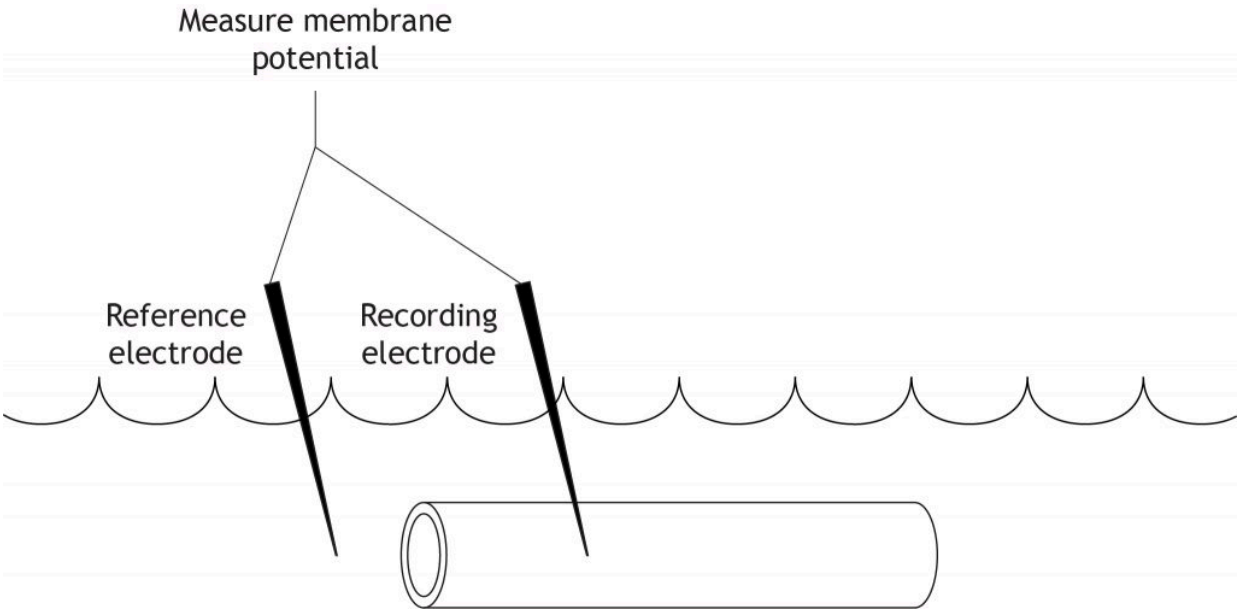

Figure 10.2. Measuring the membrane potential of the axon segment is the first step in the voltage-clamp experiment. The membrane potential is the difference in voltage between the intracellular recording electrode and the extracellular reference electrode. 'Measure Membrane Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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.

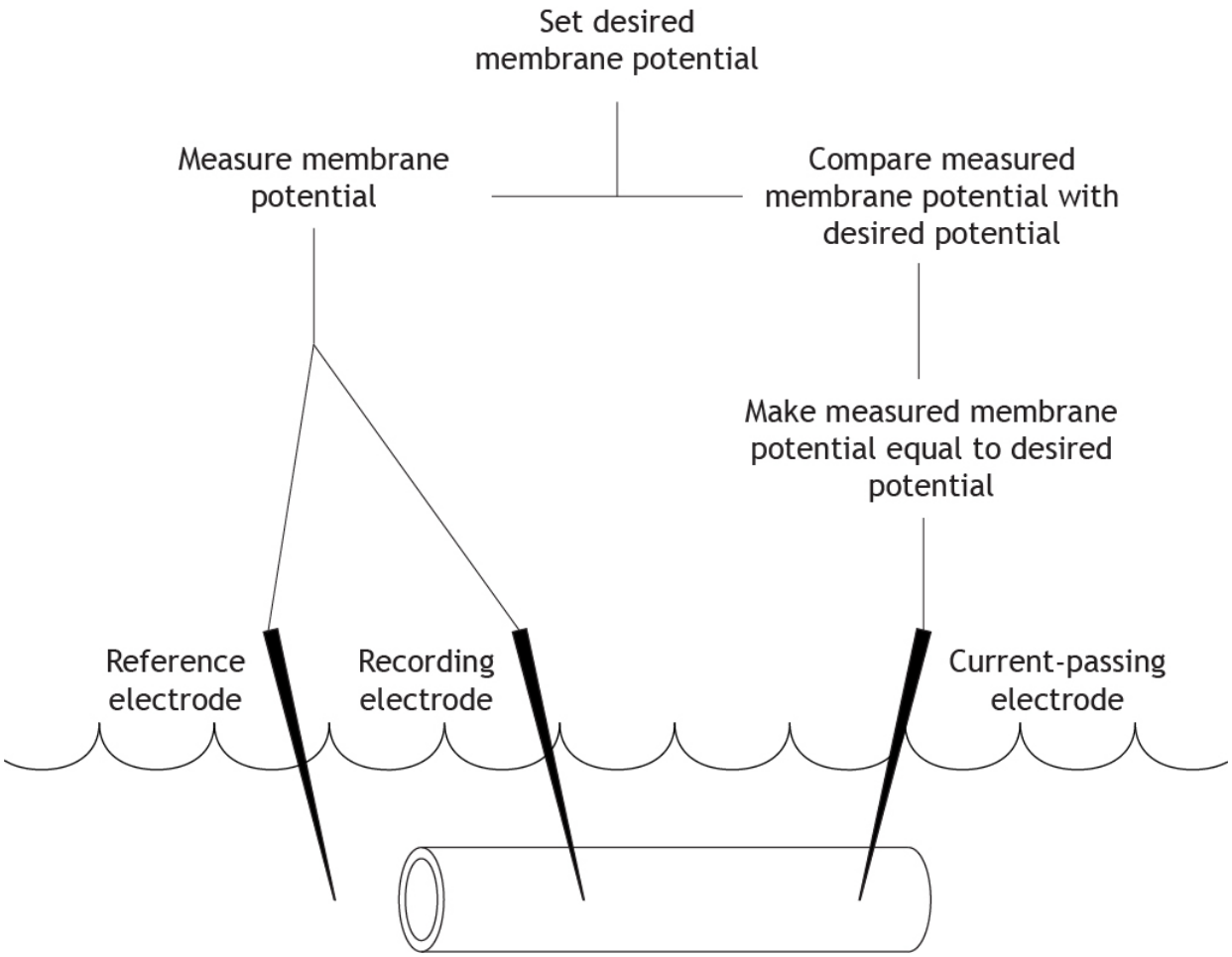

Figure 10.3. A desired membrane potential is set for the experiment. The voltage-clamp experimental equipment then compares the measured membrane potential with the desired potential. Current is then injected into the axon through a current-passing electrode to make the measured membrane potential equal to the desired potential. 'Clamping Voltage' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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.

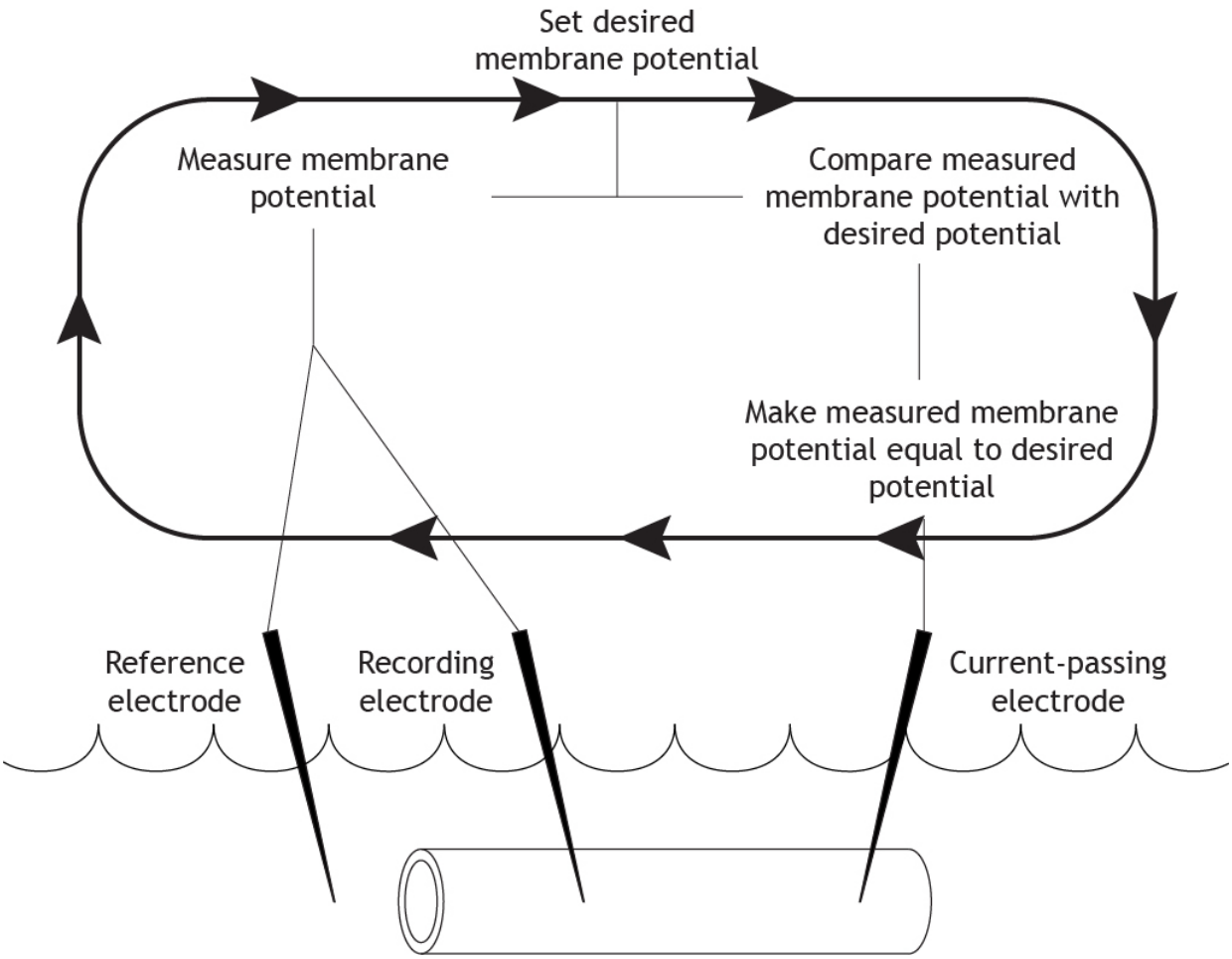

Figure 10.4. The voltage clamp cycle repeats continuously. The actual membrane potential of the axon is measured, compared to the set desired potential value, and then current is passed into the axon to keep the actual membrane potential equal to the desired potential. 'Voltage Clamp Cycle' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Voltage Clamp Experiment Example

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.

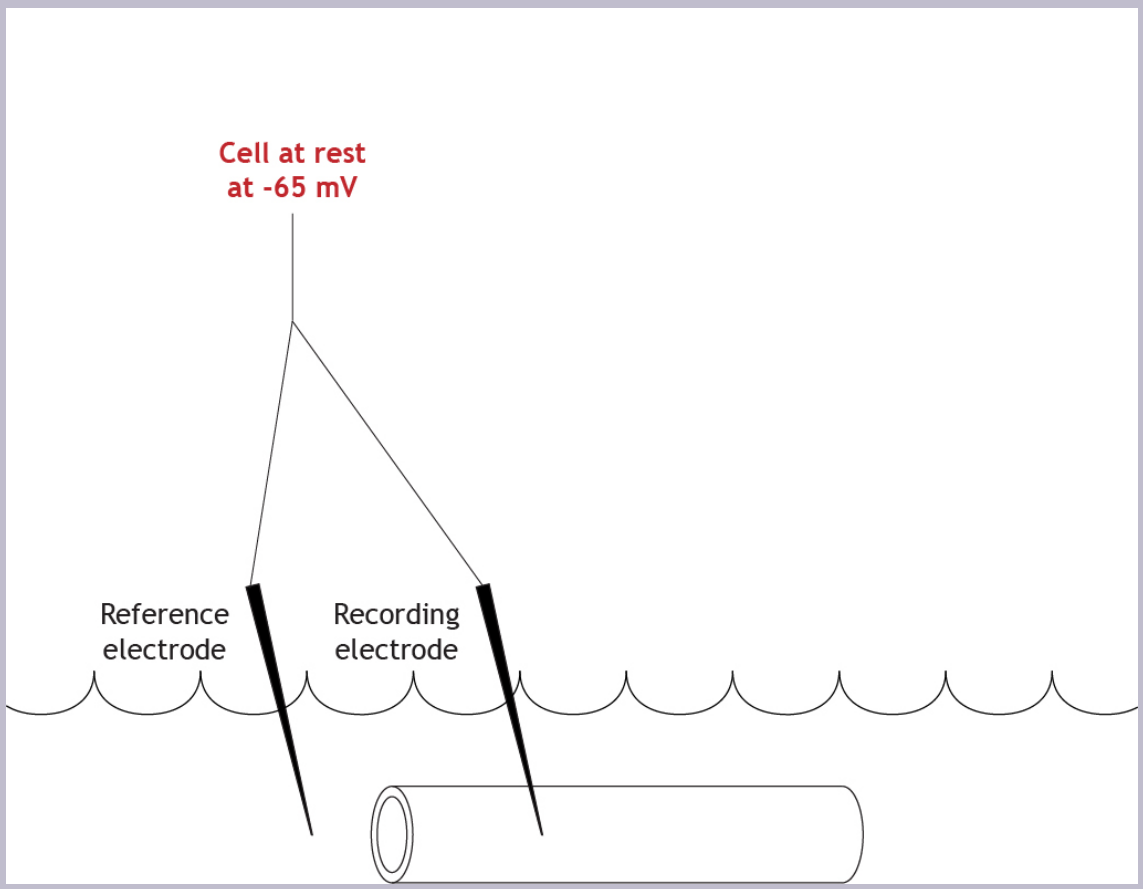

Figure 10.5. Measure the membrane potential. The membrane potential of this axon at rest is -65 mV. 'Voltage Clamp Example at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Set Clamped Membrane Potential Value

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

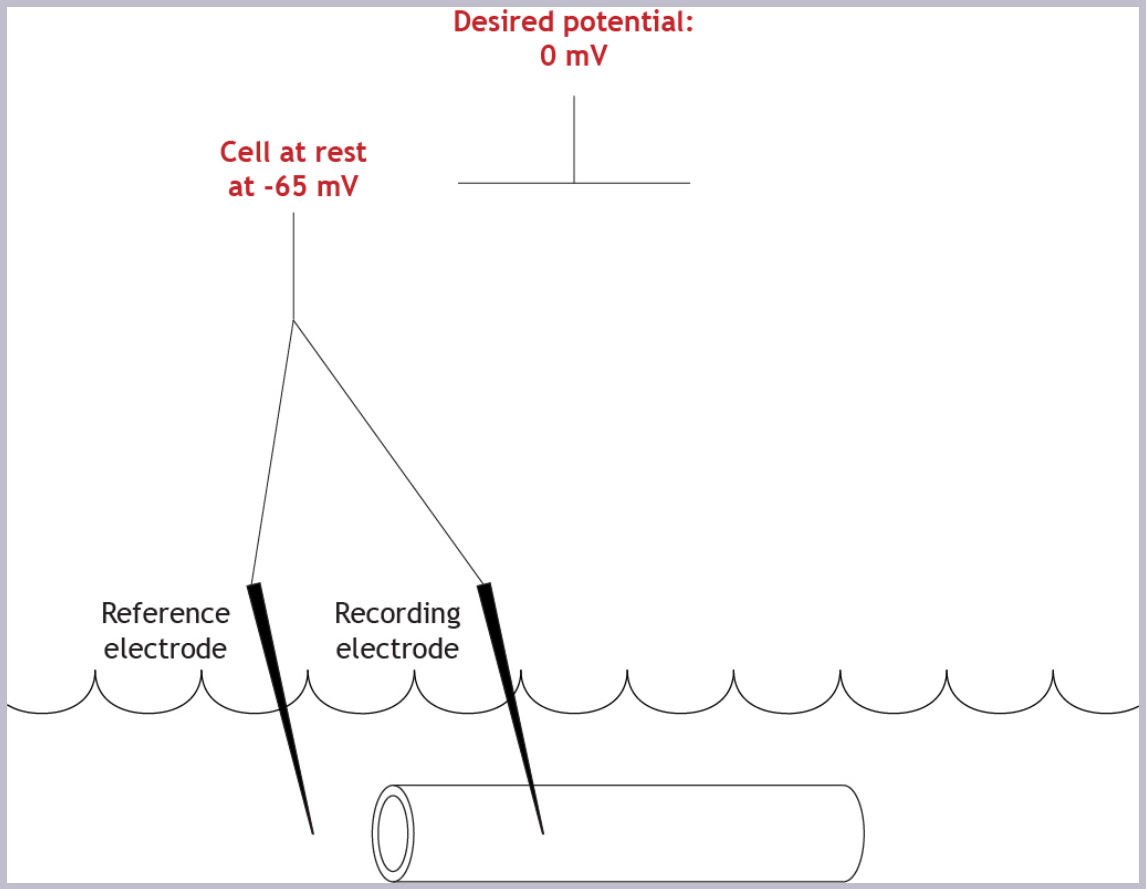

Figure 10.6. Set desired membrane potential. The set value for this experiment is 0 mV. 'Voltage Clamp Example Set Value' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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.

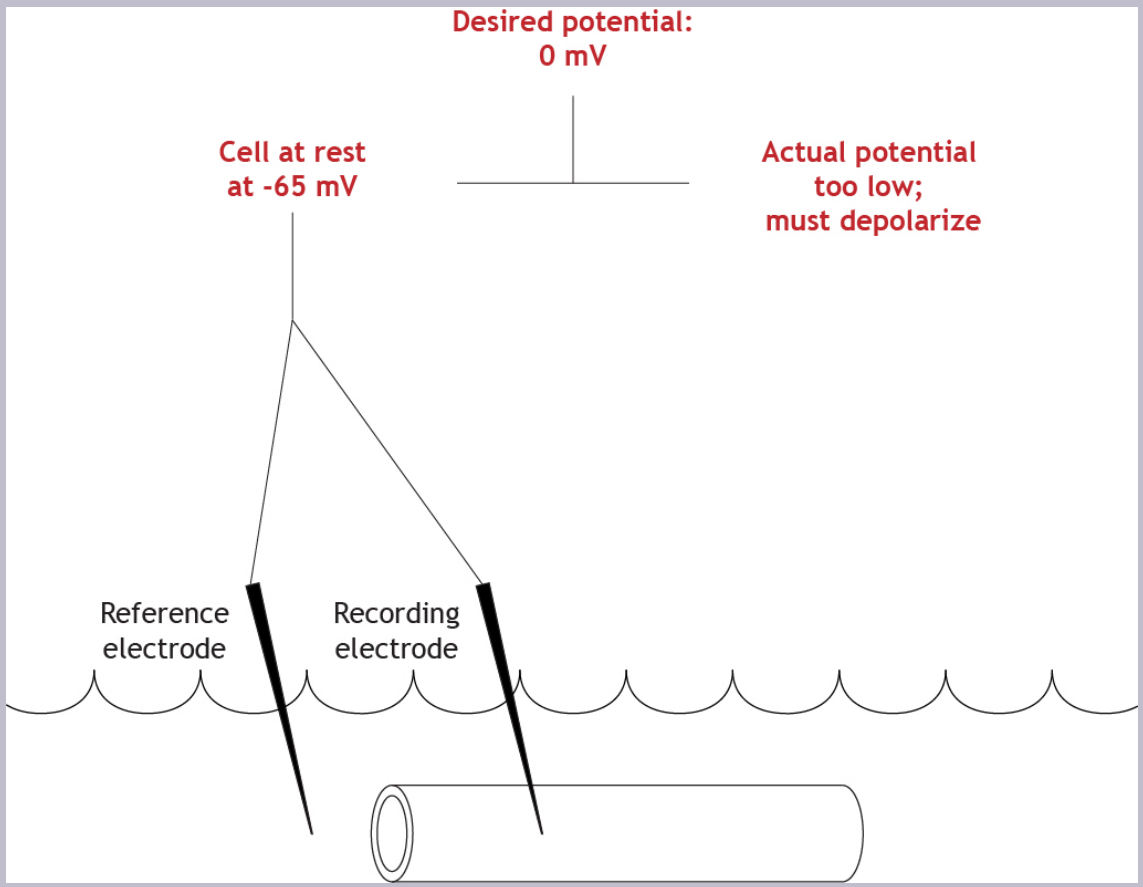

Figure 10.7. Compare measured membrane potential to desired potential. The actual membrane potential of the axon is at -65 mV, so the cell needs to be depolarized to reach the desired potential of 0 mV. 'Voltage Clamp Example Comparison' by Casey Henley is licensed under a Creative Commons Attribution 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.

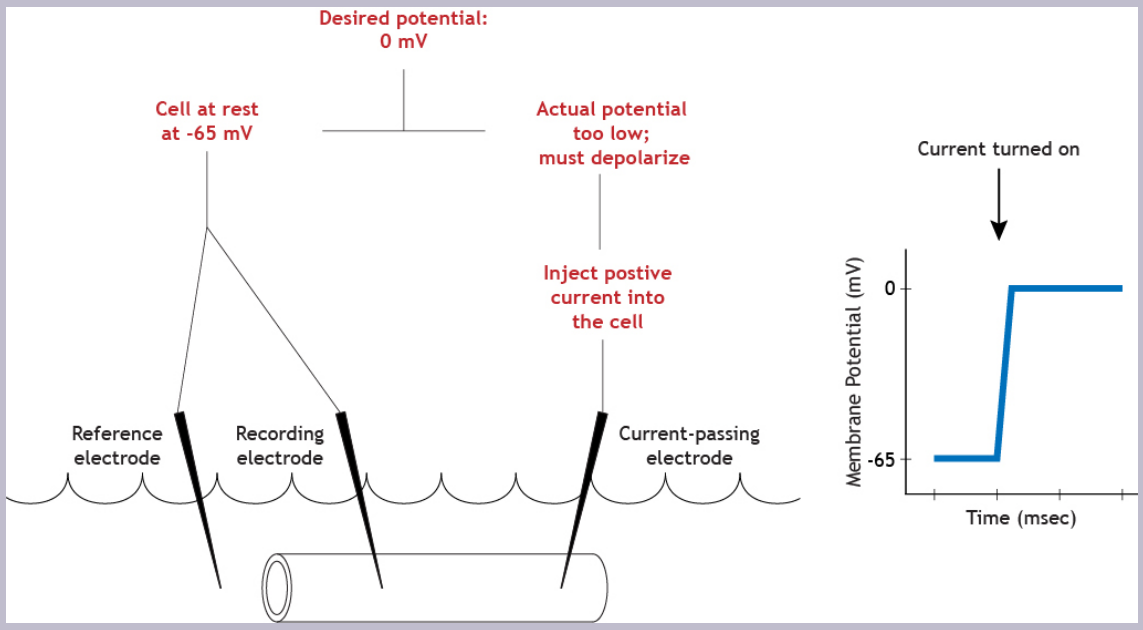

Figure 10.8. Correct actual membrane potential. To depolarize this axon from rest at -65 mV to the desired clamp value of 0 mV, positive current will be injected into the cell. The membrane potential will then depolarize to 0 mV and remain there. 'Voltage Clamp Example Current' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Ion Channels Continue to 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 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.

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Animation 10.1. 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. This is 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.

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Animation 10.2. 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. The voltage-clamp setup 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

Test Yourself!

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PART III

NEURONAL COMMUNICATION

11.

SYNAPSE STRUCTURE

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

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

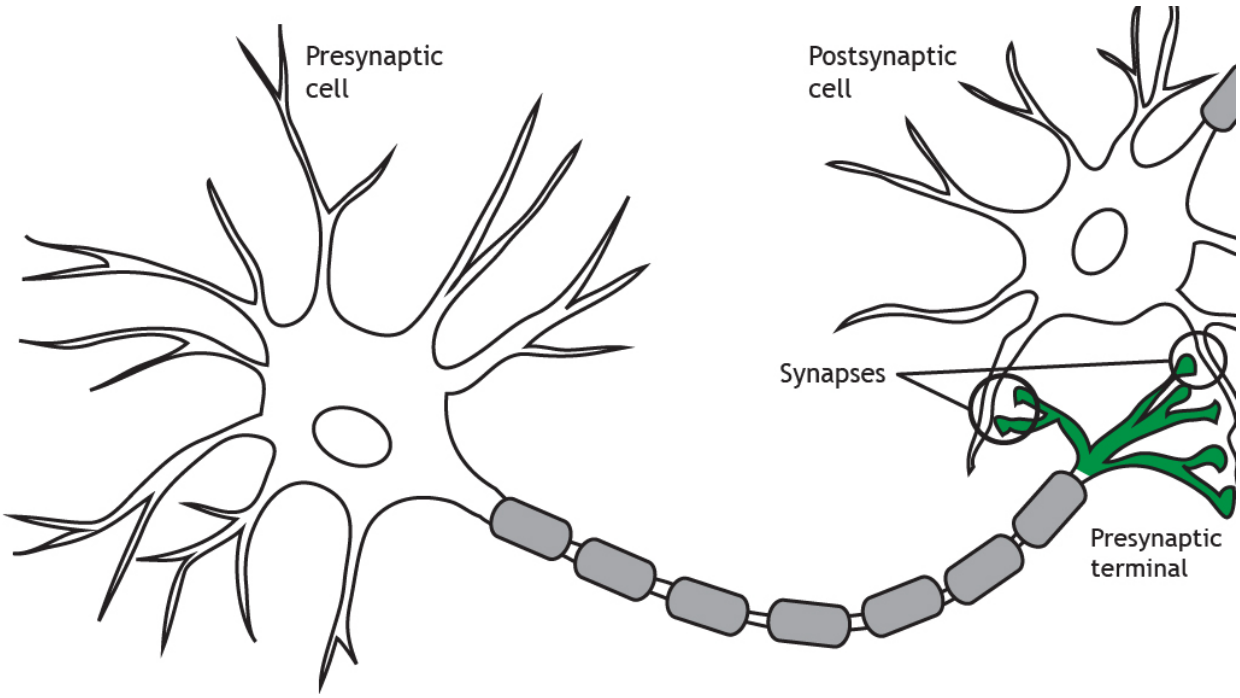

Figure 11.1. The terminal of a presynaptic neuron comes into close contact with a postsynaptic cell at the synapse. 'Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Synapse Types

There are two types of synapses: electrical and chemical.

Electrical

Electrical synapses are a direct connection between two neurons. Imagine two neurons that are connected by an electrical synapse. First of all, both of them are complete cells on their own. Each one contains a complete plasma membrane surrounding the neuron, a nucleus, and all the individual organelles needed to carry out that cell's basic life processes.

Cell membrane proteins called **connexons** form gap junctions between the neurons. The **gap junctions** form pores that allow ions to flow between neurons, so, as an action potential propagates in the presynaptic neuron, the influx of sodium can move directly into the postsynaptic neuron and

depolarize the cell. The response in the postsynaptic cell is almost immediate, with little-to-no delay between signaling in the pre- and postsynaptic neurons.

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Animation 11.1. 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.

This means that a signal does not always move sequentially from the presynaptic cell to the postsynaptic cell. Rather, ions and signaling molecules are free to move through the connexons in either direction. Also, each cell within an electrically-coupled network can receive inputs at any of the cells, making it able to detect several signals at once—the same way a huge satellite dish can detect more signals than a small dish.

Electrical synapses likely evolved because of evolutionary pressures that selected for speed. These synapses can pass signals as fast as electrical charges can move through an electrolyte-rich fluid like cytoplasm; almost instantaneous.

Another advantage of electrical synapses is that they can form a large network of interconnected neurons with synchronized activity. For example, neuroendocrine cells in the hypothalamus are connected by electrical synapses. When the "go" signal arrives, all the cells depolarize at once, which can result in the massive release of hormones into the bloodstream. A network can also cause sudden, powerful inhibition. Like an angry mob of people chanting, a network of electrical synapses

connecting inhibitory interneurons allows the network to send an immediate "shutdown" signal under specific circumstances.

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Animation 11.2. 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.

Electrical synapses share the cytoplasm between the two connected cells, so ions, ATP, and larger signaling molecules and proteins are able to move between the two cells. These signaling molecules play an important role in cellular mechanisms, which we will see in a later chapter.

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Animation 11.3. 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

At a chemical synapse, a signaling molecule is released by the presynaptic cell to influence the postsynaptic cell by binding to postsynaptic receptors. Since chemical synapses do not rely on a direct physical protein "tunnel" to connect the two neurons, the distance between the two cells can be much larger.

On average, a chemical synapse is a distance of about 20-40 nanometers, roughly a thousand times smaller than the diameter of a human hair. A chemical synapse can pass a variety of signals, depending on the neurotransmitter and the receptor. For example, some signals are directly excitatory and allow positively charged cations to enter the neuron causing depolarization. Other signals are hyperpolarizing, and therefore inhibitory. And yet other signals are much more complex, inducing changes in protein expression that can modify cellular excitability over the course of minutes or hours.

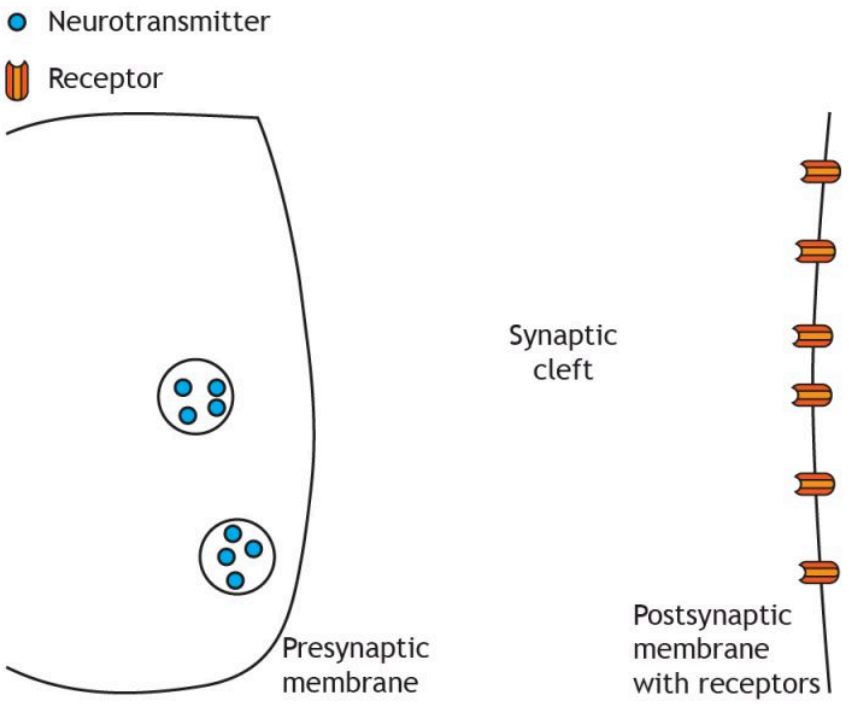

Figure 11.2. A chemical synapse does not make direct contact between the two neurons. The presynaptic terminal and the postsynaptic membrane are separated by the synaptic cleft. Neurotransmitters are stored in the presynaptic cell, and the postsynaptic cell has neurotransmitter receptors in the membrane. '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**. These neurotransmitters are synthesized and stored in neurons. After being released, these neurotransmitters diffuse randomly across the synapse, where they are able to affect nearby neurons once the chemical binds to its corresponding receptor 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.

Because of the complexity of the signals that chemical synapses can convey, evolutionary development through time has allowed for a tremendous variety of responses. Chemical synapses allow for fine-tuning of neural networks, giving these nervous systems a larger range of possibilities. The nervous systems of "higher" organisms like humans tend to have several chemical synapses since these signals are likely necessary for complex behaviors and cognition.

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Animation 11.4. 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 (axon) 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.

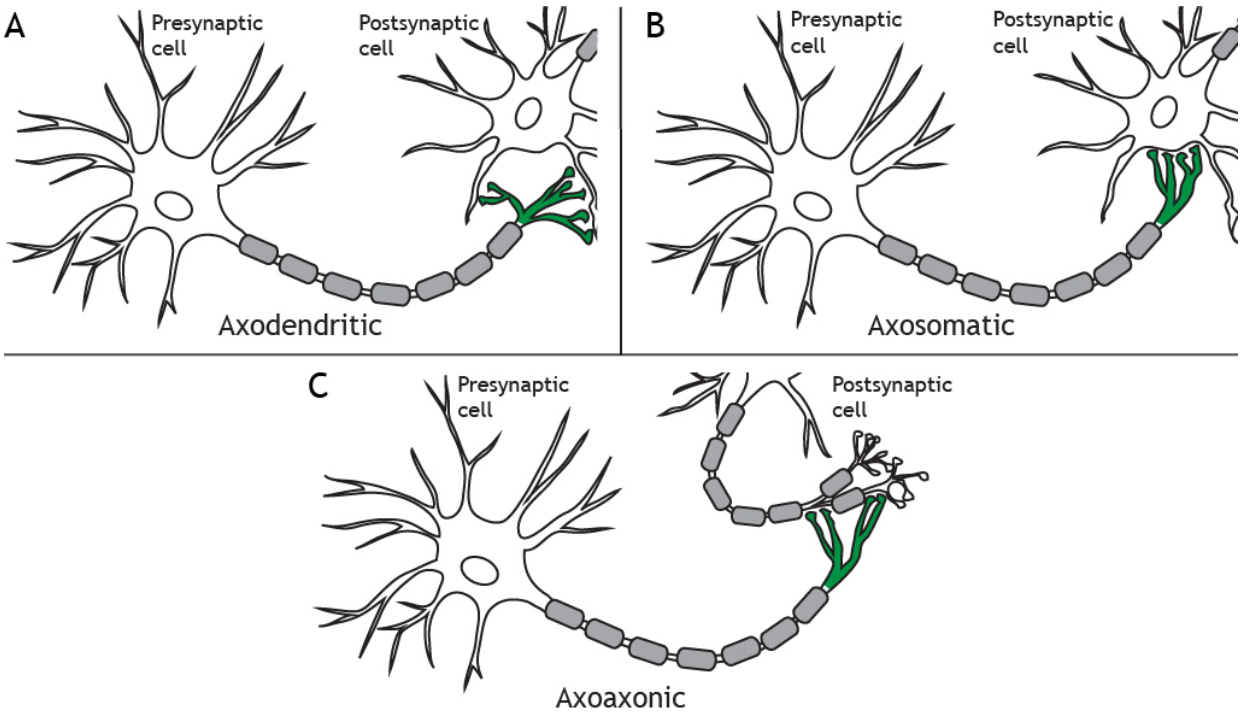

Figure 11.3. A) Axodendritic synapses occur when the presynaptic terminal makes a synaptic connection with the dendrite of a postsynaptic neuron. B) Axosomatic synapses occur when the presynaptic terminal makes a synaptic connection with the cell body of a postsynaptic neuron. C) Axoaxonic synapses occur when the presynaptic terminal makes a synaptic connection with the axon of a postsynaptic neuron. 'Chemical Synapse Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

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

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

Test Yourself!

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12.

STEPS IN SYNAPTIC SIGNALING

Steps in Chemical Signaling

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

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.

At a chemical synapse, the process of neurotransmitter release is very tightly regulated. If there were no mechanisms to control the release of chemicals at the synapse, nerve cells would deplete their entire stock of neurotransmitter. Regulation of release depends on several proteins that are important parts of the process. These proteins are often embedded within cell membranes of the vesicles or the neuronal membrane.

Step 1: An action potential arrives at the axon terminal

There are a series of steps that take place during chemical synaptic transmission.

First, an action potential propagates down the axon until it arrives at the axon terminal, depolarizing the membrane of the presynaptic terminal.

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Animation 12.1. 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

Step 2: Membrane depolarization from action potential causes influx of calcium ions

When the action potential reaches the terminal, there is an influx of sodium ions. This inward positive current causes a depolarization of the terminal, activating **voltage-gated** calcium channels that are embedded in the cell membrane of the axon terminals. Due to the electrochemical gradient of calcium, when the voltage-gated calcium channels are opened, calcium will rush into the cell. The concentration of intracellular calcium, generally in the range of 100 nM, is much lower than the concentration outside the cell, therefore there is a strong electrochemical gradient that moves calcium into the terminal. As it turns out, an elevation of Ca^{2+} in the intracellular space is the "go ahead" signal that causes neurotransmitter release.

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Animation 12.2. 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. They are, therefore, slower to release than the small molecule transmitters.

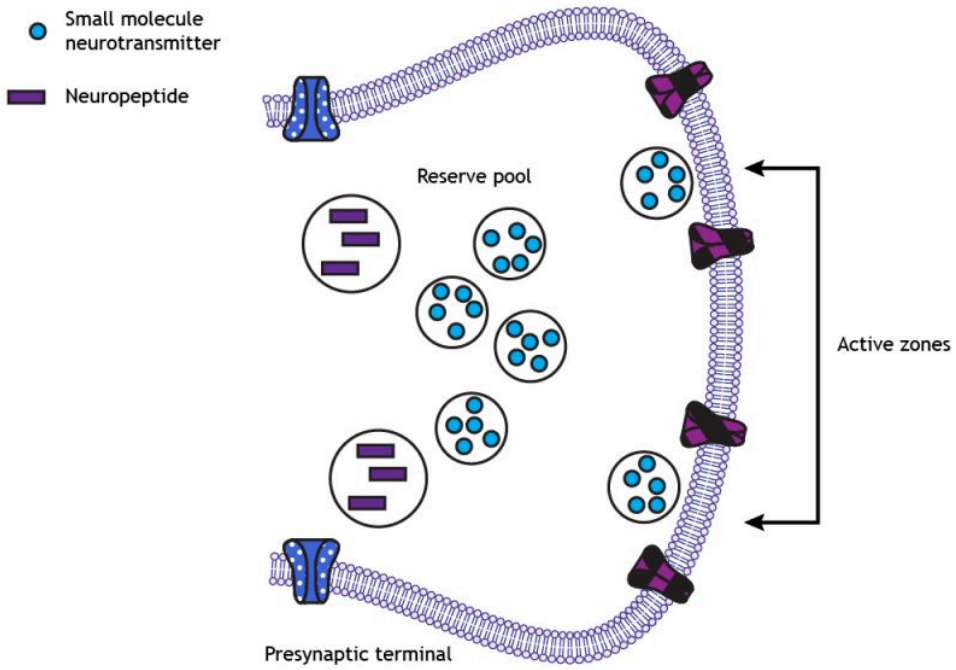

Figure 12.1. Some synaptic vesicles filled with small molecule neurotransmitters dock at active zones on the presynaptic membrane, ready for immediate release. Other synaptic vesicles remain nearby in reserve pools, ready to move into empty active zones. Neuropeptide-filled vesicles do not dock at active zones. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Active Zones' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Location of vesicles

Synaptic vesicles can be found in one of three places at the axon terminal.

1. **Readily releasable pool**. These vesicles are located close to the cell membrane at the axon terminal. In fact, many of them are already "docked", meaning that their coat proteins are already interacting closely with the proteins on the inside of the cell membrane. When the depolarizing charge of an action potential reaches the terminal, these vesicles at the readily releasable pool are the first ones that fuse with the cell membrane and release their contents.
2. **Recycling pool**. These vesicles are the ones that have been depleted due to release. They are currently in the process of being refilled or reloaded with neurotransmitter. They are farther

from the cell membrane, and the protein machinery is not primed for release, so it requires a more intense stimulation to release the contents of these vesicles.

3. **Reserve pool**. These vesicles are the farthest from the surface of the cell membrane, and most vesicles are held in this reserve pool. For these neurotransmitters to be released, very intense stimulation is required.

Step 3: Docking of synaptic vesicles at the membrane

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**.

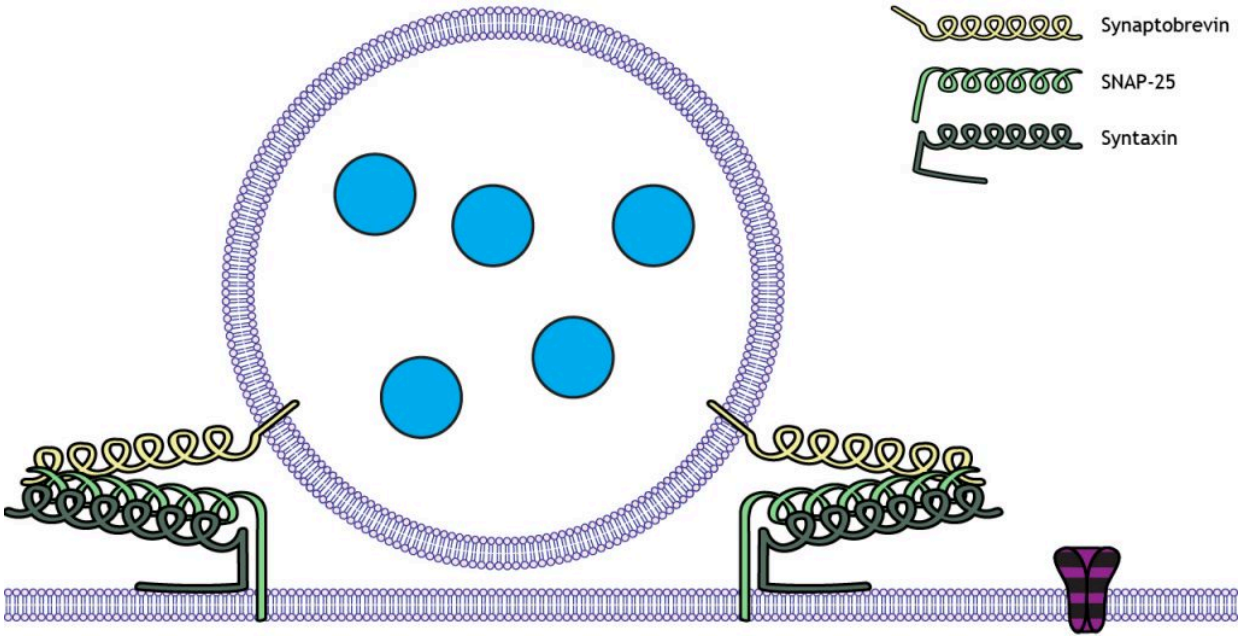

Figure 12.2. Synaptic vesicles filled with small molecule neurotransmitters are able to dock at active zones by the interaction of v- and t-SNARE proteins. Synaptobrevin is embedded in the membrane of the vesicle whereas SNAP-25 and Syntaxin are embedded in the presynaptic terminal membrane. The purple, striped channels represent voltage-gated calcium channels. 'SNARE proteins' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

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 a vesicle-bound protein called **synaptotagmin**. Synaptotagmin is a calcium sensor that detects elevated levels of calcium in the axon terminal.

In the presences of calcium, the *v-SNAREs* and the *t-SNAREs* interact with one another, forming a molecular structure called a SNARE complex. The SNARE complex looks a lot like two twist ties that are wound tightly together. As they twist tighter together, it causes the vesicle membrane to approach the inside of the cell membrane, which results in vesicular fusion.

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Animation 12.3. 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

Step 4: Release of neurotransmitters into the synapse

The last step of neurotransmitter release is the fusing of the cell membrane. In order to release their chemical contents into the synapse, vesicles need to fuse with the cell membrane. As the vesicular membrane merges with the interior of the neuronal membrane, the membranes fuse and the contents of the vesicle become exposed to the extracellular space. The neurotransmitters then float across the aqueous synapse, giving them the opportunity to interact with postsynaptic receptors.

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Animation 12.4. 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.

Step 5: Receptor Activation

After exocytosis of the transmitter molecules, neurotransmitters traverse across the synapse and bind to **receptors** on the postsynaptic membrane. Receptors fall into two main categories: **ionotropic receptors** (also called ligand-gated channels) and **metabotropic receptors** (also called G-protein coupled receptors). These two types of receptors will be covered in upcoming chapters.

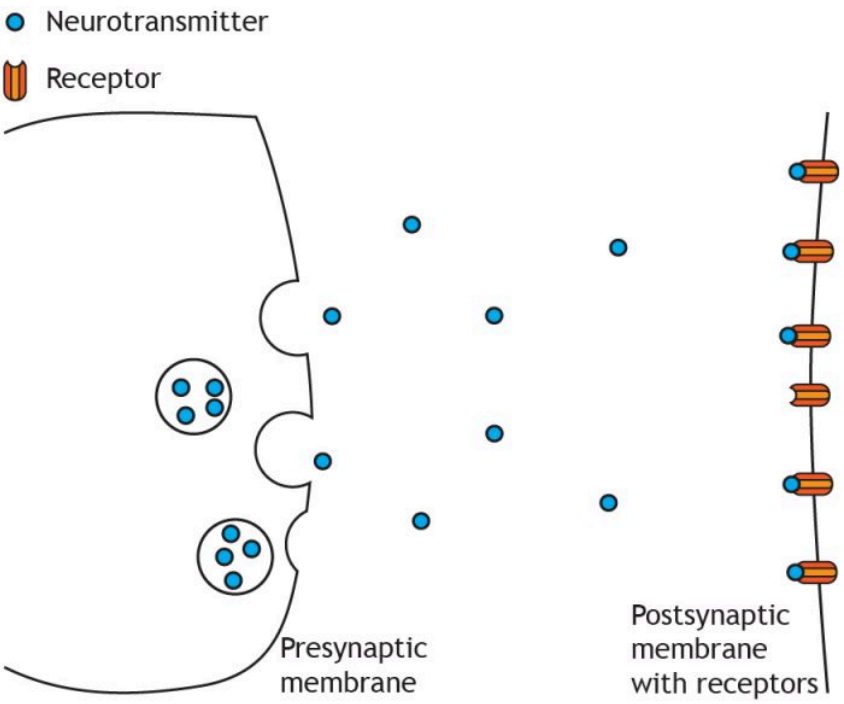

Figure 12.4. After exocytosis of the neurotransmitters into the synaptic cleft, the transmitters bind to receptors present on the postsynaptic membrane. 'Neurotransmitter in Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Step 6: Postsynaptic potentials generated in postsynaptic cell summate

Recall the process of summation from Chapter 8. The postsynaptic potentials generated from neurotransmitter binding **summate** at the axon hillock. If the membrane potential is over **threshold** potential for the cell, then a new action potential will be generated in the postsynaptic cell.

Postsynaptic potentials (graded potentials) can occur following different types of stimulation.

When neurotransmitters bind to receptors on postsynaptic cells, they cause the receptor proteins to undergo a conformational change, and open ligand-gated ion channels that produce depolarization or hyperpolarization.

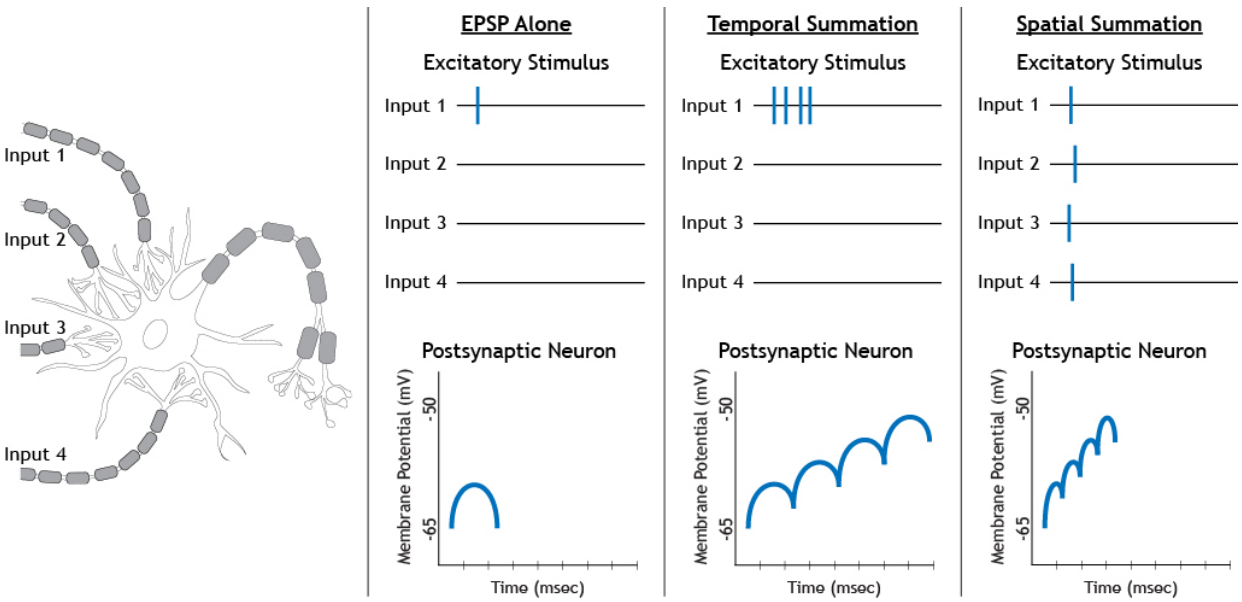

Figure 12.5. EPSPs can summate via temporal or spatial summation. Temporal summation occurs when a presynaptic neuron (Input 1 in the figure) stimulates the postsynaptic neuron multiple times in a row. Spatial summation occurs when more than one presynaptic neuron (Inputs 1 through 4 in the figure) each 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.

Step 7: Neurotransmitter Inactivation

It is important that neurotransmitter signaling be tightly regulated. This means that there needs to be ways to terminate chemical signaling. Inactivation can be accomplished in three different ways.

1. After being released, neurotransmitters can be altered into inactive substances.
2. Neurotransmitters can go through the **reuptake** process, where they are recycled by being transported back into the presynaptic cell and repackaged into synaptic vesicles.
3. Some neurotransmitters simply float away from the synapse due to the aqueous environment surrounding neurons.

Key Takeaways

- In order for neurotransmitter release to be initiated, an action potential (depolarizing stimulus) needs to arrive at the axon terminal to open voltage-gated calcium channels
- Neurotransmitter release is dependent on the influx of calcium into the terminal through voltage-gated calcium channels
- SNARE proteins are important for vesicle docking at active zones and exocytosis of neurotransmitters into the synapse
- Synaptotagmin is a calcium sensor
- Neurotransmitters bind to postsynaptic receptors and cause postsynaptic potentials that summate within the postsynaptic cell
- Neurotransmitter signaling is terminated through chemical inactivation, reuptake, or through diffusion away from the synapse.

Test Yourself!

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13.

NEUROTRANSMITTER IDENTIFICATION AND ACTION: IONOTROPIC RECEPTORS VERSUS METABOTROPIC RECEPTORS

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Neurotransmitters are chemicals that are released at the synapse. In this chapter, we will introduce basic information about neurotransmitters and how they are identified. Next, an overview of neurotransmitter receptors will be provided.

Receptors are proteins located on the postsynaptic cell that are capable of sending a signal to change the function or activity of the postsynaptic neuron. Most receptors that function in neurotransmission are large transmembrane proteins. On the extracellular surface of the protein is a specific series of amino acid residues called the active site. The active site, also called the orthosteric site, is shaped to allow molecules of neurotransmitter to bind to the receptor. Receptors are classified into one of two main categories: **Ionotropic receptors** and **Metabotropic receptors** (G-protein coupled receptors).

Neurotransmitters

Neurotransmitters are the chemicals released at the presynaptic terminal that then bind to the postsynaptic cell. A neurotransmitter system is the neurotransmitter and everything needed for the synthesis of the transmitter, the packaging of the transmitter into vesicles, the proteins necessary for reuptake of the transmitter into the presynaptic cell, degradation of the transmitter, and postsynaptic

signaling of the transmitter. In the following chapters, we will discuss various neurotransmitter systems.

Though there are neurons that can release more than one type of neurotransmitter (referred to as co-transmitters), most neurons release just one type of neurotransmitter, allowing neurons to be identified by the neurotransmitter they release (e.g. dopaminergic neurons). The different neurotransmitters can be separated into three different chemical categories:

1. Amino Acids (Glutamate, GABA, Glycine)
2. Amines (Acetylcholine, Dopamine, Epinephrine, Histamine, Norepinephrine, Serotonin)
3. Peptides (Dynorphin, Enkephalin, Substance P, Neuropeptide Y)

To identify whether a chemical can be classified as a neurotransmitter, it must meet the following requirements:

1. The chemical has to be stored or located within the presynaptic neuron. Both immunohistochemistry and immunocytochemistry can use antibodies directed against a specific protein important for neurotransmitter synthesis or storage to localize the protein to a neuron and determine whether a neuron has the appropriate machinery to make the neurotransmitter and thus likely release the neurotransmitter.
2. The chemical has to be released from the presynaptic neuron following appropriate stimulation.
3. When the chemical is applied to the postsynaptic cell by an experimenter, the response of the postsynaptic cell should be similar to the response following normal release from the presynaptic cell.

Neurotransmitters can be classified on their function as either ‘excitatory’ or ‘inhibitory’. In the following chapters, we will see that glutamate is an example of an excitatory neurotransmitter. This is because the binding of glutamate to the postsynaptic cell typically generates excitatory postsynaptic potentials, which makes the inside of the cell closer to zero and thus closer to threshold potential for the cell, increasing the likelihood of firing an action potential. GABA and Glycine, however, are typically considered as inhibitory neurotransmitters. This is because the binding of either GABA or glycine to the postsynaptic cell typically generates inhibitory postsynaptic potentials, which makes the inside of the cell more negative and further from threshold potential of the cell, decreasing the likelihood of firing an action potential.

Most neurotransmitters, however, can produced either excitatory postsynaptic potentials or inhibitory postsynaptic potentials depending on the properties of the postsynaptic receptor that they bind to. Neurotransmitters each bind to specific receptors that produce specific postsynaptic responses.

The subsequent chapters will review the main neurotransmitters including their synthesis, storage, and their receptors.

Neurotransmitter Receptors

Ionotropic Receptors

Ionotropic receptors are also called neurotransmitter-gated or ligand-gated channels. They 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. Ionotropic receptors are important for receiving incoming information from other neurons.

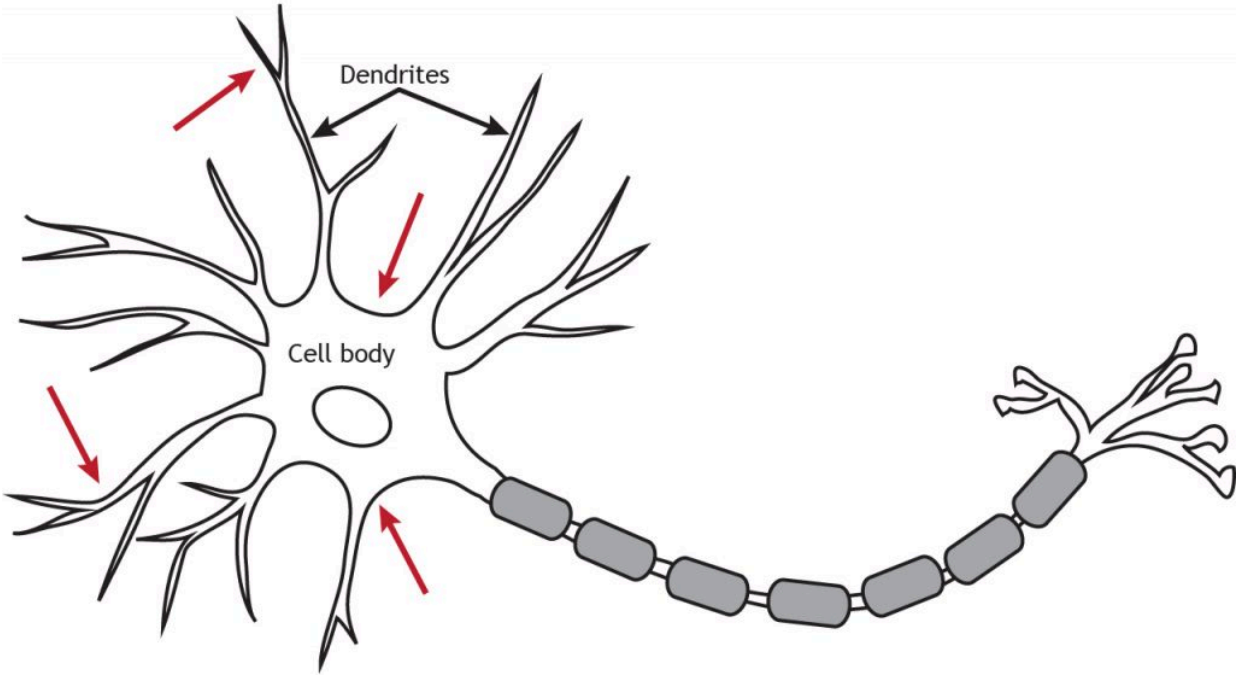

Figure 13.1. Ligand-gated channels critical for receiving incoming synaptic information are primarily located along the dendrites and cell body. 'Receptor Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Physically, ionotropic receptors are transmembrane proteins with a large-diameter pore through which ions can pass. Although ionotropic receptors are ion channels, they open in a different way than the voltage-gated ion channels needed for propagation of the action potential. The ionotropic receptors are ligand-gated, which means that a specific molecule, such as a neurotransmitter, must bind to the receptor to cause the channel to open and allow ion flow. As seen in previous chapters, the voltage-gated channels open in response to the membrane potential reaching **threshold** (a specific voltage).

Ionotopic channels are often said to use a **direct signaling mechanism** because the neurotransmitter binds *directly* to the ion channel that it is going to open.

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Animation 13.1. 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.

These channels only open when a specific ligand binds to the active site on the extracellular side of the protein. Neurotransmitters and receptors fit together like a lock and key; only certain neurotransmitters are able to bind to and open certain receptors.

Once a neurotransmitter activates the ionotropic receptor, ions will move through the channel based on the electrochemical gradient for that ion. As a result of ion movement, the cell's membrane potential will change. For example, if the ionotropic channel allowed for movement of sodium, the electrochemical gradient for sodium will promote sodium rushing into the cell, causing the inside of the cell to get more positive (decrease in membrane potential).

Ionotropic receptors are able to induce a change in membrane potential very rapidly, on the scale of milliseconds. Due to the nature of the amino acid residues that make up the pore of ionotropic receptors, they can be very selective for certain ions. For example, negatively charged residues lining the inside of the pore repel negatively charged Cl^- ions while allowing positively charged cations to pass through the channel.

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Animation 13.2. 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.

Metabotropic Receptors (G-protein-coupled receptors)

Metabotropic receptors (also called G-protein-coupled receptors [GPCRs]), are membrane-bound proteins. These receptor complexes cause the cell to change its metabolism in a way that leads to either excitation or inhibition of the postsynaptic cell. 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.

Unlike ionotropic receptors (direct mechanism), ions do not pass through GPCRs. Instead, metabotropic receptors use the actions of G proteins, proteins which induce changes in neuronal excitability through the action of second messenger signaling molecules. Due to these extra steps, 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. There are multiple types of alpha subunits ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$), and each initiate different cellular cascades in the neuron.

Functionally speaking, these G-proteins are capable of binding to molecules of guanosine triphosphate (GTP) or guanosine diphosphate (GDP). Chemically similar to ATP, GTP can function as a source of energy. G-proteins themselves exhibit catalytic activity of GTP. This means that they are capable of breaking down GTP into the less-energetic GDP. When GTP is bound to the GPCR, the receptor is active. When this molecule is hydrolyzed into GDP, the receptor becomes inactive.

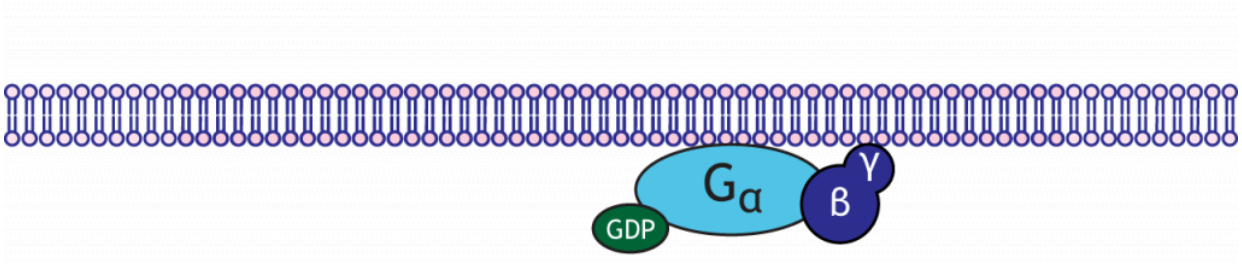

Figure 13.2. The unactivated G-protein complex in the cell consists of three subunits (alpha, beta, and gamma) and a bound GDP molecule. 'G-protein Complex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Metabotropic Receptors

A metabotropic receptor or GPCR is a transmembrane protein that has an extracellular binding site for a neurotransmitter. Metabotropic receptors are physically linked to G-proteins, which exist on the inner surface of the cell membrane.

When a neurotransmitter binds to a GPCR it undergoes a conformational change, which allows the receptor to interact with an associated inactivated G-protein complex.

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

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Animation 13.3. 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.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=95#video-95-4*

Animation 13.4. 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 animnullation.

Adenylyl Cyclase / cAMP Second Messenger Cascade

The cyclic AMP (cAMP) second messenger pathway is used by many GPCRs. When a neurotransmitter binds to a GPCR, it causes activation of the $G\alpha_s$ alpha subunit. The $G\alpha_s$ subunit ("s" for stimulatory) translocates within the cell to stimulate an effector enzyme called **adenylyl cyclase**. When activated, adenylyl cyclase converts ATP to cAMP in the cytoplasm. cAMP is considered a 2nd messenger (the 1st messenger was the neurotransmitter). As a second messenger, cAMP has the ability to alter proteins inside the cell. Specifically, cAMP activates another enzyme called **protein kinase A (PKA)** by binding to the regulatory subunits, allowing the catalytic (functional) subunits to separate and become active. PKA is a **kinase**, a group of enzymes that 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. Typically, phosphorylation activates proteins within the cell.

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Animation 13.5. GPCRs that couple to the G_s alpha subunit initiate the adenylyl cyclase / cAMP pathway. The G_s subunit activates adenylyl cyclase, which then converts ATP to cAMP. cAMP binds to and activates protein kinase A (PKA), which phosphorylates proteins in the cell. 'Adenylyl Cyclase Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

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

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Animation 13.6. The adenylyl cyclase / cAMP pathway can alter many cellular functions. One example is that both cAMP and PKA can open ion channels. Like ligand-gated channels, there are also cAMP-gated channels, which open after cAMP binding. PKA is able to phosphorylate and modulate ion channel function by converting ATP to ADP. 'Second Messenger Ion Channel Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

In addition to altering ion channel function, PKA can phosphorylate other proteins important for

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

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

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Animation 13.7. 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.

Alternatively, a GPCR that is coupled with $G\alpha_i$ causes a decrease in excitability. In many ways, $G\alpha_i$ proteins serve the opposite function as $G\alpha_s$ proteins—the "i" stands for inhibitory. Whereas activation of $G\alpha_s$ increases the action of adenylyl cyclase, $G\alpha_i$ proteins decrease adenylyl cyclase activity. Therefore, $G\alpha_i$ activation decreases the intracellular concentration of cAMP, in turn decreasing PKA activity. Given the function of PKA as a **kinase** that increases cellular excitation as described above, a GPCR coupled to $G\alpha_i$ that causes decreased PKA activity inhibits cellular activity through multiple mechanisms, some of which include decreased current through receptors, decreased trafficking of receptors to the presynaptic neuronal membrane, and decreased transcription of certain genes.

Phosphlipase C / IP3 / DAG Second Messenger Cascade

Generally, $G\alpha_q$ is an excitatory G-protein alpha subunit. The $G\alpha_q$ subunit initiates a separate signaling

pathway in the cell by activating the effector enzyme **phospholipase C**. Phospholipase C targets **PIP2** (phosphatidylinositol 4,5-bisphosphate), which is a phospholipid present in the plasma membrane of the cell. PLC will split PIP2 into two separate second messenger molecules: the soluble **IP3** (inositol 1,4,5-trisphosphate) and membrane-embedded **DAG** (diacylglycerol).

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Animation 13.8. 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. 'IP3-DAG Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

DAG remains in the membrane and interacts with **protein kinase C** (PKC). PKC is an enzyme that can act to increase neurotransmitter release probability.

One function of IP3 is to move to the **endoplasmic reticulum**, where it opens calcium channels embedded in the endoplasmic reticulum and allows calcium to flow into the cytosol, elevating intracellular calcium levels. This increase in calcium concentration can depolarize the cell and activate calcium-dependent processes, which often lead to cellular excitation.

Calcium also acts as a second messenger in the cell. One important effect is the binding of calcium to the **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.

So, depending on the type of Gα subunit that the G-protein is associated with, there will be different outcomes for the cell. In general, $G\alpha_s$ will "stimulate" the cell by activating adenylyl cyclase. $G\alpha_i$ will "inhibit" the cell by inhibiting adenylyl cyclase. $G\alpha_q$ will "stimulate" the cell by activating phospholipase C.

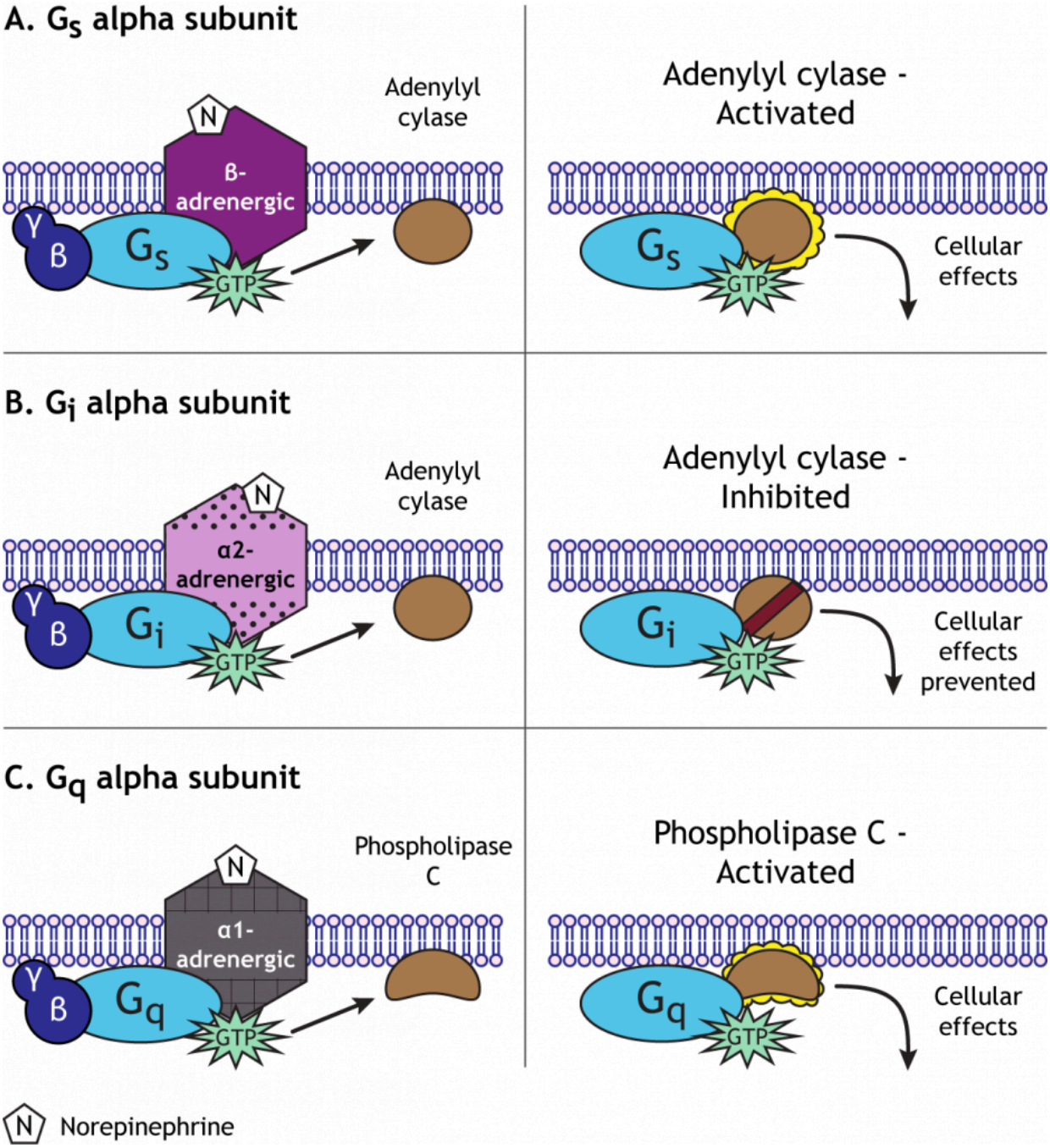

Figure 13.3. The second messenger pathway used, and whether that pathway is stimulated or inhibited, depends on the type of alpha subunit in the G-protein complex. Different receptors couple to different G-protein complexes. This allows one neurotransmitter to initiate multiple types of signaling cascades. A) The norepinephrine beta-adrenergic receptor couples to the G_s subunit and activates 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. 'Alpha Subunit Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

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.

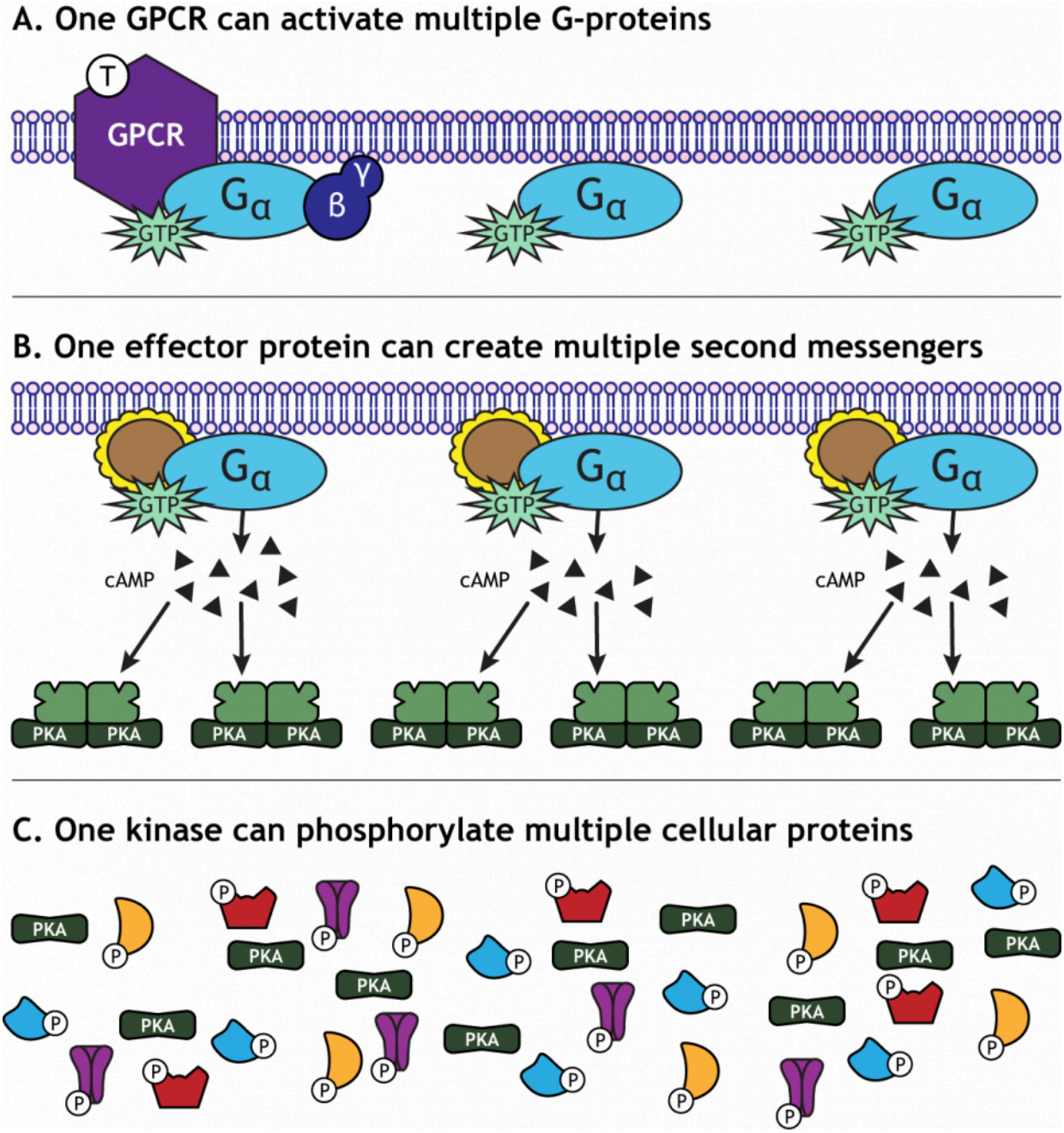

Figure 12.4. The second messenger cascades initiated by GPCRs undergo significant signal amplification. A) Multiple G-proteins can be activated by a GPCR. B) Each effector protein is able to synthesize numerous second messenger molecules. C) Each protein kinase activated by the second messengers can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

Signal Termination

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

Key Takeaways

- Ionotropic receptors are ligand-gated ion channels that open when a specific neurotransmitter binds
- Ionotropic receptors represent a direct mechanism to alter the postsynaptic cell because the neurotransmitter binds to the ion channel directly
- Metabotropic receptors represent an indirect mechanisms to alter the postsynaptic cell because the neurotransmitters binds to a separate protein from the effector proteins that alter the postsynaptic cell
- G-protein-coupled receptors rely on the activation of G-proteins to cause cellular changes
- G-protein-coupled receptors have slower effects than ligand-gated receptors
- G-proteins can open ion channels, alter protein function via phosphorylation, and alter gene transcription
- The G_s subunit initiates the adenylyl cyclase / cAMP signaling pathway
- The G_i subunit inhibits the adenylyl cyclase / cAMP signaling pathway
- The G_q subunit initiates the phospholipase C / IP_3 / DAG signaling pathway

Test Yourself!

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14.

INTRODUCTION TO SMALL MOLECULE NEUROTRANSMITTERS

Neurotransmitters are the substances that are released at chemical synapses, and they are the signaling molecules that allow neurons to communicate with one another. To date, scientists have identified more than 100 neurotransmitters.

Resources

- Key Takeaways
- Test Yourself

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

The next several chapters will cover a subset of neurotransmitter systems. For each neurotransmitter system, we will provide information on: the synthesis and storage of the neurotransmitter in the presynaptic cell; the receptors that the neurotransmitter binds to on the postsynaptic cell and the postsynaptic effects; and how neurotransmitter signaling is terminated.

Neurotransmitter Vesicles: Types of Vesicles

There are two main categories of neurotransmitters: **small molecule neurotransmitters** and **peptide neurotransmitters (covered in Chapter 19)**. Synthesis and storage of these neurotransmitter groups differ. Small molecule neurotransmitters are synthesized and stored in the terminal for fast release. Neuropeptides are synthesized in the cell body and must be transported to the terminal, which can

lead to slower release. Additionally, a neuron typically will synthesize and release only one type of small molecule neurotransmitter, but can synthesize and release more than one neuropeptide.

Molecules of neurotransmitters are often stored in synaptic vesicles before being released. Synaptic vesicles are tiny spheres of neurotransmitter enclosed by a phospholipid bilayer just like the cell membrane. These vesicles can be roughly characterized into two classes:

1. **Small vesicles**. Small vesicles are responsible for storage of small molecule neurotransmitters. Given the size of neurotransmitters, we can estimate that thousands to tens of thousands of molecules of neurotransmitter can be stored in each vesicle. Small vesicles store many of the neurotransmitters we most often think of, including glutamate, GABA, dopamine, and norepinephrine. Small vesicles are almost always exclusively found in the axon terminals.
2. **Large dense-core vesicles**. These vesicles are much larger than small vesicles. They store peptides such as dynorphin or enkephalin, which have chemical structures much larger than the small molecule neurotransmitters. Since these peptides are packaged into their vesicles near the nucleus, large dense-core vesicles can be found in the cell bodies and all along the axons in addition to the axon terminal.

Small Molecule Transmitters

Let's first discuss the small molecule neurotransmitters. The small molecule neurotransmitters can be divided into two main groups: **amino acid neurotransmitters** and **biogenic amines (also called monoamines)**. In addition to acting as neurotransmitters, the amino acids glutamate and glycine are used to synthesize proteins in all cell types throughout the body. GABA (γ-Aminobutyric acid) is a metabolite of glutamate, but is not used in protein synthesis in the body. The biogenic amines include serotonin, histamine, and the subgroup catecholamines: dopamine, norepinephrine, and epinephrine. Acetylcholine does not fit into either division but is still considered a small molecule neurotransmitter.

Most small molecule neurotransmitters are synthesized by enzymes that are located in the cytoplasm (the exception is norepinephrine, see Chapter 17). This means that small molecule neurotransmitters can be synthesized and packaged for storage in the presynaptic terminal using enzymes present in the terminal.

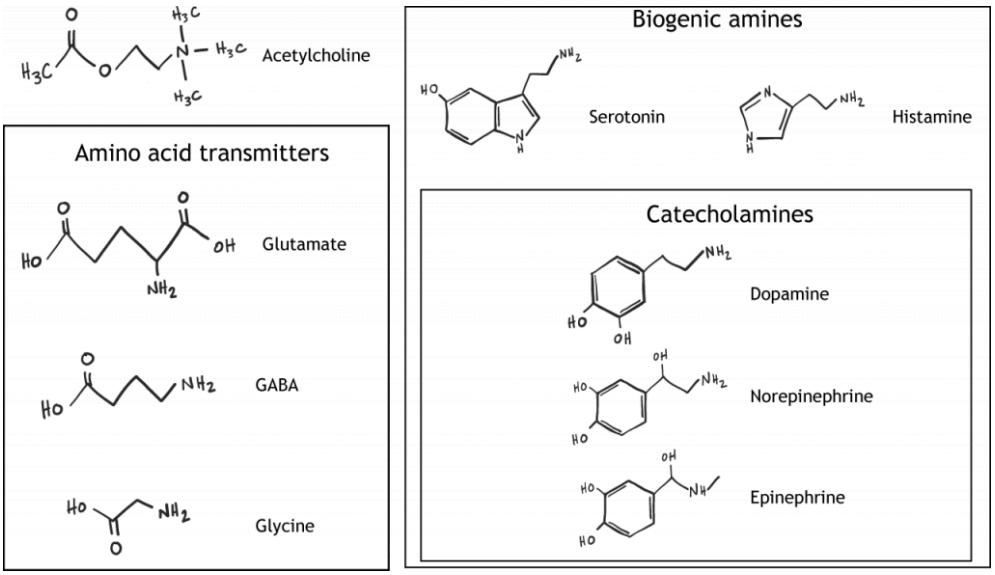

Figure 14.1. Small molecule neurotransmitters can be subdivided into groups based on chemical structure. Amino acid transmitters include glutamate, GABA, and glycine. The biogenic amines include serotonin and histamine, and the catecholamines, a subgroup of the biogenic amines, include dopamine, norepinephrine, 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.

The effect of the neurotransmitter is dependent

on the properties of the postsynaptic receptor

In the last chapter, the mechanisms of ionotropic and metabotropic (GPCRs) were covered. In the chapters that follow, we will focus on a subset of neurotransmitter systems and identify the different neurotransmitter receptors and their function.

Key Takeaways

- Small molecules neurotransmitters are synthesized and packaged into vesicles in the presynaptic terminal
- There are different types of vesicles that hold small molecule neurotransmitters versus neuropeptide neurotransmitters

Test Yourself

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15.

NEUROTRANSMITTERS: ACETYLCHOLINE

Resources

- Scientist Links to Learn More
- Glossary Terms
- Key Takeaways
- Test Yourself

Acetylcholine was the first neurotransmitter discovered and chemically isolated, a feat which earned two researchers the shared Nobel Prize in Physiology or Medicine in 1936. One of the two scientists, a German pharmacologist named Otto Loewi, stimulated the vagus nerve connected to an isolated frog heart, which caused the heart rate to slow down. When he applied the surrounding solution from this experiment to a second heart, he observed that the second heart also slowed down, despite having no physical connection to the first heart. From this, he concluded that a chemical was being released by the vagus nerve that was decreasing the heart rate. This chemical was first called Vagusstoff, the German word meaning Vagus substance. Today, we know it as **acetylcholine**.

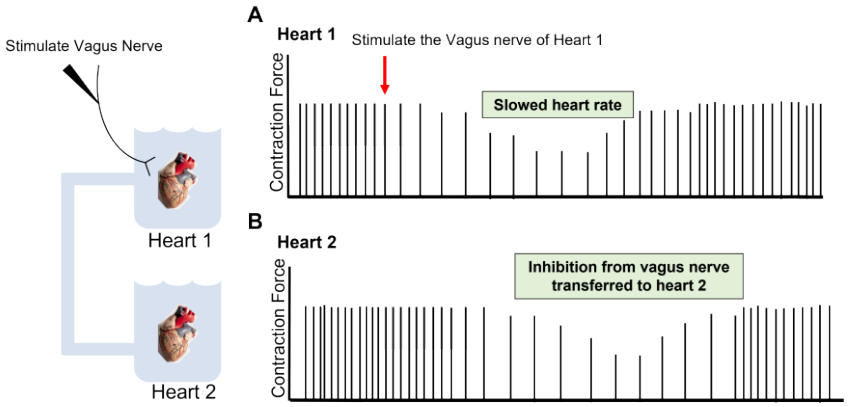

Figure 15.1. Otto Loewi Experiment. The vagus nerve that served an isolated frog heart was stimulated and the contractile force of the heart was measured. Stimulation of the vagus nerve resulted in a slowed heart rate. When the solution surrounding the heart was removed and applied to a second separate frog heart, that second heart also showed a slowed heart rate. 'Otto Loewi Experiment' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Acetylcholine Synthesis and Storage

Acetylcholine (ACh) is a small molecule neurotransmitter best known for its role at the

neuromuscular junction, the synapse between a motor neuron and a muscle fiber. In the presynaptic terminal, acetylcholine is synthesized from **acetyl coenzyme A (acetyl CoA)** and **choline** via the enzyme **choline acetyltransferase (ChAT)**. The level of enzyme activity is the rate-limiting step in the synthesis pathway. The presence of ChAT in a neuron is used as a biochemical marker for neurons that produce acetylcholine. Acetylcholine is packaged into small vesicles for storage in the terminal via the **vesicular acetylcholine transporter (VAChT)**, a protein found in the synaptic vesicle membrane.

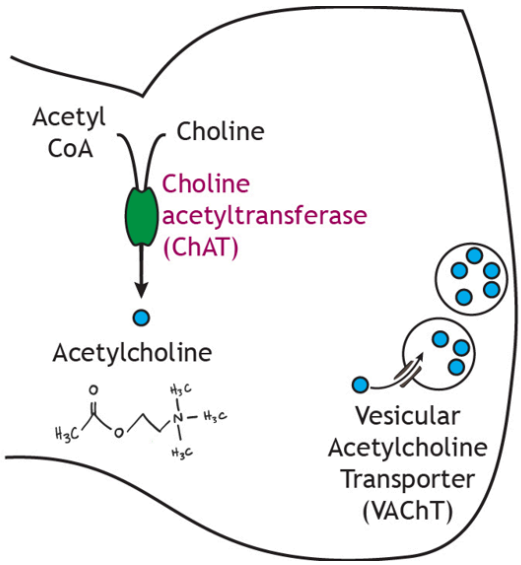

Figure 9.2. Acetylcholine is synthesized from acetyl CoA and choline by choline acetyltransferase, the rate-limiting step in the pathway. Acetylcholine is then packaged into vesicles by vesicular acetylcholine transporter. 'Acetylcholine Synthesis' by Casey Henley is licensed under a Creative Commons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

Acetylcholine Receptors

Nicotinic Acetylcholine Receptors

Acetylcholine is able to act at both ionotropic and metabotropic receptors, and activity at both receptor classes is essential for normal function. The ionotropic receptors of the nervous system are called **nicotinic acetylcholine receptors** because they can be activated by nicotine in addition to acetylcholine. Nicotinic receptors are located primarily outside of the central nervous system in the periphery. Specifically, the nicotinic receptors are used at the **neuromuscular junction**, which is the junction of a motor neuron and a skeletal muscle. Acetylcholine is released by motor neurons, where it activates nicotinic acetylcholine receptors on skeletal muscle cells. This excites the muscle cells and causes them to contract.

Nicotinic acetylcholine receptors are non-selective cation channels. The channel is closed when acetylcholine is not bound to the receptor. The nicotinic receptor has two binding sites for acetylcholine. When acetylcholine is bound to both sites on the receptor, the pore of the channel opens to allow movement of both sodium and potassium. This ionotropic receptor is an example of a direct mechanism of action, due to the fact that the receptor and the channel are located on the same protein. The properties of the receptors cause more sodium to enter than potassium leaves, ultimately causing the membrane to depolarize. Thus, nicotinic receptors are always excitatory (produce **EPSPs**) and cause **depolarization** of the postsynaptic cell.

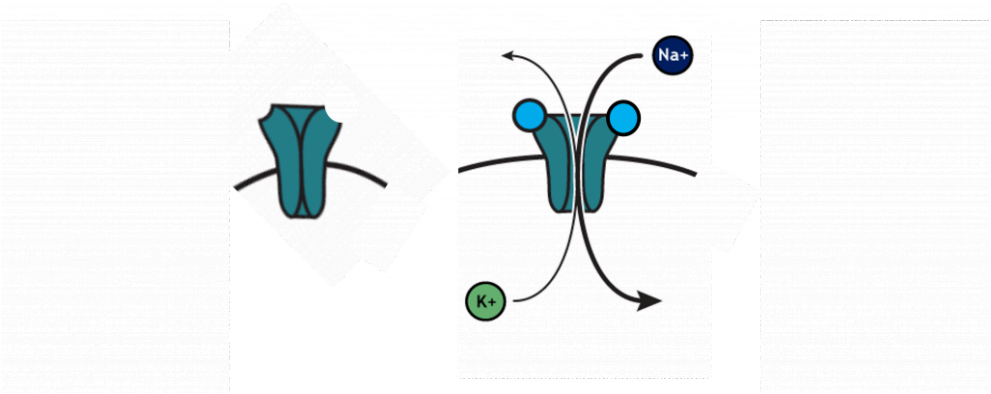

Figure 15.3. Nicotinic Acetylcholine Receptor. The nicotinic acetylcholine receptor is an ionotropic receptor. Without acetylcholine bound, the nicotinic receptor is inactive and in a closed state (left). When two molecules of acetylcholine (shown as blue circles) are bound to the receptor, the channel pore opens and allows for movement of potassium (K^+) out of the cell and also movement of sodium (Na^+) into the cell. The movement of sodium (Na+) dominates, leading to depolarization or excitatory postsynaptic potentials in the postsynaptic cell (right).

Muscarinic Receptors

On the other hand, **muscarinic acetylcholine receptors** are GPCRs (or metabotropic receptors) and utilize an indirect mechanism of action. When acetylcholine binds to muscarinic receptors, the beta-gamma subunit of the G-protein complex translocates in the cell to affect potassium channels in the cell membrane, causing them to open. Due to the electrochemical gradient of potassium, potassium will leave the cell and cause membrane **hyperpolarization**, or IPSPs.

Muscarinic receptors are located in the heart, and their activation causes a decrease in heart rate due to this hyperpolarization caused by the muscarinic receptors (as Otto Loewi demonstrated with the isolated frog heart preparation.)

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Animation 15.1. 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.

Neuropharmacology and Acetylcholine Systems

Different drugs have the ability to interact within a neurotransmitter system, in many cases by directly interacting with a neurotransmitter receptor protein. There are two main classes of drugs that we will discuss: **agonists** and **antagonists**. An **agonist** is a drug that binds to a receptor and acts to activate the normal function of that receptor. An **antagonist** is a drug that binds to a receptor that acts to block the normal function of that receptor. The acetylcholine neurotransmitter system can be used as an example to see the function of both agonists and antagonists.

Drugs that interact with the nicotinic acetylcholine receptor

Nicotine is an agonist for the nicotinic acetylcholine receptor (which is how the receptor got its name). Normally, the nicotinic receptor causes excitatory postsynaptic potentials. Because nicotine is an agonist for this receptor, when it binds to the nicotinic acetylcholine receptor it also causes excitatory post synaptic potentials and lead to an overall increase in activity.

There are also antagonists for the nicotinic acetylcholine receptor. **Curare**, a substance that comes from the resin of a tree in South America and **α-bungarotoxin**, a toxin found in Krait snake venom, are both examples of antagonists for the nicotinic acetylcholine receptor. Recall that normally the nicotinic acetylcholine receptor causes excitatory post synaptic potentials. As antagonists, curare and α-bungarotoxin will block excitatory postsynaptic potentials, leading to an overall decrease in activity.

Drugs that interact with the muscarinic receptor

Muscarine, a substance found in certain mushrooms, is an agonist for the muscarinic receptor (and how the receptor got its name). As an agonist, muscarine will promote the normal function of the receptor. Normally, muscarinic receptors produce inhibitory post synaptic potentials. Thus, muscarine binding to muscarinic receptor will cause inhibitory post synaptic potentials, causing an overall decrease in activity.

Atropine is a drug that acts as an antagonist at the muscarinic receptor. Antagonists block the normal function of the receptor. Because normally the muscarinic receptor is inhibitory, atropine will block the normal inhibitory effects, leading to an overall increase in activity.

Termination of Acetylcholine Signaling

The enzyme **acetylcholinesterase**, located in the synaptic cleft and within the postsynaptic membrane, chemically breaks down acetylcholine into acetic acid and choline.

Choline can also undergo the process of **reuptake** which will remove choline from the synapse (which will effectively stop acetylcholine signaling) and bring it into the presynaptic cell through the **choline transporter**. Acetylcholinesterase is an important enzyme to regulate acetylcholine within the body. Recall that acetylcholine is used at the neuromuscular junction between motor neurons and

skeletal muscles. The acetylcholinesterase enzyme prevents continuous stimulation of our muscles, allowing tight control. In fact, acetylcholinesterase is one of the fastest acting enzymes within the body. Nerve gas and neostigmine (in Nigerian beans) both act to inhibit acetylcholinesterase, causing excessive acetylcholine signaling.

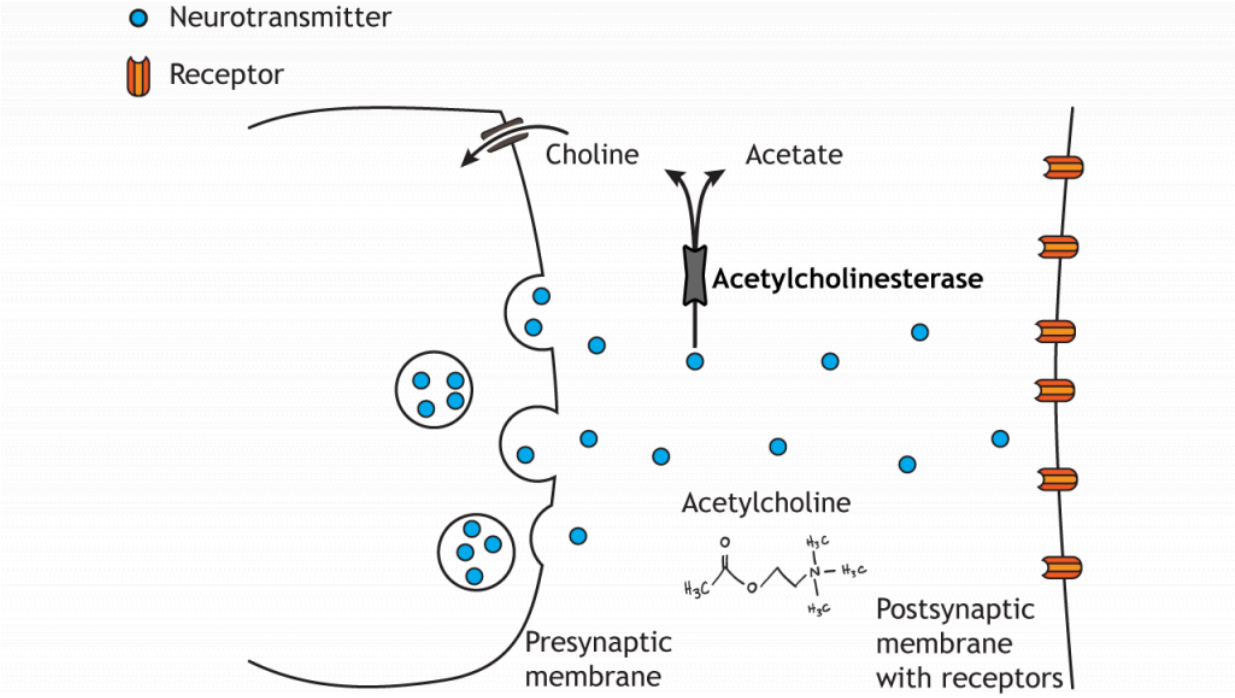

Figure 15.4. Acetylcholine is degraded into choline and acetate within the synaptic cleft via acetylcholinesterase. Choline is then transported back into the presynaptic terminal. 'Acetylcholine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Acetylcholine was the first identified neurotransmitter and was discovered by Otto Loewi
- Acetylcholine is synthesized within the presynaptic terminal from choline and acetate through ChAT and packaged into vesicles by VAchT
- Acetylcholine binds to both ionotropic (nicotinic) and metabotropic (muscarinic) receptors
- Nicotinic receptors are excitatory and muscarinic receptors are inhibitory
- Agonists are drugs that promote the normal activity of the receptor that they bind to
- Antagonists are drugs that block the normal activity of the receptor that they bind to
- Acetylcholine signaling is terminated through the enzymatic activity of acetylcholinesterase

Test Yourself!

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16.

NEUROTRANSMITTERS: AMINO ACID NEUROTRANSMITTERS (GLUTAMATE, GABA, GLYCINE)

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Glutamate

Glutamate is an amino acid transmitter and is the primary excitatory neurotransmitter in the brain. **Glutamate** is the same as the amino acid glutamic acid. There is more glutamate per volume of brain tissue than any other neurotransmitter.

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 small vesicles for storage via the **vesicular glutamate transporter (vGLUT)**. Staining for the presence of vGLUT is one way that researchers are able to identify glutamatergic neurons.

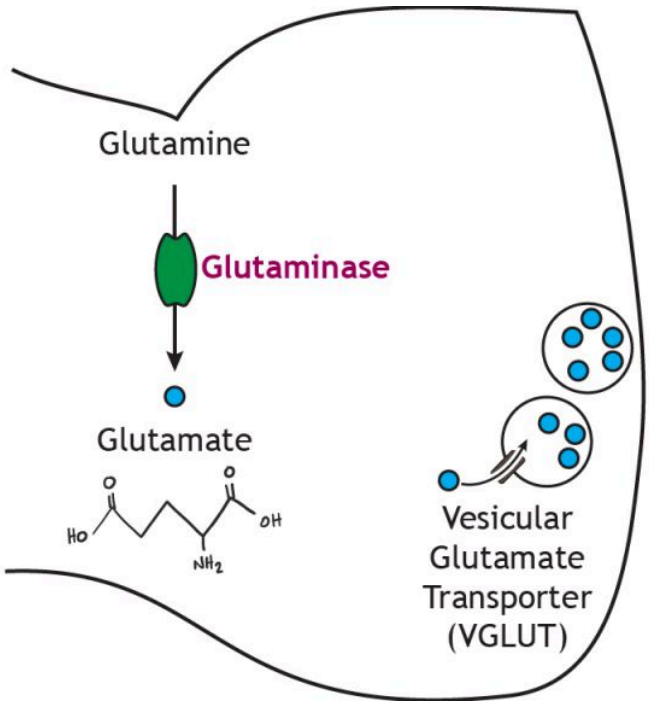

Figure 16.1. Glutamate is synthesized from glutamine by glutaminase, the rate-limiting step in the pathway. Glutamate is then packaged into vesicles by vesicular glutamate transporter. 'Glutamate Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Glutamate Receptors

Glutamate can activate both ionotropic and metabotropic receptors. Glutamate is the primary excitatory neurotransmitter in the central nervous system and opens non-selective cation channels. There are three subtypes of ionotropic glutamate receptors: AMPA, kainate, and NMDA receptors.

The **AMPA** (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and **kainate** receptors allow both sodium and potassium to cross the membrane. Although potassium can leave the cell when the receptors open, the electrochemical gradient driving sodium ion movement is stronger than the gradient driving potassium movement, resulting in a **depolarization** of the membrane potential.

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can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=482#video-482-1

Animation 16.1. AMPA and kainate glutamate receptors are non-selective ion channels that allow both sodium and potassium to flow across the membrane. When glutamate binds, sodium flows in and potassium flows out. The lined, teal channel represent 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.

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Animation 16.2. NMDA receptors are opened by a combination of glutamate binding and a voltage trigger. At low levels of stimulation, when the the membrane potential is near rest, a magnesium ion blocks the open NMDA receptor channel preventing ion flow. Ions can flow through open AMPA receptors, which begins to depolarize the membrane. The voltage change eventually expels the magnesium ion from the channel, allowing sodium, potassium, and calcium to cross the membrane. The lined, teal channel represents AMPA receptors; the dotted, violet channel represents NMDA receptors. 'AMPA and NMDA' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Termination of Glutamate Signaling

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.

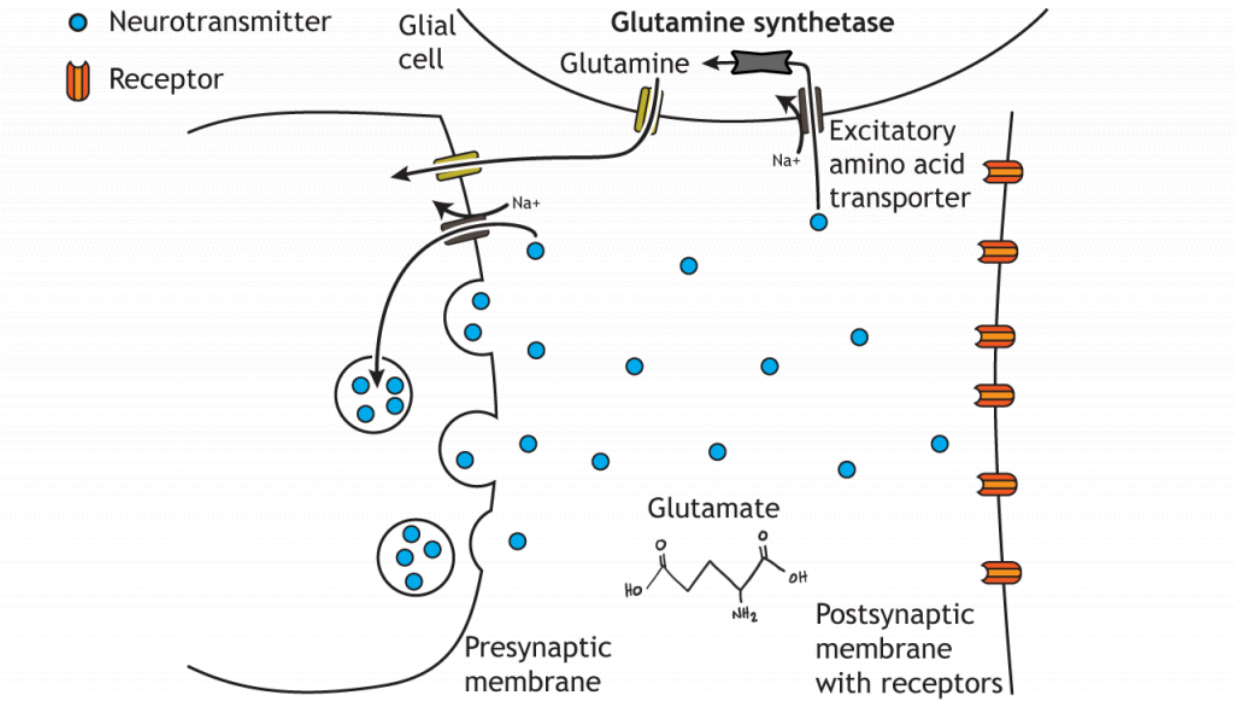

Figure 16.2. Glutamine needs to removed from the synapse. The excitatory amino acid transporter that uses sodium to drive glutamate movement across the membrane can move glutamate into glial cells or back into the presynaptic terminal. In the terminal, glutamate is repackaged into synaptic vesicles. 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

Glutamate is then used to synthesize **Gamma-aminobutyric acid (GABA)**, the main inhibitory neurotransmitter in the brain. According to one estimate, about 25% of neurons in the brain are GABAergic.

In the presynaptic terminal, glutamate is converted into GABA via the enzyme **glutamic acid decarboxylase (GAD)**, which—like the other synthesis pathways—is the rate-limiting step. GAD is often used as a biochemical marker for the presence of GABAergic neurons. GABA is packaged into small vesicles for storage in the terminal via the **vesicular inhibitory amino acid transporter (VIAAT)**.

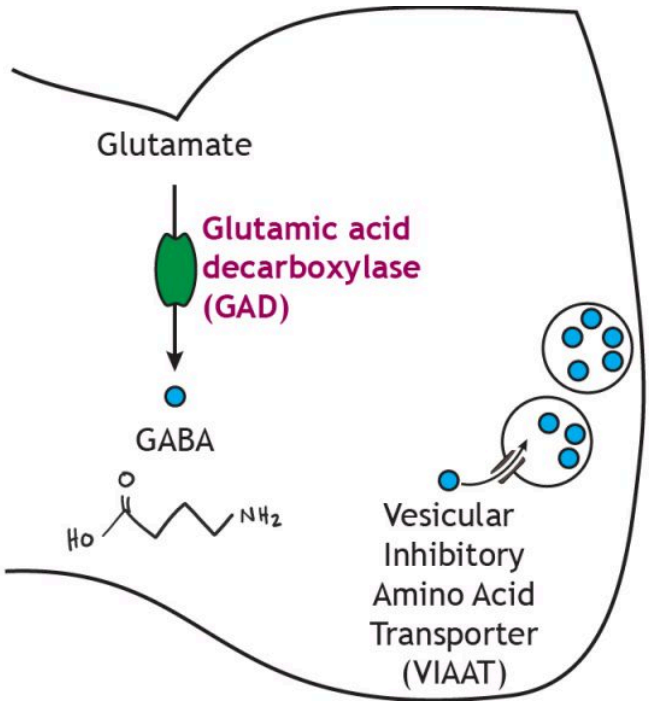

Figure 16.3. GABA is synthesized from glutamate by glutamic acid decarboxylase, the rate-limiting step in the pathway. GABA is then packaged into vesicles by vesicular inhibitory amino acid transporter. 'GABA Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Glycine

Glycine is another inhibitory amino acid neurotransmitter, but unlike GABA, is mostly used by neurons of the spinal cord and brain stem. **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 small vesicles by the **vesicular inhibitory amino acid transporter (VIAAT)** like GABA.

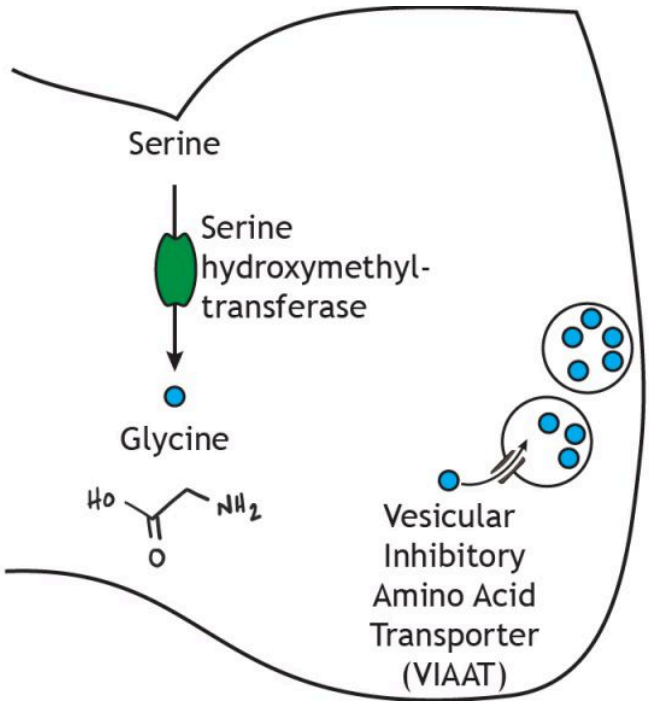

Figure 16.4. Glycine is synthesized from serine by serine hydroxymethyltransferase. Glycine is then packaged into vesicles by vesicular inhibitory amino acid transporter. 'Glycine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

GABA and Glycine Receptors

GABA and glycine receptors are chloride channels. Since an increase in 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 16.3. 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.

Termination of GABA and Glycine Signaling

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.

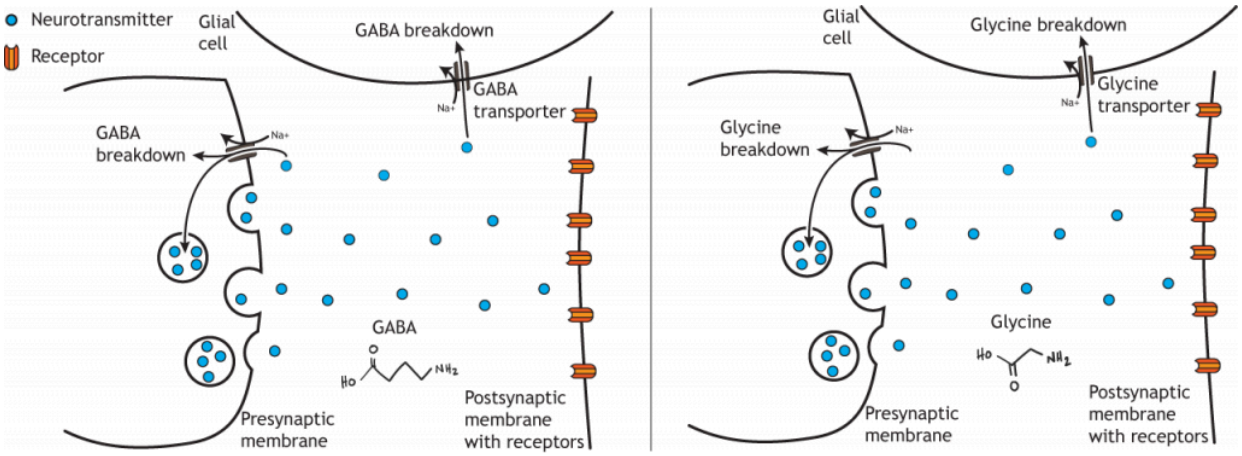

Figure 16.5. GABA and glycine action is terminated by reuptake by sodium co-transporters into either glial cells or back into the presynaptic terminal. In both locations, the neurotransmitters can be broken down by enzymes, whereas in the presynaptic terminal, the transmitters can be repackaged in synaptic 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.

Key Takeaways

- Glutamate is the primary excitatory neurotransmitter in the brain
- Glutamate binds to both ionotropic (AMPA, NMDA, and kainate) receptors and metabotropic receptors
- GABA is the primary inhibitory neurotransmitter in the brain
- Glycine is the primary inhibitory neurotransmitter in the periphery
- GABA and Glycine bind to ionotropic receptors that open chloride channels

Test Yourself!

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17.

NEUROTRANSMITTERS: BIOGENIC AMINES (SEROTONIN, HISTAMINE)

The biogenic amines encompass multiple neurotransmitters, including serotonin, histamine, dopamine, norepinephrine, and epinephrine. Included within the biogenic amines is a separate group of neurotransmitters, the catecholamines.

This chapter will provide information for only serotonin and histamine. Catecholamines are covered in the following chapter.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Serotonin

Serotonin, a biogenic amine neurotransmitter, is known for its role in mood. As with dopamine (another monoamine neurotransmitter), there are only a few areas of the brain that synthesize serotonin, the major one being the Raphe nucleus in the brain stem.

Synthesis

The enzyme **tryptophan hydroxylase** is the first step of serotonin biosynthesis, converting the amino acid **tryptophan** into **5-hydroxytryptophan** and is often used as a marker to identify serotonergic neurons. 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 small vesicles by the **vesicular monoamine transporter** similar to the other monoamine neurotransmitters: dopamine, norepinephrine, and epinephrine.

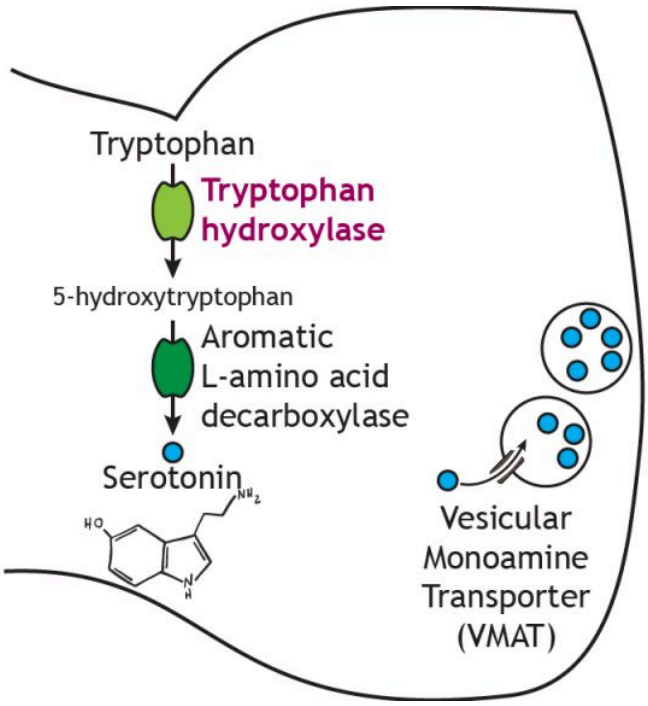

Figure 18.1. Serotonin is synthesized in a two-step process. Tryptophan is converted into 5-hydroxytryptophan by tryptophan hydroxylase, the rate-limiting step in the pathway. Then serotonin is synthesized from 5-hydroxytryptophan by aromatic L-amino acid decarboxylase. Serotonin is then packaged into 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.

Serotonin Receptors

Serotonin binds to many different classes of receptors, including both ionotropic and metabotropic receptors. Most of the serotonin receptors are metabotropic receptors that utilize G-proteins to cause the opening of ion channels, or alter the activity of phospholipase C or adenylyl cyclase. Due to the large number of different serotonin receptors, the effects of serotonin can vary depending on the properties of the postsynaptic receptor. Only one class of serotonin receptors are ligand-gated ion channels and utilize a direct mechanism of action.

Termination of Serotonin Signaling

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

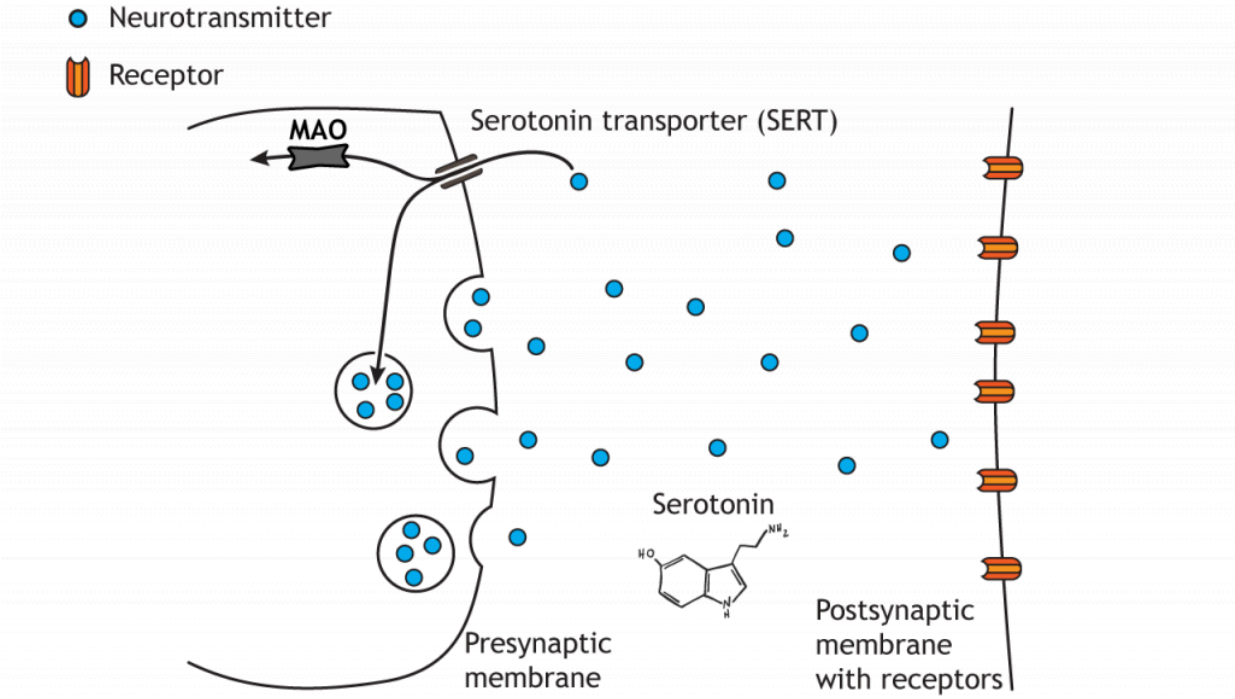

Figure 18.3. Serotonin action is terminated by reuptake into the presynaptic terminal via SERT. Serotonin is then either degraded by MAO or repackaged into synaptic vesicles. 'Serotonin Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Histamine

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

Though histamine has known roles in the immune system with allergic reactions and the inflammatory response, this chemical can also act as a hormone and a neurotransmitter within the central nervous system.

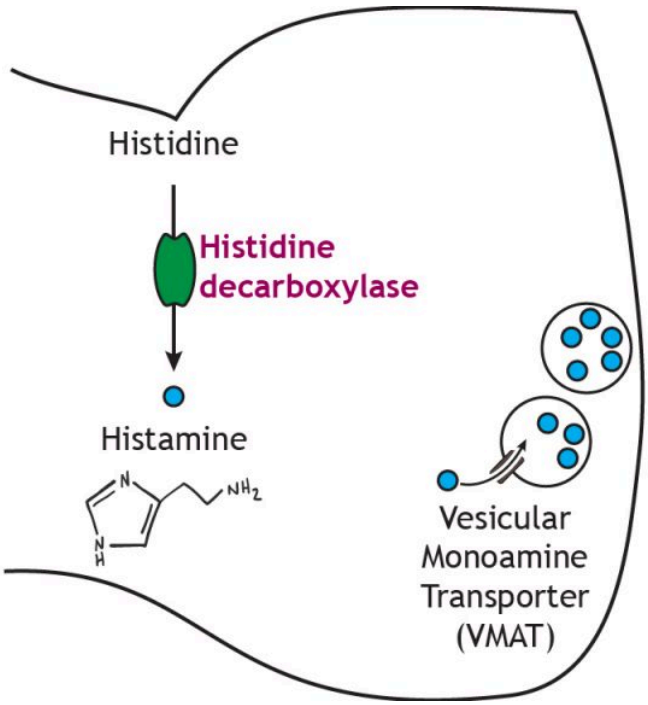

Figure 18.4. Histamine is synthesized from histadine by histadine decarboxylase, the rate-limiting step in the pathway. Histamine is then packaged into vesicles by vesicular monoamine transporter. 'Histamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Serotonin and histamine are both examples of biogenic amine neurotransmitters

- Serotonin and histamine have different synthesis pathways, but are both packaged into vesicles by the same protein, VMAT
- Serotonin binds to both ionotropic and metabotropic receptors

Test Yourself!

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18.

NEUROTRANSMITTERS: CATECHOLAMINES (DOPAMINE, NOREPINEPHRINE, EPINEPHRINE)

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Catecholamines are a class of neurotransmitters that are found within the larger class of neurotransmitters, biogenic amines. The catecholamines share many characteristics.

Dopamine

Dopamine, a catecholamine transmitter, plays many roles in the nervous system, but it is best known for its roles in reward and movement.

Synthesis

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 small synaptic vesicles by the **vesicular monoamine transporter (VMAT)**.

Unlike glutamate or GABA, dopamine-producing neurons are not widely abundant in the brain. Instead, there are generally only a few patches of neurons that produce dopamine, most of which are found in the midbrain. Two areas include the ventral tegmental area and the substantia nigra.

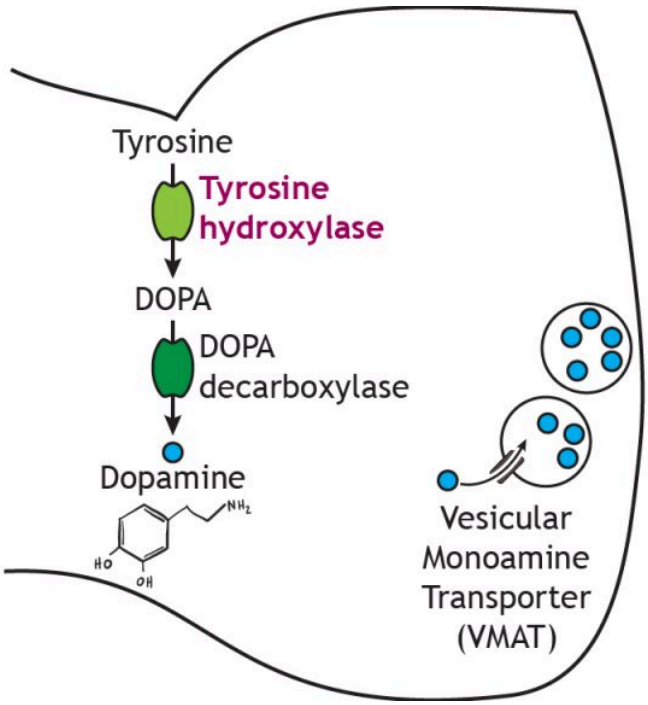

Figure 18.1. Dopamine is synthesized in a two-step process. Tyrosine is converted into DOPA by tyrosine hydroxylase, the rate-limiting step in the pathway. Then dopamine is synthesized from DOPA by DOPA decarboxylase. Dopamine is then packaged into vesicles by vesicular monoamine transporter. 'Dopamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Dopamine Receptors

Dopamine binds to metabotropic receptors on postsynaptic cells. There are two classes of dopamine metabotropic receptors: **D1-like receptors** and **D2-like receptors**. D1-like receptors are typically associated with $G\alpha_s$ and cause activation of the cAMP/adenylyl cyclase second messenger system and the generation of EPSPs in the postsynaptic cell.

D2-like receptors, however, are typically associated with $G\alpha_i$ that inhibits the cAMP/adenylyl cyclase second messenger system and generate IPSPs in the postsynaptic cell.

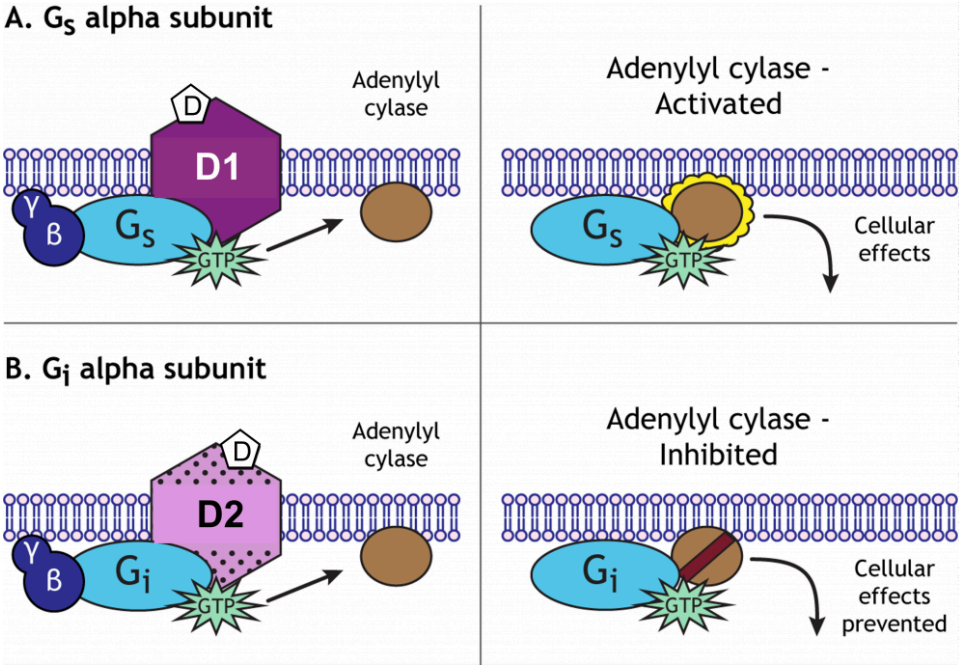

Figure 18.2. Dopamine Receptors. Dopamine (shown by the 'D') binds to metabotropic receptors. The D1-like class of receptors couples to the Gαs subunit and activates adenylyl cyclase, which initiates downstream cellular effects. B) The D2-like class of dopamine receptors couples to the Gαi subunit and inhibits adenylyl cyclase, which prevents downstream cellular effects.

Termination of Dopamine Signaling

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.

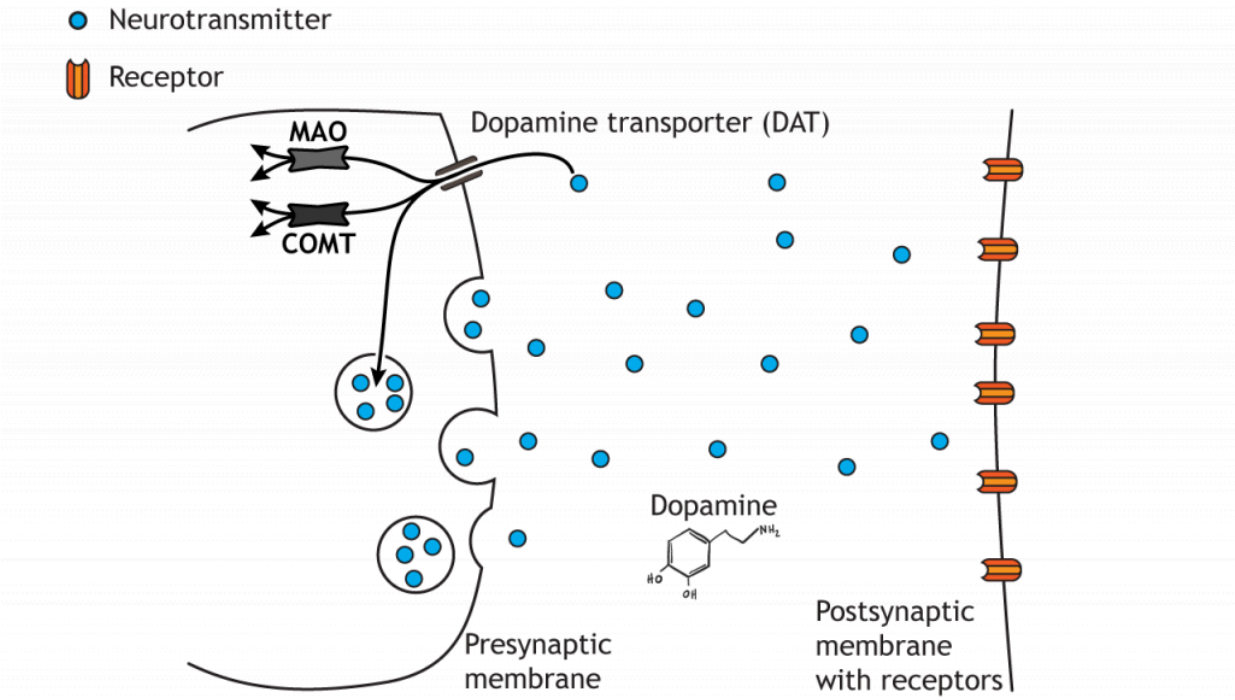

Figure 18.3. Dopamine action is terminated by reuptake into the presynaptic terminal via DAT. Dopamine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Dopamine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Norepinephrine

Norepinephrine-producing cells are localized in the pons of the brain stem, a structure called the locus coeruleus. The locus coeruleus is very small, but these neurons send projections widely throughout the brain. Outside of the brain, we think of norepinephrine as being responsible for triggering the sympathetic nervous system response of the body, the "fight-or-flight" reaction that prepares the body for physical activity in times of fear or acute stress.

Synthesis

In neurons that release norepinephrine, which is another catecholamine transmitter, once dopamine is packaged into small 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.

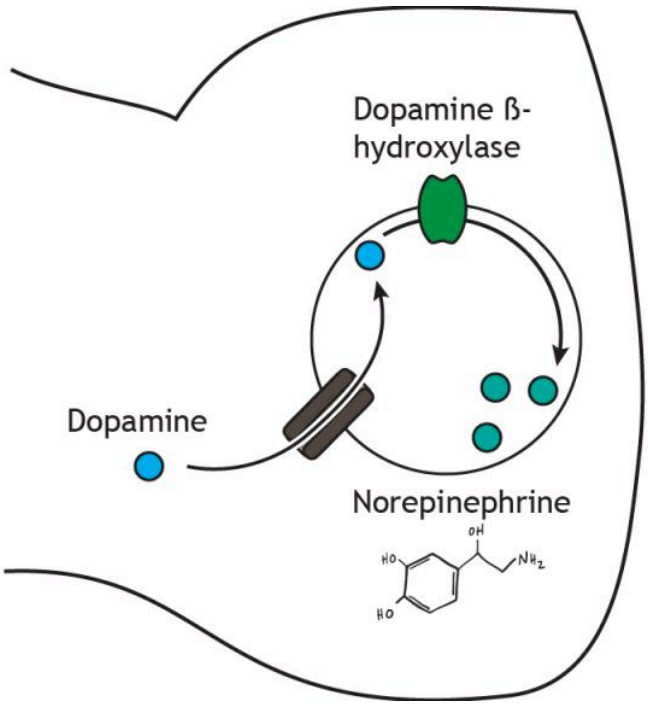

Figure 18.4. Norepinephrine is synthesized from dopamine by dopamine beta-hydroxylase after packaging into vesicles. 'Norepinephrine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Norepinephrine Receptors

Norepinephrine binds to **metabotropic** adrenergic receptors (α1, α2, and β). The binding of norepinephrine to its receptor activates second messenger signaling cascades that will cause either EPSPs or IPSPs, depending on the receptor subtype.

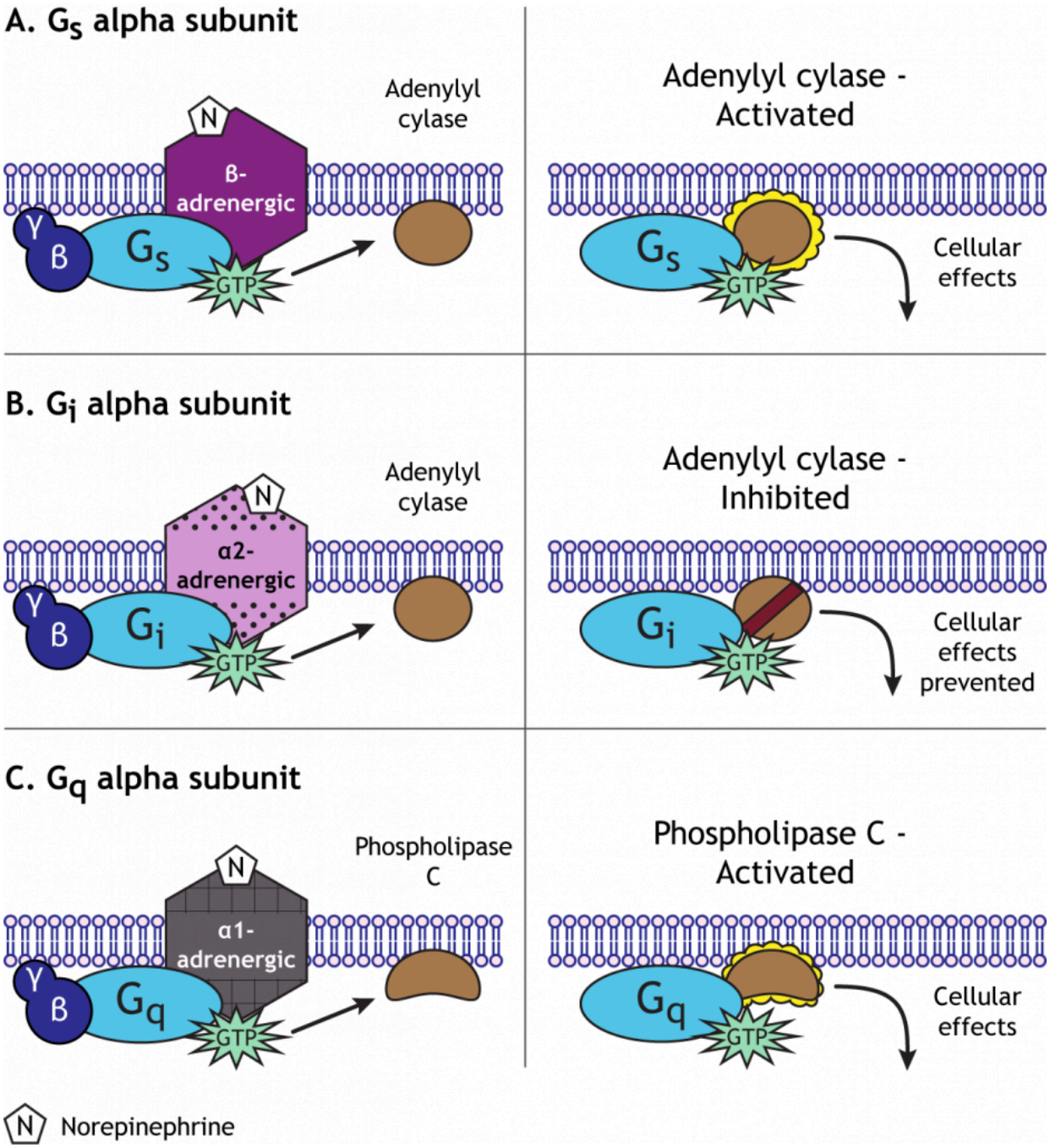

Figure 18.5. The norepinephrine beta-adrenergic receptor couples to the $G\alpha_s$ subunit and activates adenylyl cyclase, which initiates downstream cellular effects. B) The norepinephrine alpha 2-adrenergic receptor couples to the $G\alpha_i$ subunit and inhibits adenylyl cyclase, which prevents downstream cellular effects. C) The norepinephrine alpha 1-adrenergic receptor couples to the $G\alpha_q$ subunit and activates phospholipase C, which initiates downstream cellular effects. 'Alpha Subunit Effects' by Casey Henley is

Termination of Norepinephrine Signaling

Termination of norepinephrine signaling is similar to the termination of dopamine signaling. 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.

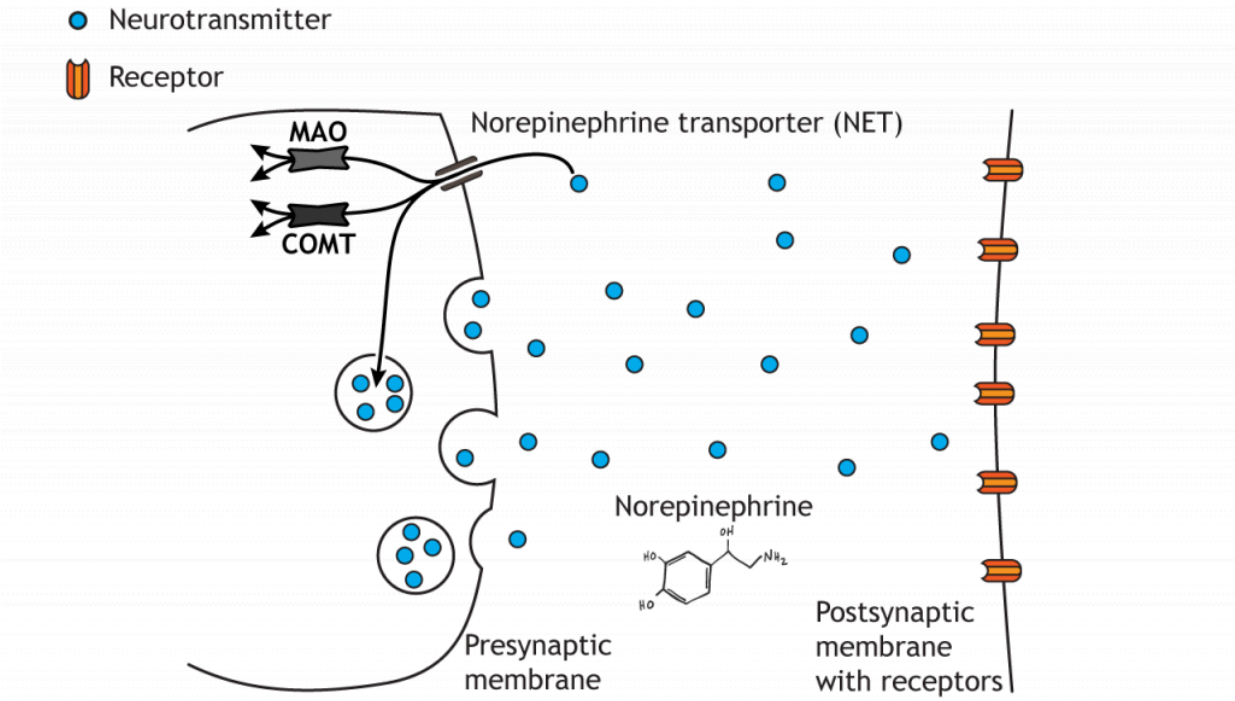

Figure 18.6. Norepinephrine action is terminated by reuptake into the presynaptic terminal via NET. Norepinephrine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Norepinephrine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial 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.

Synthesis

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 small vesicles via the **vesicular monoamine transporter**.

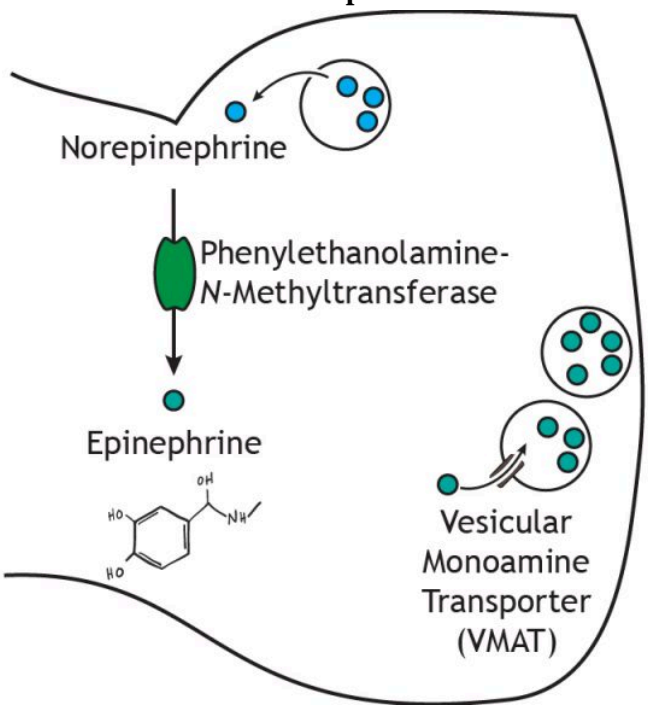

Figure 18.7. Epinephrine is synthesized from norepinephrine by phenylethanolamine-N-methyltransferase in the cytoplasm. Epinephrine is then packaged into vesicles by vesicular monoamine transporter. 'Epinephrine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Epinephrine Receptors

Epinephrine also binds to α and β adrenergic receptors (described above for norepinephrine) and causes similar activity when bound to these receptors.

Termination of Epinephrine Signaling

Epinephrine, similarly to norepinephrine, also goes through reuptake into the presynaptic cell. Further, it is also degraded within the cell by both **MAO** or **COMT** or repackaged into synaptic vesicles.

Key Takeaways

- The catecholamines are synthesized from the amino acid tyrosine
- The synthesis pathways overlap and share many enzymes and proteins
- The catecholamines bind to metabotropic receptors
- The catecholamines are inactivated via similar mechanisms: reuptake, MAO and COMT

Test Yourself!

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19.

NEUROTRANSMITTERS: ATYPICAL NEUROTRANSMITTERS

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Although we generally think of neurotransmitters as neurochemicals that function as described above, there are a few atypical neurotransmitters that don't quite fit the mold of the other chemical signals.

Neuropeptides

Neuropeptides are a class of large signaling molecules that some neurons synthesize. Neuropeptides are different from the traditional neurotransmitters because of their chemical size. 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.

Synthesis and Storage

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.

Monoamines like dopamine, norepinephrine, or serotonin have a molecular weight around 150-200, while one of the smaller neuropeptides, enkephalin, has a molecular weight of 570. One of the largest neuropeptides, dynorphin, has a molecular weight greater than 2,000. Because of their large size, neuropeptides have to be packaged in dense core vesicles very close to the site of production near the nucleus, rather than in clear vesicles right at the terminal. These large vesicles must then move from the soma to the terminal.

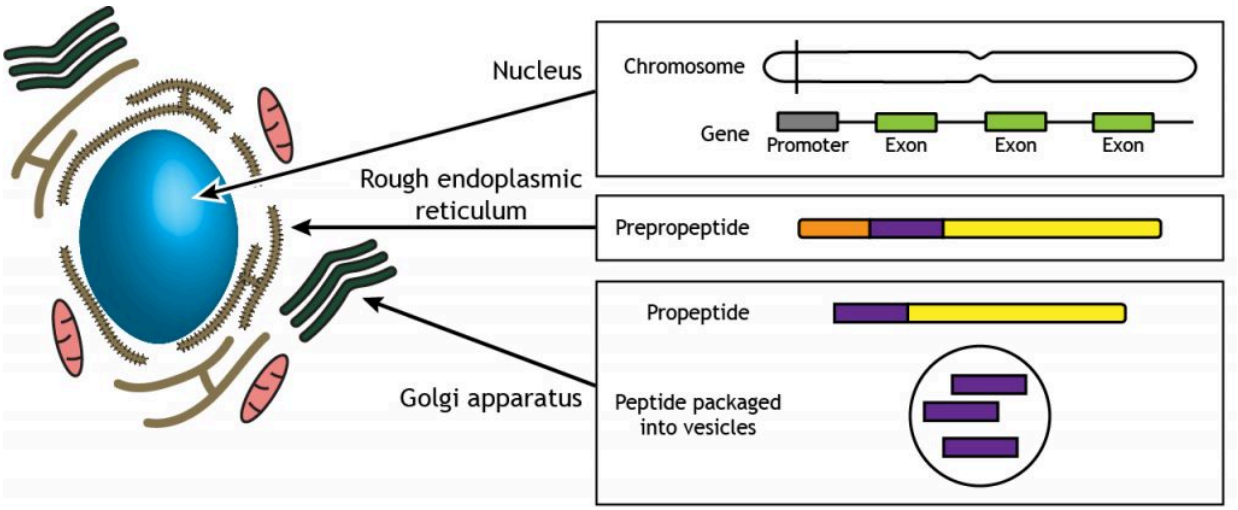

Figure 19.1. Neuropeptide synthesis occurs in the cell body. Each neuropeptide is encoded by a gene on the DNA located in the nucleus. mRNA is translated into an amino acid sequence for a precursor molecule called a prepropeptide in the rough endoplasmic reticulum. Further processing and packaging of 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 of Neuropeptides

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.

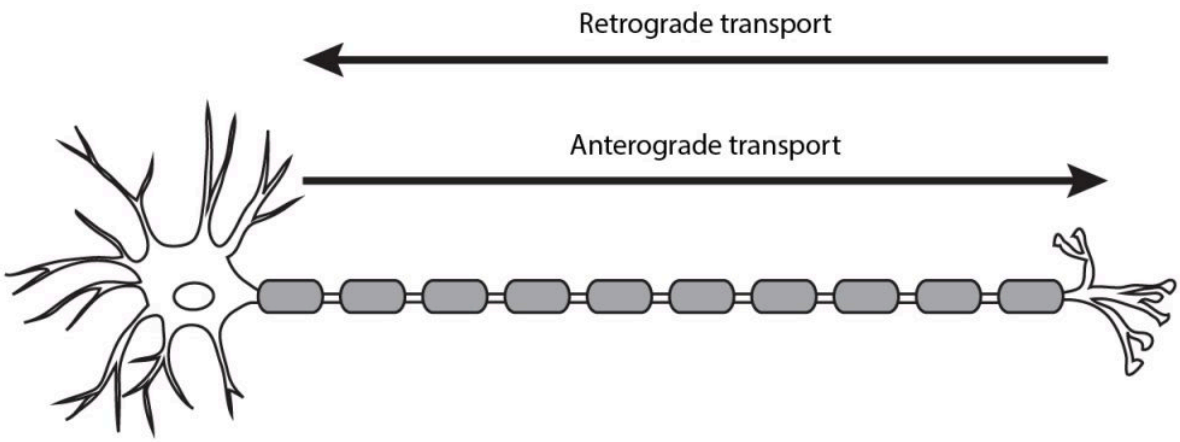

Figure 19.2. Cellular components need to be able to move throughout the cell to have proper functioning. Anterograde transport moves components from the cell body toward the terminal. Retrograde transport moves components from the terminal toward the cell body. 'Axonal Transport' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Neuropeptide Receptors

Neuropeptides such as enkephalin and dynorphin are agonists at a class of receptors called the opioid receptors. These opioid receptors fall into four main types. The three classical opioid receptors are named using Greek letters: δ (delta), μ (mu), and κ (kappa); the fourth class is the nociceptin receptor. All of these receptors are inhibitory metabotropic receptors which signal using the $G\alpha_i$ protein. These receptors are expressed in several brain areas, but expression is particularly heavy in the periaqueductal gray, a midbrain area that functions to inhibit the sensation of pain. Drugs that activate the opioid receptors, like morphine, oxycontin, or fentanyl, are the most effective clinical treatments that we know of for acute pain. Unfortunately, these same drugs also represent a tremendous health risk, as opioid drugs can be lethal in overdose and have a high risk of substance use disorder.

Endocannabinoids

Endocannabinoids are **endogenous** lipid neurotransmitters that are a bit unusual compared to the other neurotransmitters that we have covered. First, they signal in a **retrograde** manner. This means

that the endocannabinoids neurotransmitters are released by the postsynaptic cell and bind to receptors on the presynaptic cell. Additionally, endocannabinoids are not packaged into vesicles and released by fusion with the cell membrane.

Instead, when the postsynaptic cell has an action potential, it causes **voltage-gated** calcium channels in the postsynaptic cell to open, and for calcium ions to rush into the postsynaptic cell. The local increase in calcium concentration within the postsynaptic cell triggers the cell to synthesize endocannabinoids. Again, these neurotransmitters are not stored in vesicles like the other neurotransmitters that have been discussed. Instead, these lipid neurotransmitters are made on demand, or synthesized 'de novo'. As lipids, the endocannabinoids are membrane **permeable** and can diffuse out of the cell through the cell membrane. The two most well-characterized eCBs in humans are called 2-Arachidonoylglycerol (2-AG) and Anandamide (ANA).

The endocannabinoids bind to one of two receptors, CB1 or CB2. Both receptor types are inhibitory **metabotropic** receptors that are located on the presynaptic cell and coupled to $G\alpha_i$. Generally, CB1 receptors are found in the nervous system, while the CB2 receptors are found elsewhere in the body, such as in the immune system. Activity of the metabotropic CB1 receptors causes presynaptic calcium channels to close, reducing the concentration of calcium in the presynaptic cell, and thus decreasing the amount of neurotransmitter released by the presynaptic cell.

The endocannabinoid system is widely used by various systems in the body. It is estimated that endocannabinoid receptors are the most abundant GPCRs in the whole body. These substances were named because they are endogenous chemicals that are functionally similar to compounds found in plants of the genus Cannabis. One reason cannabis is used is because of its ability to interact with our endocannabinoid receptors.

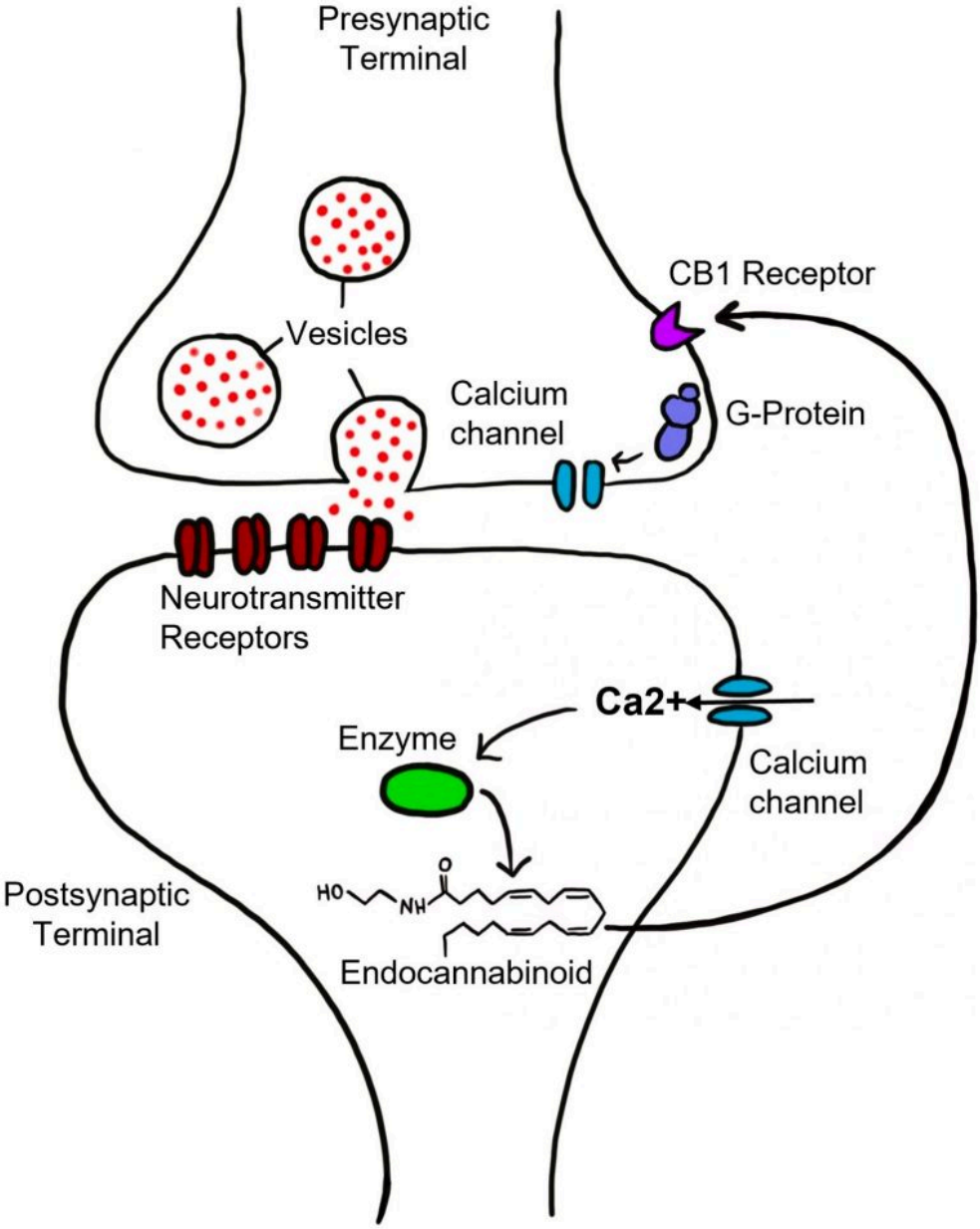

Figure 19.3. Endocannabinoid Signaling. When the postsynaptic terminal is stimulated, it causes the voltage-gated calcium channels to open in the postsynaptic cell. Calcium rushes into the postsynaptic cell and causes intracellular enzyme (shown in green) to produce lipid endocannabinoids. The endocannabinoids signal in a retrograde fashion to the presynaptic cell, where they bind to metabotropic CB1 receptors. Activation of the CB1 receptors causes closing of presynaptic voltage-gated calcium channels, and decreased release of neurotransmitters from the presynaptic cell. 'Endocannabinoid Signaling' by Valerie Hedges is licensed under a Creative

Nitric Oxide

The nervous system is capable of signaling via the gas nitric oxide (NO). This gas transmitter is not stored in vesicles, but is synthesized as it is needed. NO is formed when the amino acid arginine is degraded by the enzyme NO synthase (NOS). Because NO is a gas, it easily permeates across cell membranes. Therefore, the receptors for NO do not need to be transmembrane proteins expressed on the cell surface. Instead, the receptor for NO is an intracellular receptor called soluble guanylate cyclase (sGC). SGC works through a signaling pathway that is different from other metabotropic receptors so far described. SGC is linked with the signaling molecule cyclic GMP (cGMP), which activates protein kinase G (PKG). PKG can either be excitatory or inhibitory, depending on the intracellular components.

Key Takeaways

- Neuropeptides are proteins that are synthesized in the cell body and are transported in vesicles to the axon terminal
- Endocannabinoids are lipid neurotransmitters that use retrograde signaling. They are synthesized and released by the postsynaptic cell and bind to metabotropic CB1 receptors on the presynaptic cell to alter neurotransmitter release.
- Nitric oxide is a gas neurotransmitter that is not stored in vesicles but instead is made on demand. As a gas, nitric oxide can easily cross the phospholipid bilayer and bind to intracellular receptors.

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20.

DRUG AND TOXIN EFFECTS

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

Resources

- Glossary terms
- Key Takeaways
- Test Yourself

Synaptic Effects

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

Drug Effects on Neurotransmitter Release

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

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

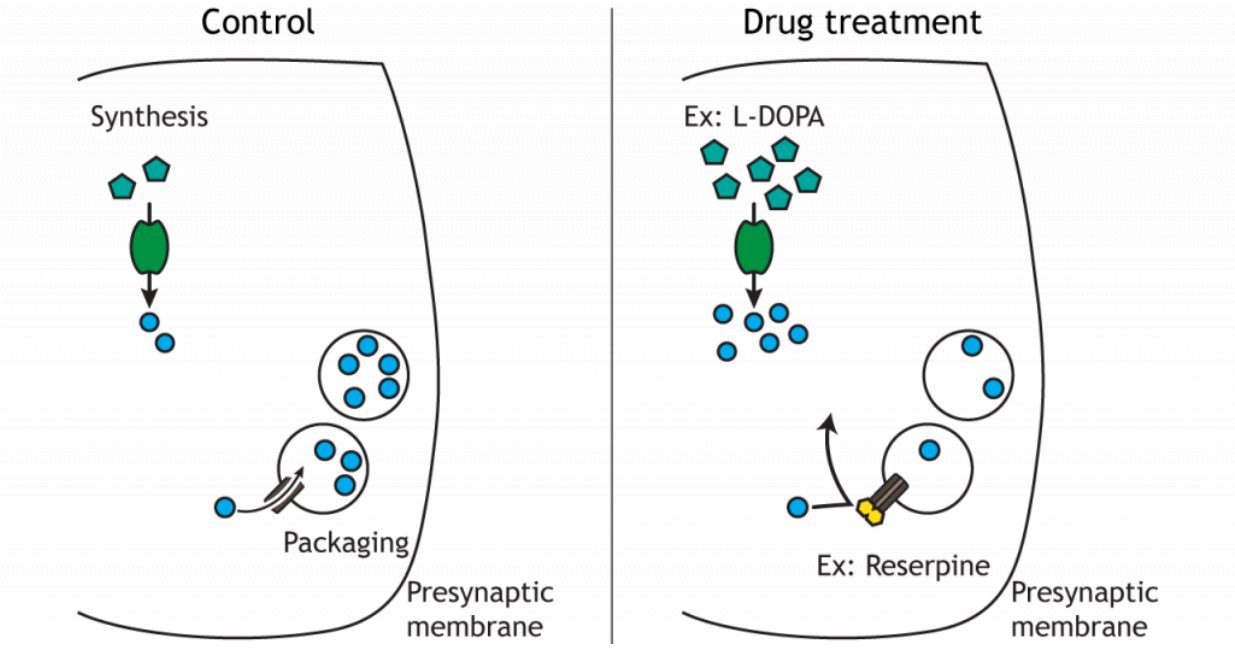

Figure 20.1. Drugs and toxins can alter neurotransmitter synthesis and packaging into synaptic vesicles. L-DOPA increases the synthesis of dopamine in the terminal. Reserpine prevents packaging of the biogenic amines, resulting in low concentrations of transmitter stored in synaptic vesicles. 'Drug Effects on Neurotransmitter Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Drug Effects on the Postsynaptic Membrane

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

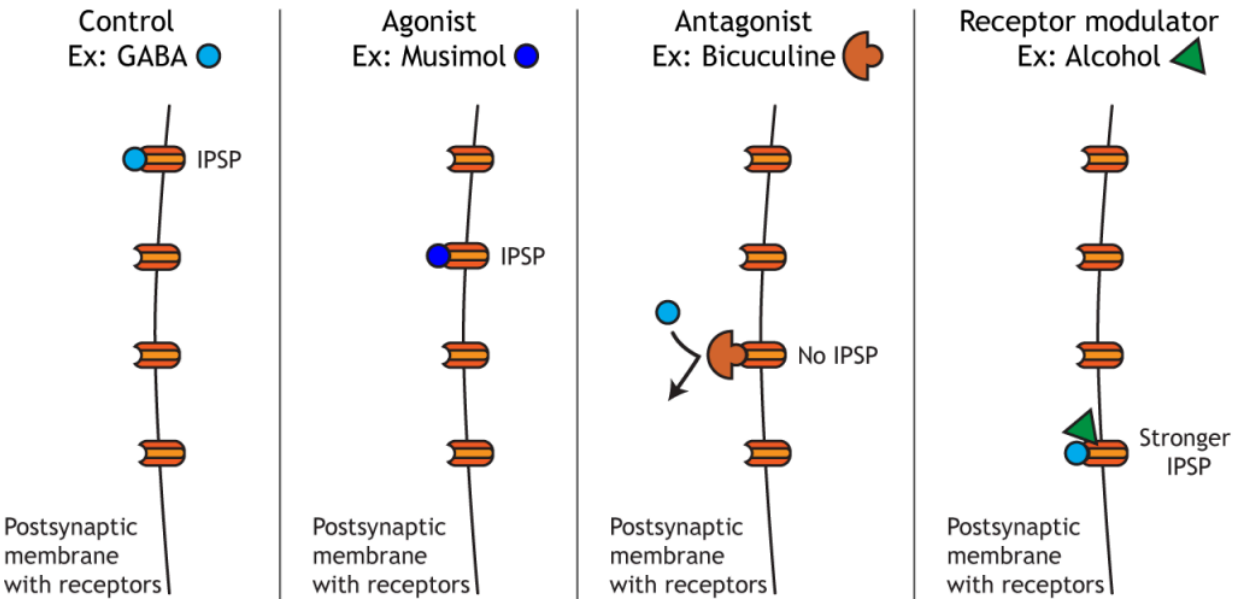

Figure 20.2. Drugs and toxins can alter neurotransmitter receptors on the postsynaptic neuron. A GABA agonist, muscimol, would replicate the actions of GABA and cause an IPSP. A GABA antagonist, bicuculine, would prevent GABA actions resulting in no IPSP. Modulators such as alcohol, alter how the receptor works, so when GABA binds the response is a stronger IPSP than when alcohol is not present. 'Postsynaptic Drug Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Drug Effects on Neurotransmitter Clearance

Finally, neurotransmitter degradation and **reuptake** can also be altered by drugs and toxins. Depending on the neurotransmitter, enzymes located in either the synapse or in the terminal are responsible for degradation of the transmitter, and these enzyme can be blocked by drugs. Organophosphates are found in many pesticides and prevent the action of acetylcholinesterase, the enzyme that breaks down acetylcholine in the synapse. This inhibition increases acetylcholine action on the postsynaptic neuron. Monoamine oxidase inhibitors (MAOIs) prevent monoamine oxidase from degrading the biogenic amine neurotransmitters. MAOIs have been used as antidepressants since they increase the amount of transmitter available. Additionally, drugs can prevent the reuptake of neurotransmitters into the presynaptic terminal. Cocaine blocks the dopamine transporter, which results in increased action of dopamine in the synapse.

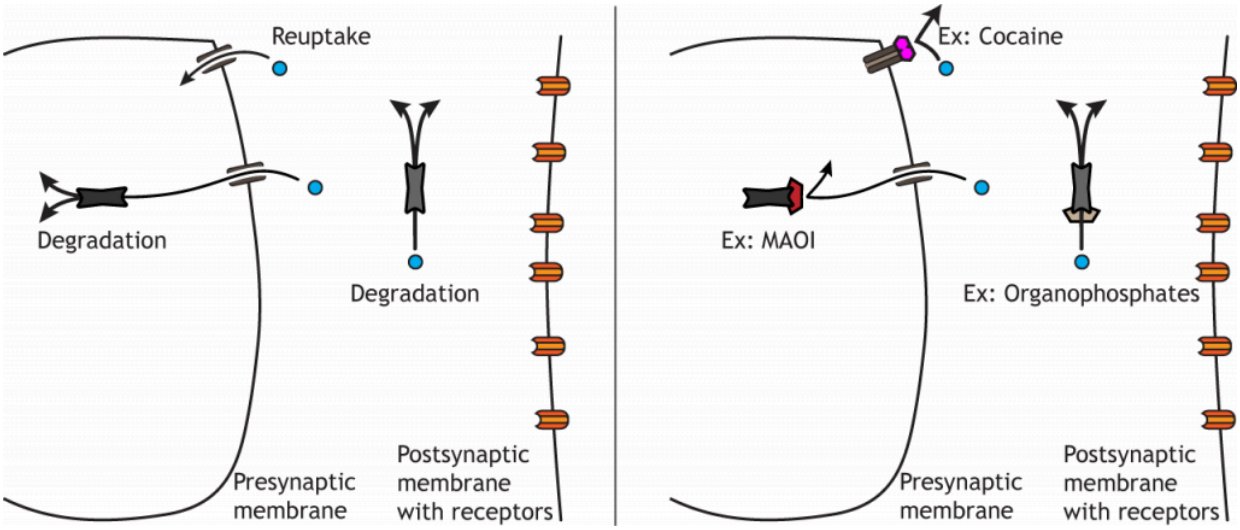

Figure 20.3. Drugs and toxins can alter neurotransmitter degradation and reuptake into the presynaptic terminal. Organophosphates prevent the degradation of acetylcholine in the synapse. MAOIs prevent the degradation of monoamine transmitters in the terminal. Cocaine prevents dopamine from being transported into the presynaptic terminal. All of these effects lead to increased neurotransmitter action and availability. 'Drug Effects on Neurotransmitter Clearance" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Non-Synaptic Effects

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

Key Takeaways

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

- Effects can be excitatory, inhibitory, or modulatory

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PART IV

NERVOUS SYSTEM ORGANIZATION

21.

ANATOMICAL TERMINOLOGY

The nervous system is one of the most complex systems that we know of. Parts of this system malfunction frequently, and the results are a wide range of neurological disorders that affect humans, from injury to genetic disorders. The gross anatomy of the nervous system is an important foundation to the studies of other aspects of neuroscience. This chapter covers some of the major anatomical structures in the nervous system.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Divisions of the Nervous System

Broadly speaking, the nervous system can be divided into two main categories: The central nervous system (**CNS**) and the peripheral nervous system (**PNS**). Simply put, the CNS is the brain and spinal cord, while the PNS is all the other nerve cells in the body in the periphery. The two systems are not isolated from each other; information passes rapidly between the PNS and the CNS, and vice versa. When a signal that originates in the PNS moves to the CNS, we sometimes say that the signal is incoming or ascending, while the CNS to PNS direction is outgoing or descending. Information that arrives into the CNS is also called an **afferent** signal, while information leaving the CNS is an **efferent** signal. These two terms are frequently confused, but you can use the knowledge of other words that start with "e" to remember that an "exit" or an "escape" is something that moves away for 'efferent', and "arrive" for 'afferent'. Alternatively, an efferent signal is something that has an effect on the outside world, while an afferent signal affects the person.

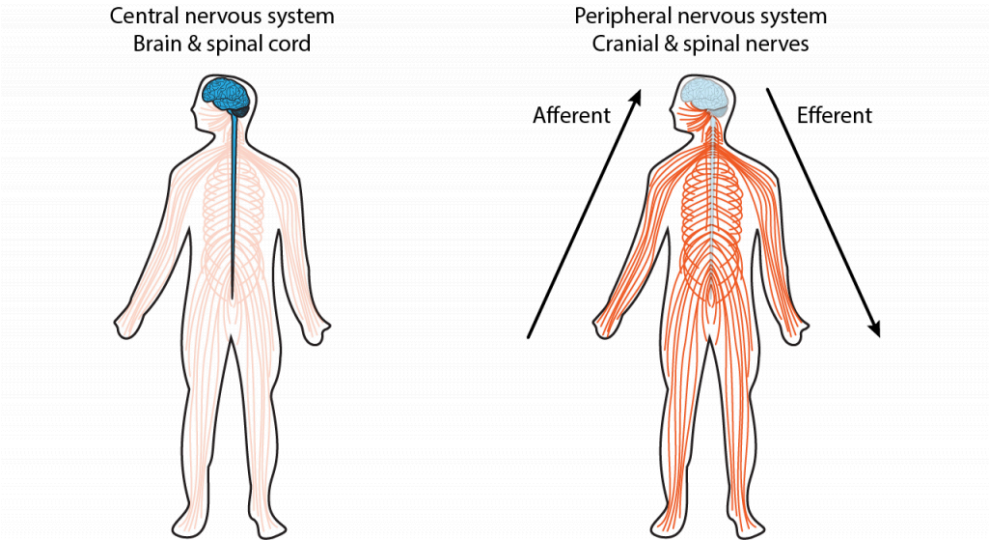

Figure 21.1. The nervous system is divided into the central nervous system, which includes the brain and spinal cord, and the peripheral nervous system, which includes the cranial and spinal nerves. Information traveling toward the brain is called afferent, whereas information traveling from the brain is called efferent. 'CNS and PNS' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Anatomically, the CNS consists of two organs, the brain and the spinal cord. The brain is the main organ where movement originates, where thoughts and plans develop, and where consciousness is housed. The brain is what pushes us to act on our drives and desires, where language begins, and where memories are stored. The intact adult brain weighs about 1.5 kg (3 pounds), which is barely 2% of total body weight. Despite this relatively small size, it is extremely power hungry, and uses up about one-fifth of the body's total energy expenditure.

Anatomical Terms

When talking about parts of the brain, it is helpful to have a set of directional terms that can describe the location of various anatomical structures unambiguously.

Familiarity with the terminology used to describe location and relationships within the nervous system is critical as we move forward into examining brain systems.

Directional Terms

Directional terms are used to locate one structure, usually in relation to another structure. Some terms, like dorsal or ventral, are relative to the axis of the central nervous system, so the direction these terms define changes if used for brain regions versus other body regions. Other terms, like superior or inferior, keep their meaning across the entire body.

- **Anterior**: In front of; toward the face
- **Posterior**: Behind; toward the back
- **Superior**: Above; toward the head
- **Inferior**: Below; toward the feet
- **Medial**: Toward the middle
- **Lateral**: Toward the edge
- **Dorsal**: Toward the top of the brain or the back of the spinal cord
- **Ventral**: Toward the bottom of the brain or the front of the spinal cord
- **Rostral**: Toward the front of the brain or the top of the spinal cord
- **Caudal**: Toward the back of the brain or the bottom of the spinal cord

Often anterior and rostral are used interchangeably and posterior and caudal are used interchangeably.

Neuroanatomists use all of these terms to describe the relationship of one structure to another. For example, we'll see in Chapter 22 that introduces the four lobes of the brain, the frontal lobe is anterior or rostral to the parietal lobe, and the parietal lobe is dorsal to the temporal lobe. These anatomical words can also be combined to subdivide complex brain regions. For example, a structure called the thalamus has many small subsections, such as the dorsomedial nucleus or the ventropostero-

lateral nucleus. Naming structures with this anatomical language is useful in identifying where they are located in a brain scan or autopsy, but these words tell us nothing about function.

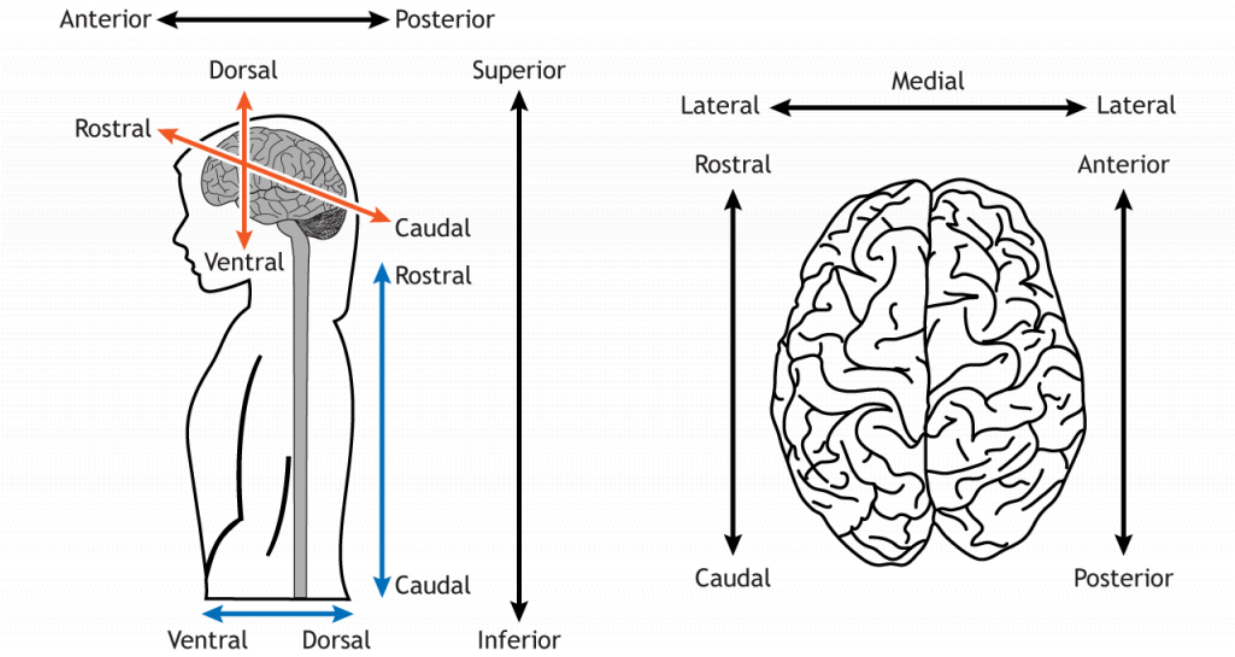

Figure 21.2. Directional terms used to locate nervous system structures. The dorsal / ventral and rostral / caudal pairs point in different directions depending on if they are referring to the axis of the brain (orange arrows) or the axis of the spinal cord (blue arrows). The definitions of each term are described in the text. 'Anatomical Directions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Visualizing the Brain: Anatomical Planes

As a three-dimensional structure, the brain can be sectioned, or cut, for visualization or analysis in several ways. Here, we will describe the three main orientations, each at right angles to the others.

1. The **frontal or coronal plane** is a vertical plane in a medial to lateral direction, dividing objects into front and back pieces.
2. The **sagittal plane** is also a vertical plane but in a rostral-caudal direction, meaning it divides objects into right and left regions.
3. Finally, the **horizontal plane** divides objects into top and bottom regions.

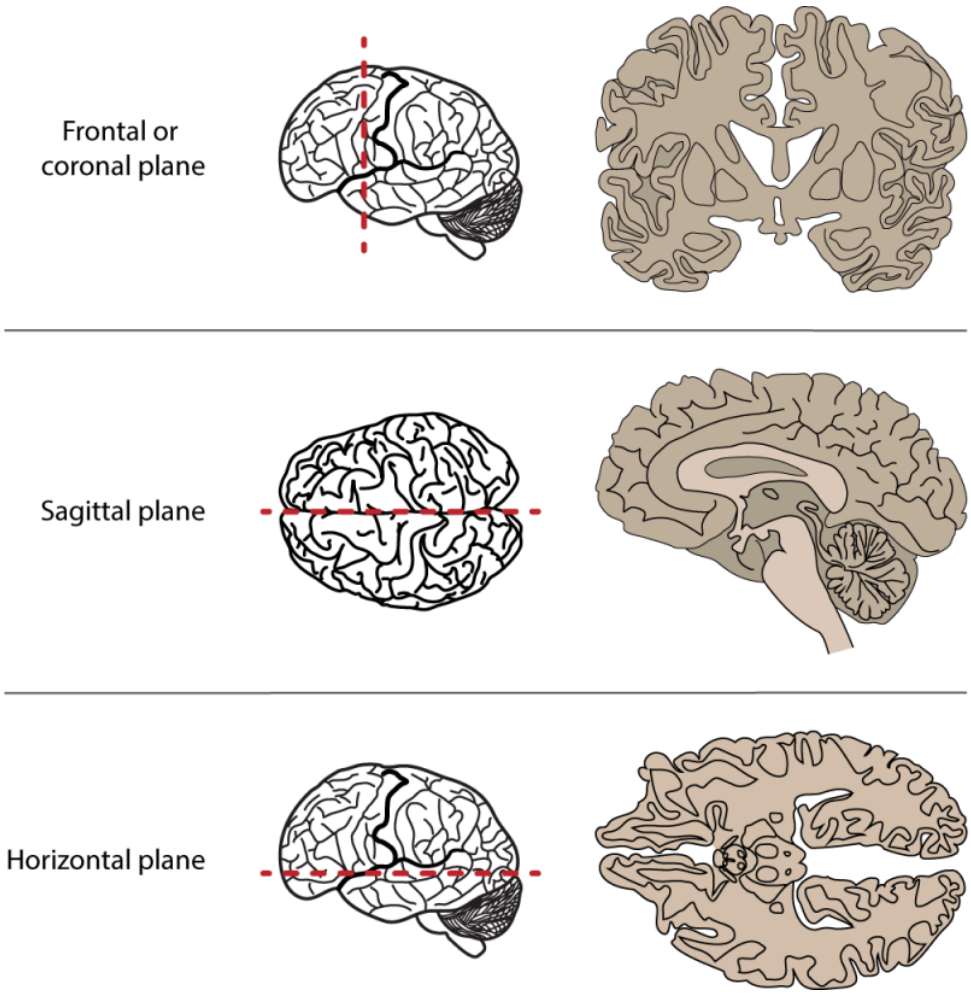

Figure 21.3. Three anatomical planes are used to divide the nervous system to be able to view internal regions and structures. The frontal or coronal plane is a vertical plane that runs parallel to the eyes or ears and will divide the body into front and back regions. The sagittal plane is a vertical plane that runs perpendicular to the eyes or ears and will divide the body into left and right regions. The horizontal plane runs parallel to the ground and will divide the body into top and bottom regions. 'Anatomical Planes' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Gray Matter and White Matter

In a sliced section of the brain, you might notice that brain tissue has different colored areas. Some brain tissue is pale and almost white, and these areas are described as **white matter**. Generally,

white matter represents pathways of communication. White matter regions are comprised of axons. It appears white due to the myelin sheath on the axons. Other sections of brain tissue have a darker pink/gray color, appropriately called **gray matter**. These areas are usually dense with cell bodies and dendrites. Gray matter is the location of most synapses.

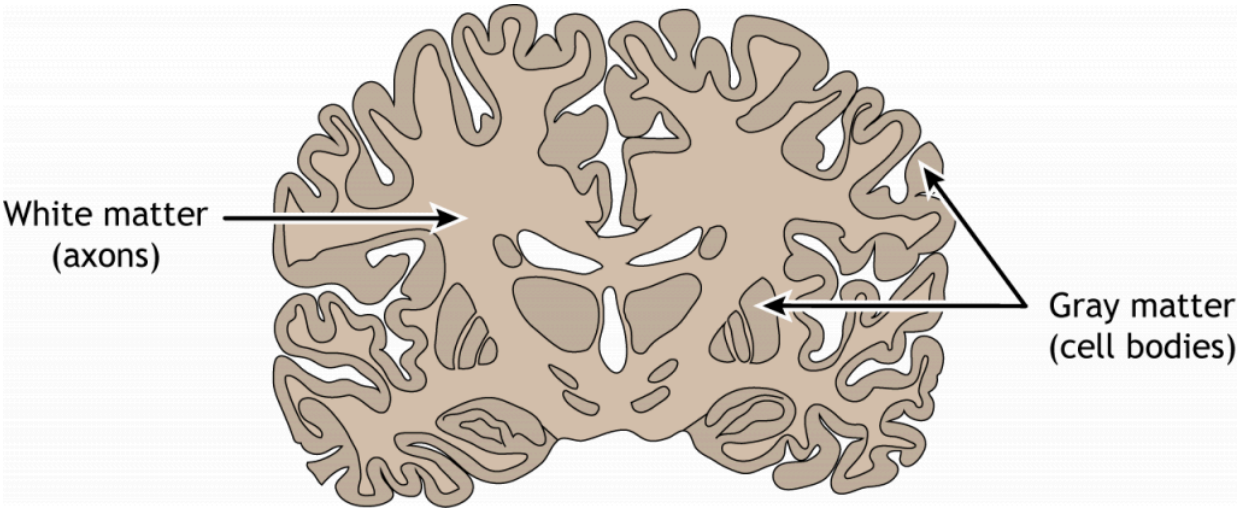

Figure 21.4. The central nervous system tissue can be divided into white and gray matter. White matter is primarily myelinated axons. Gray matter is primarily neuronal cell bodies and dendrites. In the brain, the surface of the cerebral cortex is a layer of gray matter. White matter can be found below the gray matter layer and is the location of the axons traveling to and from the cortical cell layer. Gray matter can also be found deep in the brain in subcortical regions that play critical roles in behavior. 'White and Gray Matter' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

White Matter Tracts

The brain has two very similar halves, the left and right hemisphere. Oftentimes, in the neurotypical individual, information passes between both hemispheres rapidly: what one hemisphere senses or learns, so does the other hemisphere. It is the white matter tracts that allow for this transfer of information. When a white matter pathway crosses from one side of the body to another, we call it a decussation.

Commissures are white matter tracts that connect gray matter between the left and right hemispheres of the brain. The main commissure that allows for the passage of information between the two hemispheres is called the **corpus callosum**.

Association fibers are white matter tracts that connect different bits of gray matter within the same hemisphere of the brain. These connections do not cross the midline.

Projection fibers are white matter tracts that connect the hemispheres of the brain with lower brain structures or with the spinal cord. They "project" from the cortex to the lower brain structures or spinal cord.

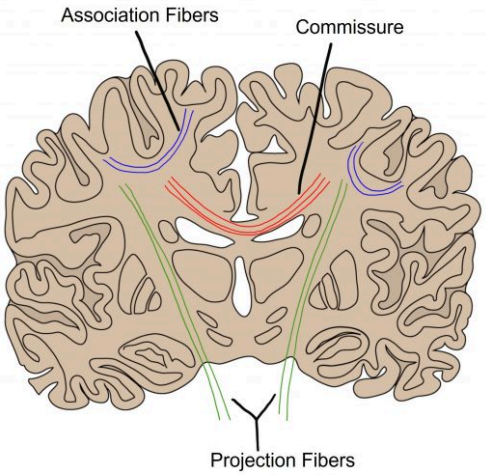

Figure 21.5. Commissures (red) connect gray matter between the left and right hemispheres. Association fibers (blue) connect gray matter within the same hemisphere of the brain. Projection fibers (green) connect gray matter with lower brain structures or the spinal cord. 'White Matter Connections' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Anatomical terminology is critical for determining neurological landmarks and discussing the anatomy of the nervous system

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22.

BRAIN STRUCTURE DIFFERENTIATION

In the following chapters, some of the many structures that make up the brain will be introduced. To begin this discussion, we will identify some of the basic development of the nervous system to understand how different areas of the brain are organized.

Very early in development, an embryo looks like a flat disc with 3 different layers of cells.

1. Endoderm: will eventually develop into the viscera (organs of the body)
2. Mesoderm: will eventually develop into the bones and muscles
3. Ectoderm: will eventually develop in the nervous system and the skin

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

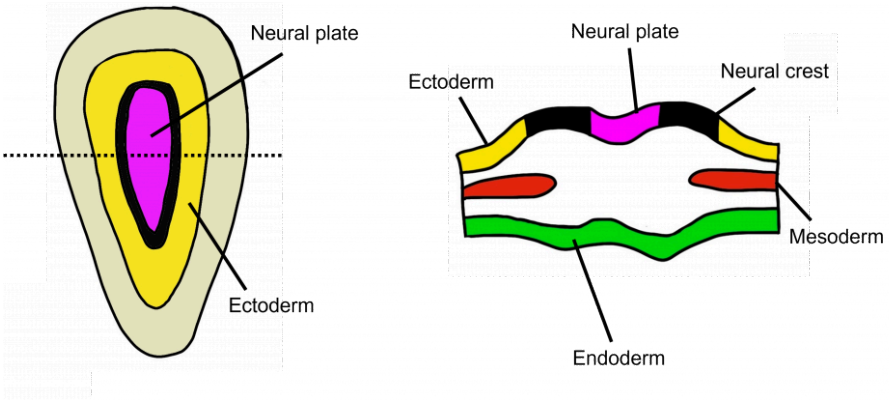

Figure 22.1. Developmental layers of the embryo. Early in development, the embryo looks like a flat disc made up of three different layers (left image). The ectoderm layer is what will develop into the nervous system. A cross section of the embryo (right image) reveals the endoderm, mesoderm, and ectoderm layers. 'Developmental layers of the embryo' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The Neural Tube

Let's focus on the **ectoderm** that will develop into the nervous system. The ectoderm layer will fold together in a process called **neurulation** to form a **neural tube**. Neurulation occurs within the first month following conception in humans.

During neurulation, the middle of the neural plate folds first, followed by the anterior and posterior

ends. The central nervous system will develop from the walls of the neural tube and the hollow lumen of the tube will become the cerebral **ventricles** and spinal canal within the central nervous system.

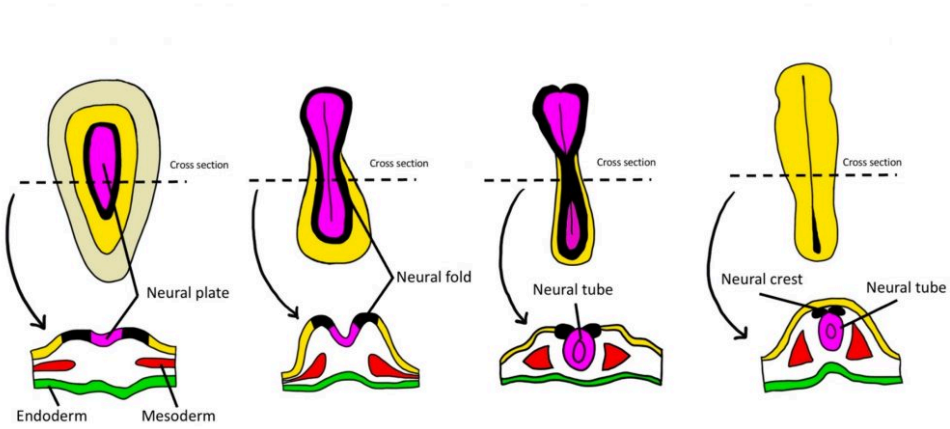

Figure 22.2. Neurulation. During the process of neurulation, the neural plate pinches together at the neural fold in the middle, and then closes at the anterior and posterior ends to form a neural tube. The structures of the central nervous system will form from the walls of the neural tube and the lumen of tube will become the ventricles of the brain and central canal of the spinal cord. 'Neurulation' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Neural Tube Defects

Early in pregnancy, there can be problems with the process of neurulation and the formation and closure of the neural tube. Collectively, these are referred to as **neural tube defects** that include defects that occur within the brain, spine, or spinal cord. One of the more common neural tube defects is **spina bifida**. In spina bifida, the neural tube fails to close completely, and as a result the backbone that typically protects the spinal cord also does not form appropriately. This event can occur anywhere along the spine, and will typically result in nerve damage at that particular site that will potentially lead to physical and / or intellectual disability ranging in severity with the degree of damage.

Anencephaly is a neural tube defect that is caused by the failure of the **anterior** portion of the neural tube to close. Anencephaly is a serious birth defect that typically prevents the development of the anterior portion of the brain and associated skull.

Unfortunately, many neural tube defects occur very early in pregnancy, such that many women do not yet know that they are pregnant. As a result, daily folic acid supplements or a diet that includes foods rich in folate is recommended to all women of reproductive age to help prevent neural tube defects in the event of a pregnancy.

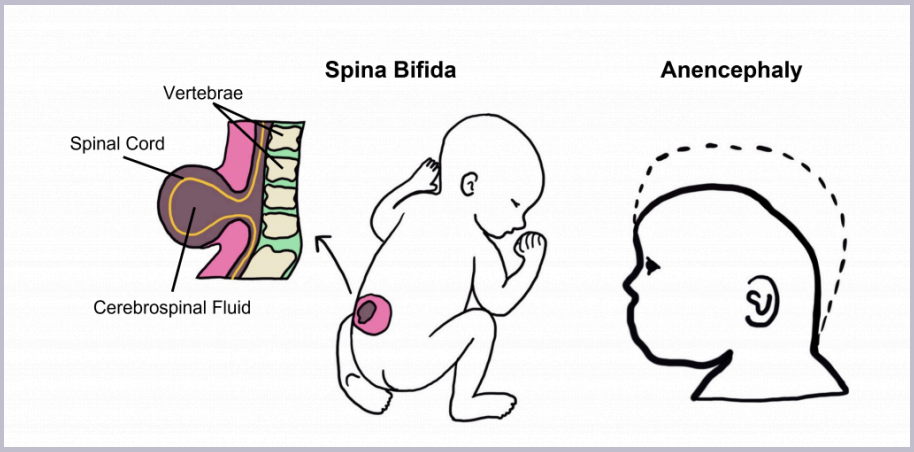

Figure 22.3. Neural Tube Defects. Spina bifida (left) occurs when the posterior neural tube fails to close. Anencephaly (right) occurs when the anterior neural tube fails to close, causing decreased development of the brain and skull. 'Neural Tube Defects' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Three Vesicle Stage of Development

Early in development, the anterior portion of the neural tube has three distinct vesicles, which will each develop into different structures. These vesicles, from most anterior to most posterior, are the **prosencephalon (forebrain)**, the **mesencephalon (midbrain)**, and the **rhombencephalon (hindbrain)**.

Through development, the walls of these vesicles will differentiate into adult brain structures. Differentiation is the process by which structures become more complex and functionally specialized during development. The names of these early vesicles can be used to describe either the stages through

development, or a grouping of structures that eventually form in adulthood. In the following chapters, we will learn more about some of these anatomical structures.

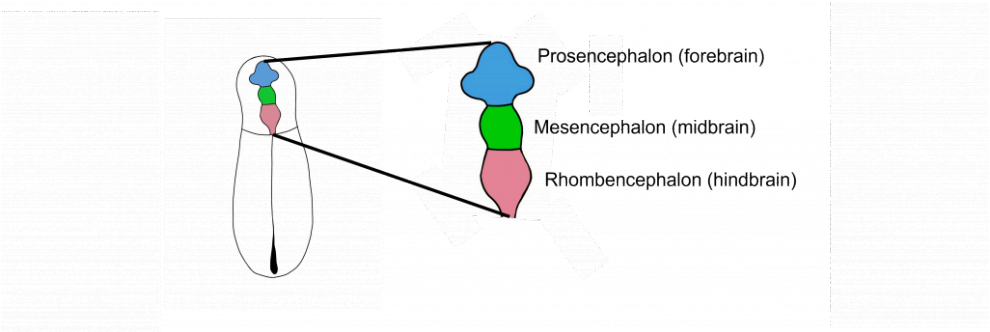

Figure 22.4. Three vesicle stage of embryonic development. Early in development the anterior portion of the neural tube can be divided into three vesicles: the prosencephalon, the mesencephalon, and the rhombencephalon. 'Three vesicle stage' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Prosencephalon (Forebrain)

The prosencephalon, or the forebrain, is most **anterior** in the neural tube and eventually develops into the "higher order" brain regions, including the cerebral cortex. Most of the time, when you see an image of an intact brain from the side or the top, the structures that are visible to you are the forebrain structures. The prosencephalon is made up of the **telencephalon** and the **diencephalon**.

As the prosencephalon continues to develop, additional structures will form that are associated with the cerebral hemispheres. For instance, the optic vesicles that bud off the surface of the prosencephalon

will differentiate into the retinas of the eyes—thus, the retina is made up of neural tissue. The olfactory bulbs will differentiate from the ventral surface of the cerebral hemispheres.

Note that as the walls of the tube develop into these structures, the lumen of the tube remains and will become the fluid-filled **ventricles** of the brain. The lateral ventricles will form from the tube within the cerebral hemispheres and the third ventricle will be found ventrally surrounded by the diencephalon.

Structures of the Telencephalon: Cerebral Cortex and the Basal Ganglia

The **cerebral cortex** makes up the outermost layer of the brain. The word "cortex" comes from the word meaning "bark", the outer layer of a tree. The cerebral cortex is the most evolved structure of the human brain and is responsible for higher order thinking. Here, the brain processes behaviors such as attention, memory, and language.

The **basal ganglia** are made up of a series of brain structures (including the caudate and putamen, globus pallidus, substantia nigra, and subthalamic nucleus) that are used for such behaviors as motor and habit learning, emotional processing, and action selection.

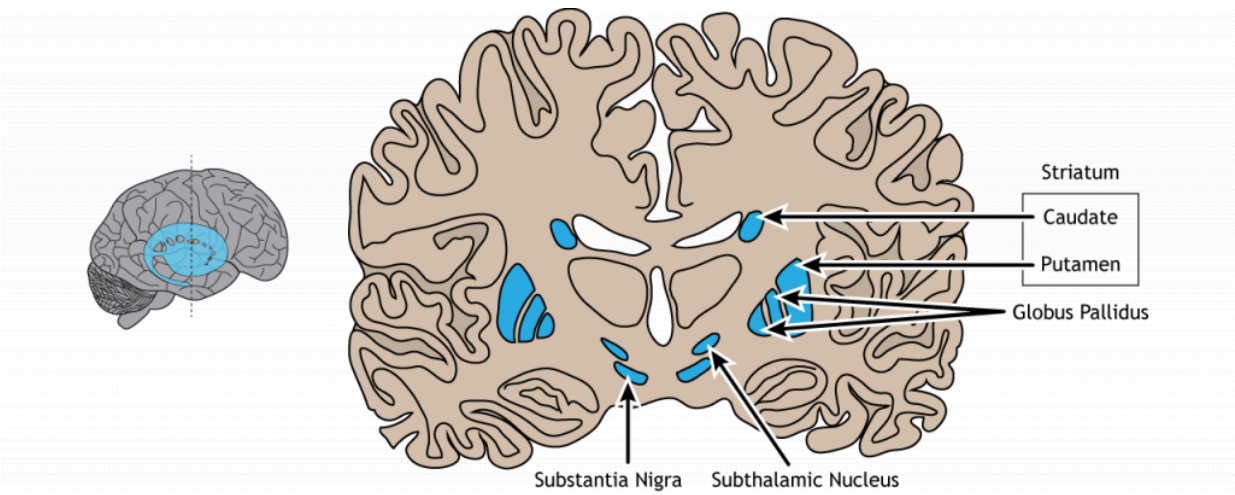

Figure 22.5. The basal ganglia are subcortical structures located at the base of the forebrain. They are comprised of the caudate and putamen, which both make up the striatum, as well as the globus pallidus, substantia nigra, and subthalamic nucleus. 'Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Structures of the Diencephalon: Thalamus and Hypothalamus

The thalamus is often referred to as a "sensory relay station" in the brain, since almost every sensory modality (sight, taste, touch, and hearing) passes information through the thalamus before being directed to the appropriate area of the cortex.

The hypothalamus is also within the diencephalon. This structure serves as an autonomic control center to alter visceral function and a communication route to the body's endocrine system through control of anterior pituitary hormones and production of posterior pituitary hormones. Neural signals originating in the hypothalamus have the capability to influence the chemistry and function of the entire body. The hypothalamus also has nuclei that function in emotional responses, and regulate body temperature, food intake, water balance, and sleep.

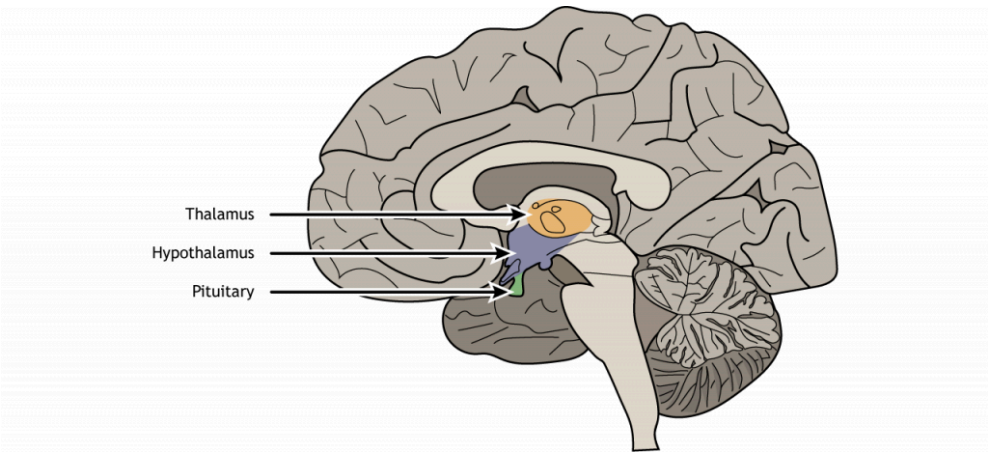

Figure 22.6. The pituitary, shown in green in a mid-sagittal section, lies inferior to the hypothalamus, shown in blue. 'Hypothalamus and Pituitary' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Mesencephalon

Moving more caudally, the mesencephalon (or the midbrain) differentiates into the tectum and the tegmentum.

Tectum

The tectum (which means "roof") is the dorsal portion of the midbrain and it has two major structures: the superior colliculus and inferior colliculus. The **superior colliculus** is important in reflexive eye movements that allow you to quickly orient to something changing in your environment. The **inferior colliculus** relays auditory information to the thalamus for auditory function.

Tegmentum

The tegmentum (which means "floor") is the ventral portion of the midbrain. There are many structures in the tegmentum and they can perform a wide variety of functions. For example, the **periaqueductal gray** allows us to respond to painful stimuli, the **red nucleus** and **substantia nigra** coordinate complex movements, and the **ventral tegmental area** is important for the processing of reward and motivation.

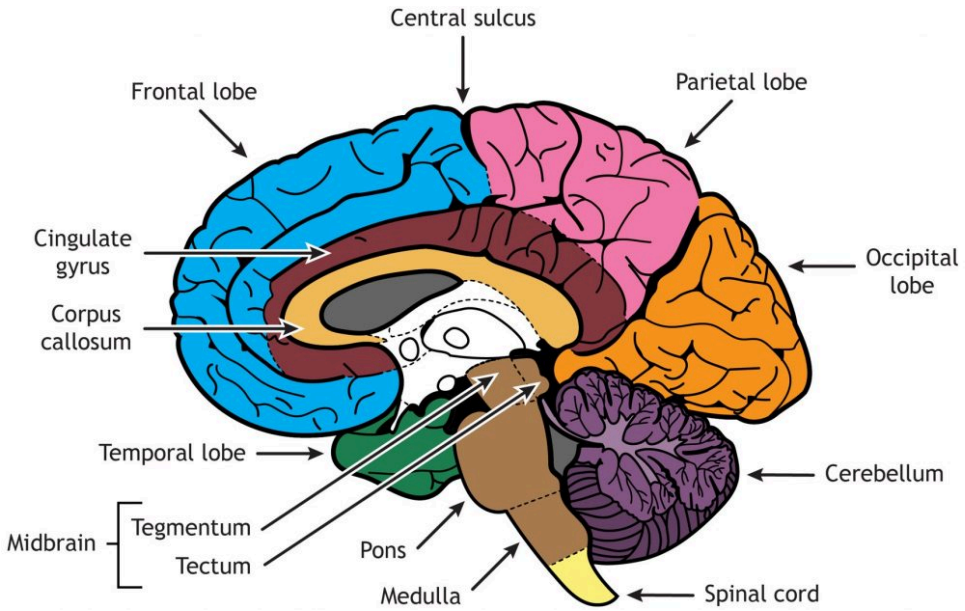

Figure 22.7. A midsagittal section of the brain. The midbrain (tectum and tegmentum) are located anterior to the pons. 'Internal Brain Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Rhombencephalon

The most posterior/caudal portion of the neural tube is the **rhombencephalon** (or **hindbrain**). Evolutionarily speaking, the rhombencephalon represents the oldest part of the central nervous system. These structures likely evolved some 570 million years ago.

Rostral Hindbrain

The more rostral portion of the hindbrain differentiates into two structures: the **cerebellum** and the **pons**. The cerebellum, or "little brain", is best known as a structure that enables motor control functions, such as balance, coordination, posture, and learning physical actions. The cerebellum helps us recognize and predict sequences of events during motor learning. More recently, the cerebellum has also been recognized to play a role in non-motor functions like learning. The pons (which means "bridge") is an important structure that relays impulses between the motor cortex and the cerebellum. It has a critical function to help us perform involuntary functions like breathing.

Caudal Hindbrain

The caudal portion of the hindbrain differentiates into the **medulla**. The medulla is found at the far posterior end of these three early developmental vesicles. The medulla contains many clumps of neurons that are responsible for functions that an organism carries out unconsciously. It contains a cardiovascular center that is especially important in maintaining and changing blood pressure and heart rate, and also has connections to the pons to help regulate breathing. The medulla contains areas that can detect toxins in the blood that come from dietary sources, triggering vomiting. Other behaviors like hiccupping, swallowing, coughing, and sneezing are also controlled by the medulla.

Moving beyond this anterior portion of the neural tube that contains the prosencephalon, mesencephalon, and rhombencephalon, the neural tube continues down the length of the embryo. The remainder of the neural tube will differentiate into the **spinal cord**, with the lumen of the tube becoming the central canal of the spinal cord. The spinal cord is important in relaying information to and from the body.

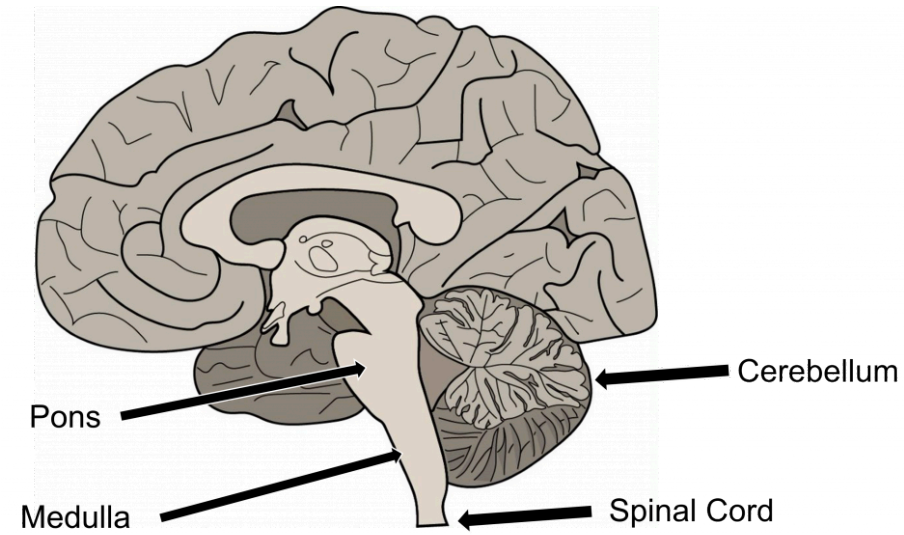

Figure 22.8. Structures of the rhombencephalon. The rostral portion of the rhombencephalon develops into the cerebellum and pons. The caudal portion of the of the rhombencephalon develops into the medulla. The spinal cord is connected to the posterior end of the medulla and continues down the length of the spine. 'Structures of the rhombencephalon' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The ectoderm layer of the embryo develops into the nervous system
- Neurulation is the process that forms the neural tube and failure for portions of the neural tube to close can cause neural tube defects
- The prosencephalon, mesencephalon, and rhombencephalon are the three vesicles at the anterior end of the neural tube. They will develop into structures in the adult brain.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/introneuroscience1/?p=614#h5p-37

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23.

BRAIN ANATOMY

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

The brain is comprised of the cerebrum, cerebellum, and brainstem. The cerebrum is the most prominent region of the brain. It is divided into left and right hemispheres. The hemispheres have many of the same functions. For example, each perceives touch on one side of the body, but some functions demonstrate laterality, meaning they are primarily controlled on one side of the brain.

Most of what we think of when we imagine the brain is the cerebral cortex in humans. The cortex has many folds to increase the surface area of the brain. The bumps or raised ridges on the outer surface are called gyri (singular **gyrus**) and the grooved indentations are called sulci (singular **sulcus**). A large, deep sulcus is sometimes also called a fissure.

Although each gyrus and sulcus has a name that either identifies its function or location, there are only three sulci that we will introduce here to help orient us around the neuroanatomical features of the cortex. The **longitudinal fissure** is the most obvious fissure in the brain. It divides the two hemispheres, running along the anterior–posterior axis, visible from a dorsal view of the brain. If you were to cut along the longitudinal fissure completely, you would get two symmetrical portions of brain: the left and right hemispheres.

The **central sulcus** is a large fissure that starts at the dorsal part of the brain at about the halfway point on the anterior–posterior axis. In a sagittal view, the central sulcus runs ventrally about half the length of the brain. The other groove worth noting is the **lateral fissure**. This one runs roughly along the anterior-to-posterior direction, and curves gently dorsally. Again, in a sagittal view, it is roughly seen in the middle third of the brain in the anterior–posterior axis.

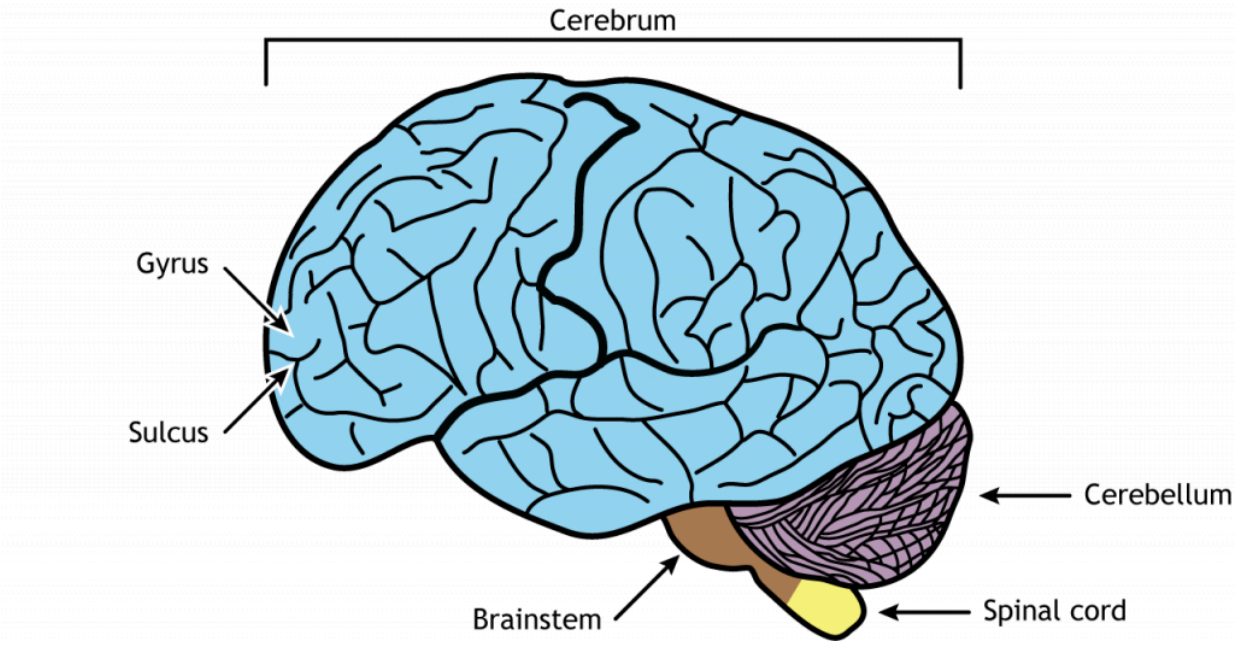

Figure 23.1 An external side view of the parts of the brain. The cerebrum, the largest part of the brain, is organized into folds called gyri and grooves called sulci. The cerebellum sits behind (posterior) and below (inferior) the cerebrum. The brainstem connects the brain with the spinal cord and exits from the ventral side of the brain. 'External Brain Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Anatomical Lobes of the Cortex

The cortex is roughly divided into four major lobes, which are named after the bones of the skull that surround each section of brain. The lobes are paired, meaning that the whole brain contains two of each, a left and a right. In general, the structures are roughly symmetrical.

Frontal Lobes

The frontal lobes are the most **rostral**, located in the front of the brain. The posterior border of the frontal lobe is the **central sulcus**. Among mammals, it is the largest of the four lobes. The frontal lobes are responsible for higher level executive functions like attention, critical thinking, and impulse control. The frontal lobes allows us to do mental math, to hold a string of letters in our head to be

repeated backward, and to suppress socially unacceptable actions. Our personality is influenced by the frontal lobe. An injury to these brain structures can result in a radical change in a person's behavior.

They are the last brain region to fully develop, not completing development until individuals reach their mid 20s. The frontal lobes are also the location of the **primary motor cortex**, the region of the brain responsible for planning and executing movement. Specifically, the primary motor cortex is located in the **precentral gyrus**, which is directly **anterior** to the central sulcus.

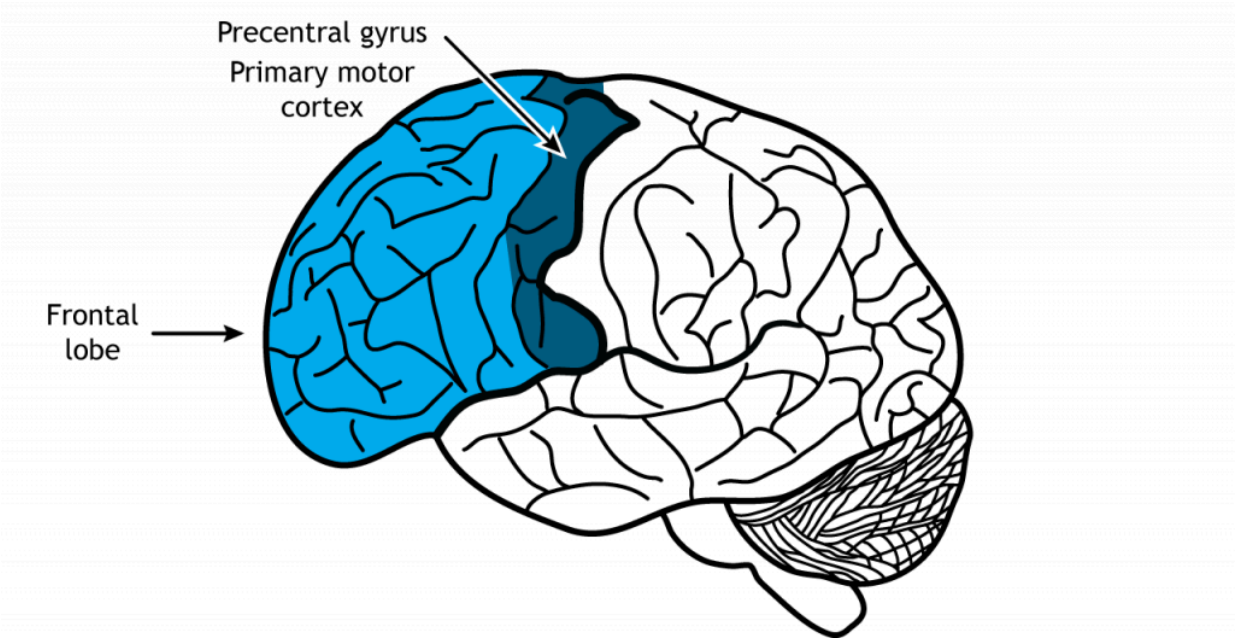

Figure 23.2. The frontal lobe is located in the front of the brain. It includes the precentral gyrus, the location of the primary motor cortex. 'Frontal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the frontal lobe using the BrainFacts.org 3D Brain

Phineas Gage

Phineas Gage, who was mentioned back in Chapter 1, is one of the most famous case studies in neuroscience.

The mid-1800s saw an expansion of industry in the United States. The most reliable and quickest way to move goods and people was with the railways that were starting to zig-zag across the growing country. The factor slowing down railway expansion was terrain: land had to be relatively flat for the tracks to be laid down. Terraforming mountains was a dangerous ordeal, and in the years before TNT (a relatively safe explosive) was developed, work accidents were a risk that these demolition workers faced.

Phineas Gage was one of those workers. In the green mountain hills of Vermont, Gage was putting explosive powder into a crack in a mountain to clear land for a new railway. As Gage packed the explosive using a three-foot-long metal rod, a spark accidentally ignited the blast prematurely, causing the tamping iron to rocket cleanly through Gage's skull. Miraculously, Gage survived the blast. Within a month, he had made an almost complete recovery. Gage was talking excitedly with his doctors, he was eating voraciously, and even reported experiencing no pain. While the doctors noticed that his entire frontal lobe had been destroyed, it was his friends who noticed the dramatic change in his personality: whereas he was once a friendly man, adored and respected by his coworkers, the new Gage was irreverent, generally unlikable, and prone to using profanity at the most inappropriate times. The pre-injury Gage was a shrewd businessman who followed through with his plans, but Gage now was unreliable and at times, acted in a more like an animal. Because of the injuries to his frontal lobe, his friends described him as being "no longer Gage".

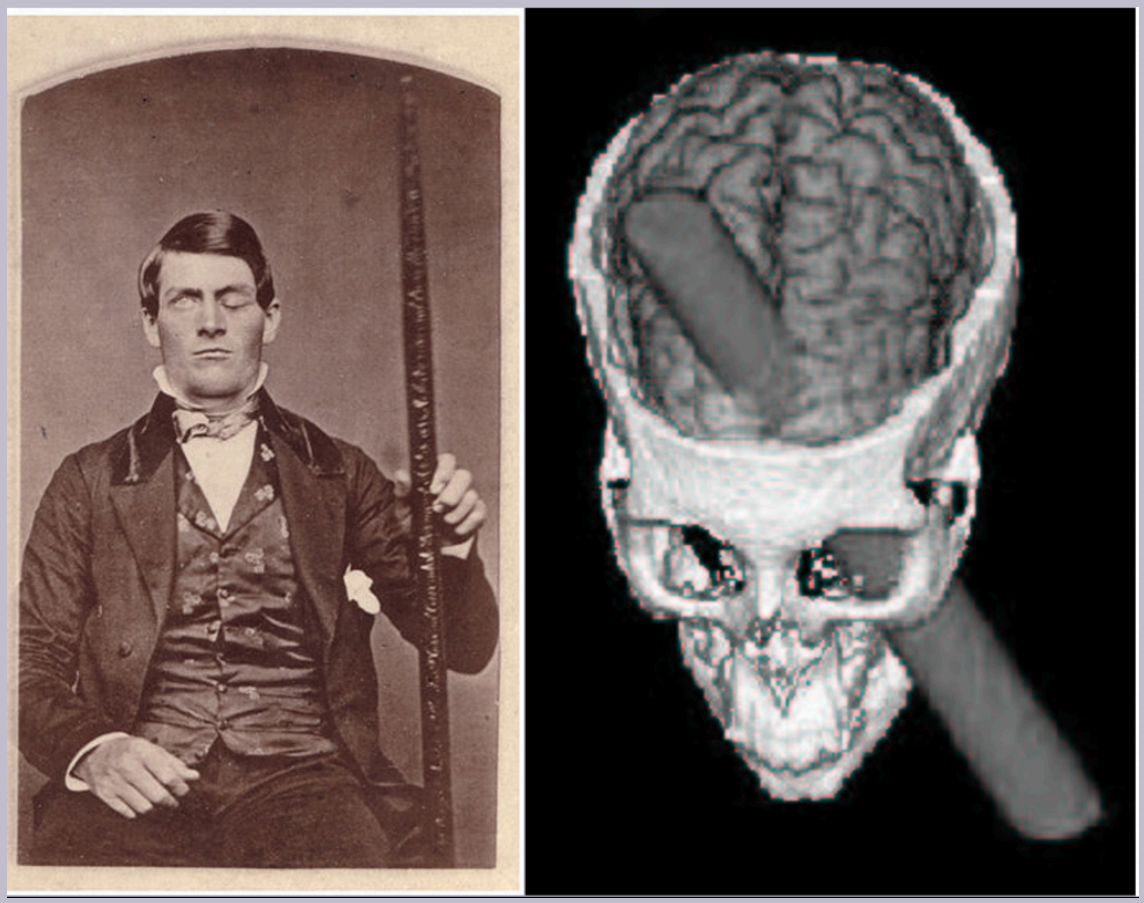

Figure 23.3. Image of Phineas Gage and his site of injury. The figure on the left is an image of Phineas Gage holding the iron rod that caused his injury. The image on the right shows a Magnetic Resonance Image rendering of the location of the rod in the injury. The rod entered below the left eye and damaged much of the left frontal cortex.

Parietal Lobes

The central sulcus lies **caudal** to the frontal lobe and divides the frontal lobes from the parietal lobes. The **primary somatosensory cortex** is located in the **postcentral gyrus** of the parietal lobe and is responsible for the perception of touch and pain. With our skin, we are able to detect light touch, temperature, pain, vibration, and many other modalities. This ability to sense different tactile

properties of things in the world around us with our body is one of the major functions of the parietal lobe. Another closely related sense, proprioception (the ability to identify where parts of your body are located), is also processed by neurons of the parietal lobe. The parietal lobes also perform higher-level visual processing.

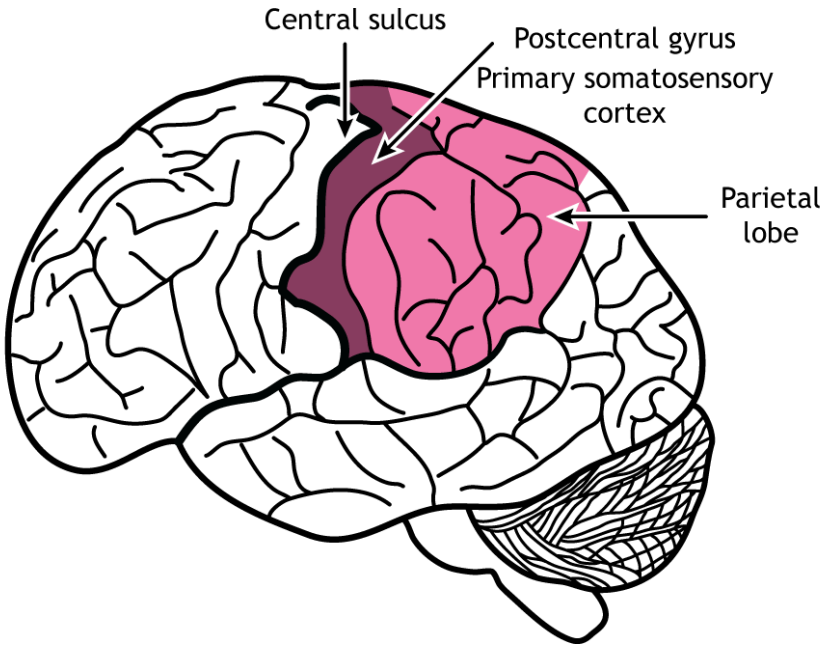

Figure 23.4. The parietal lobe is located on the top of the brain. It includes the postcentral gyrus, the location of the primary somatosensory cortex. The central sulcus divides the parietal lobe from the frontal lobe. 'Parietal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the parietal lobe using the BrainFacts.org 3D Brain

Temporal Lobes

The temporal lobes are located on the side of the brain, separated from the frontal and parietal lobes by the **lateral fissure**. Like the parietal lobe, the temporal lobe plays a role in sensory processing, specifically with hearing, smell, taste, and higher-level visual processing. The auditory system allows our brain to interpret sound waves. The ability to remember important facts depends on memory-related processes. These functions are carried out in part by a brain structure called the **hippocampus**,

which is buried medially and ventrally in the temporal lobe. The temporal lobe also houses some structures that are important for language.

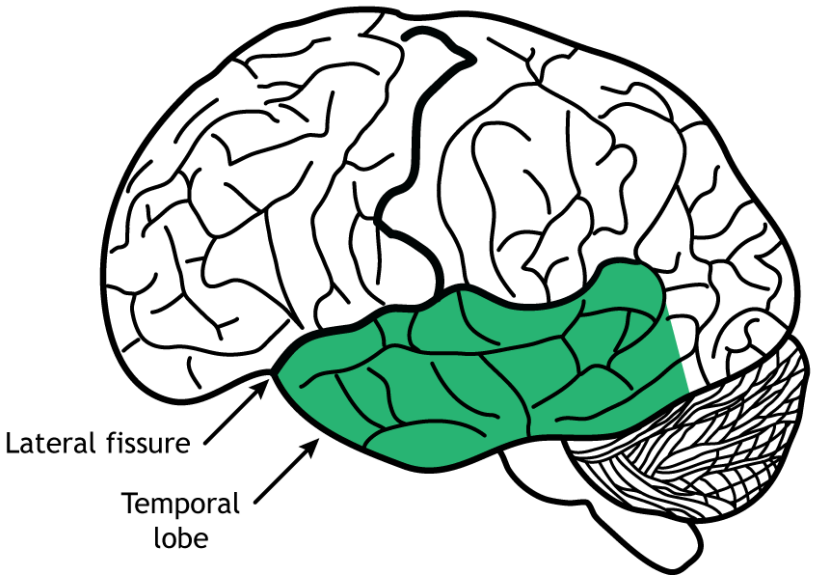

Figure 23.5. The temporal lobe is located on the side of the brain. The lateral fissure divides the temporal lobe from the frontal and parietal lobes. 'Temporal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

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Occipital Lobes

The occipital lobes, the most **caudal** lobes, are located in the back of the brain. Anatomically, there is not an obvious border that separates the occipital lobe from adjacent areas of the cortex. The occipital lobe is the smallest of the four lobes. The main function of the occipital lobe is for processing of visual stimuli. Our eyes are capable of capturing light and converting that light into signals. The **primary visual cortex** of the occipital lobe, also called **V1**, interprets those signals into a representation of the visual world. Other vision-related stimuli, such as objects in motion, object orientation, and color are also processed by neurons in the occipital lobe.

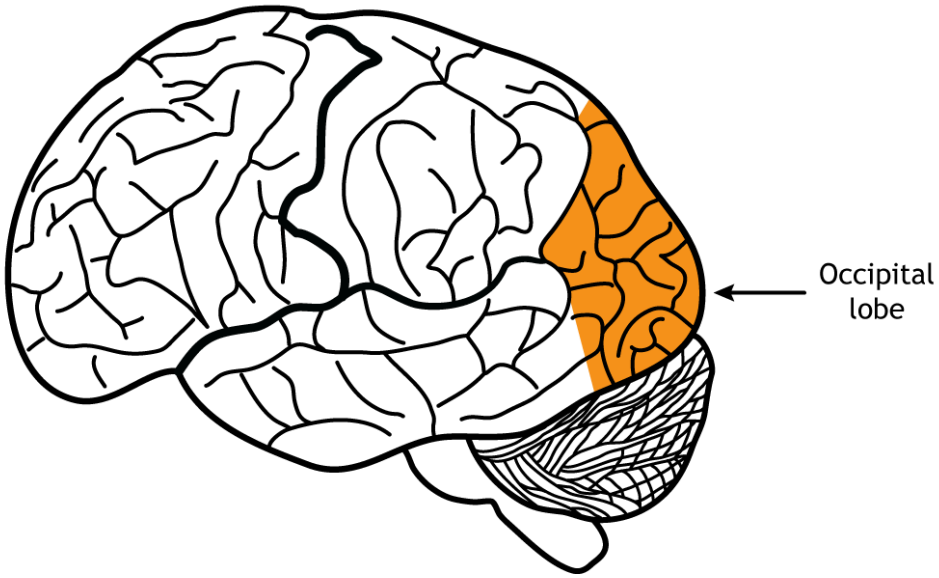

Figure 23.6. The occipital lobe is located in the back of the brain. 'Occipital Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the occipital lobe using the BrainFacts.org 3D Brain

Non-Cerebral Components

The **cerebellum** lies **inferior** to the occipital lobes. The cerebellum is divided into two hemispheres like the cerebral cortex. The cerebellum is best known for its role in regulation and control of movement, but it is also involved in cognitive functions like emotions.

The **brainstem** is located between the cerebrum and the spinal cord. It is important for regulating critical functions like heart rate, breathing, and sleep. It is also the location of most of the cranial nerves.

The **spinal cord**, which is part of the **central nervous system** but not part of the brain, is responsible for receiving sensory information from the body and sending motor information to the body. Involuntary motor reflexes are also a function of the spinal cord, indicating that the spinal cord can process information independently from the brain.

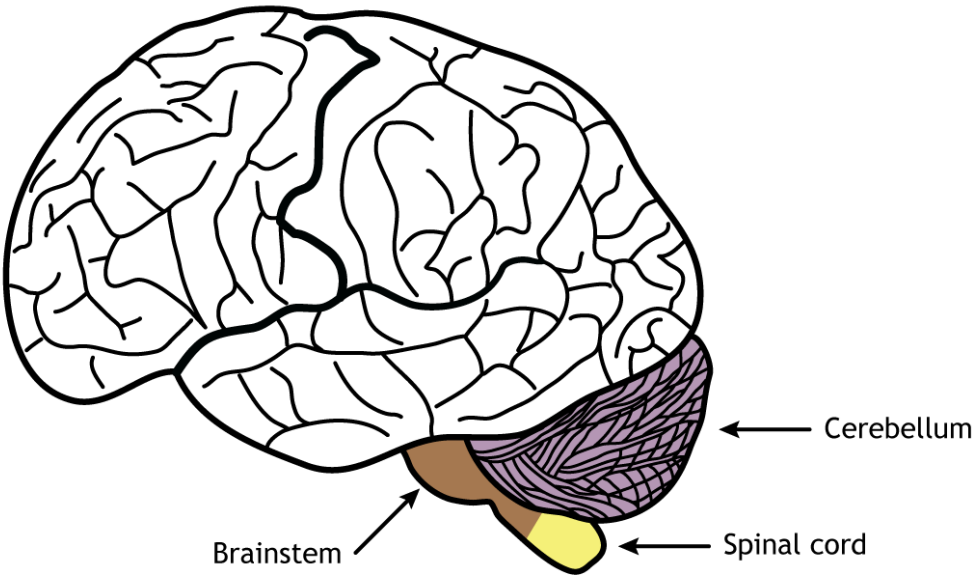

Figure 23.7. The cerebellum, brainstem, and spinal cord are located below the brain. 'Hindbrain' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the brainstem using the BrainFacts.org 3D Brain

View the cerebellum using the BrainFacts.org 3D Brain

Dorsal View

Viewing the brain from above shows the bilateral symmetry of the left and right cerebral hemispheres, which are separated by the **longitudinal fissure**. The frontal, parietal, and occipital lobes can be seen. Similar to the lateral view, the central sulcus divides the frontal lobe from the parietal lobe. The precentral gyrus—which is the location of the primary motor cortex—sits rostral to the central sulcus, whereas the postcentral gyrus—which is the location of the primary somatosensory cortex—lies caudal to the central sulcus.

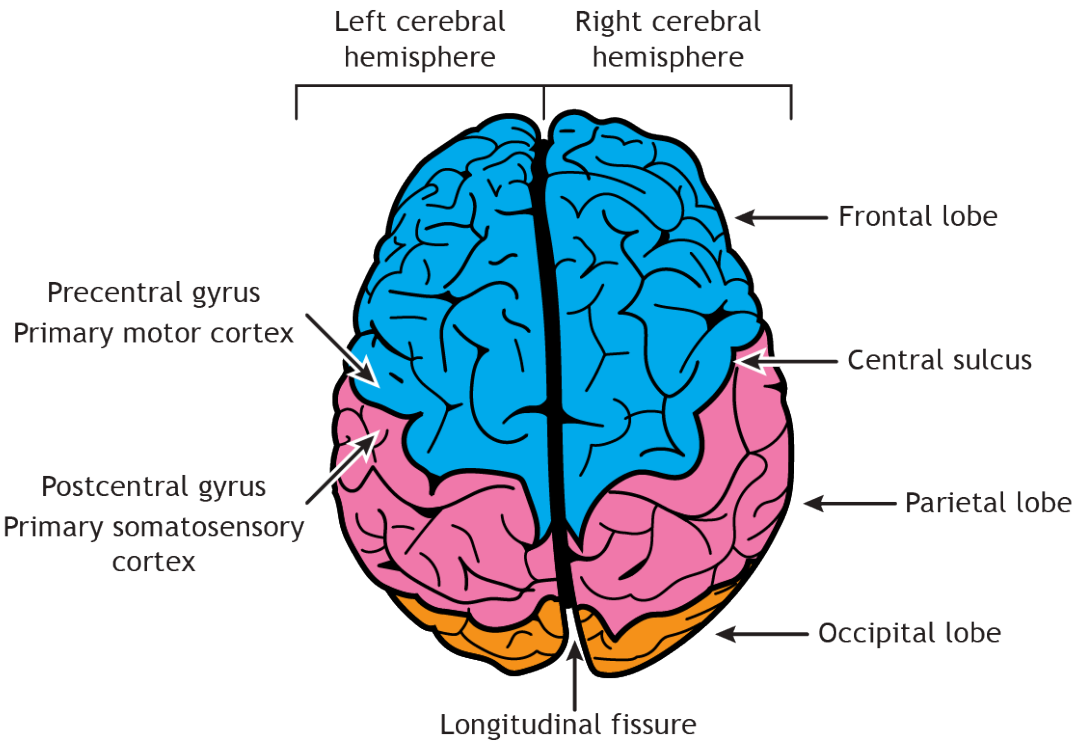

Figure 23.8. The dorsal view of the brain. The left and right cerebral hemispheres are separated by the longitudinal fissure. Three of the four lobes (the frontal, parietal, and occipital) can be seen in this view. 'Dorsal Surface of Brain' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ventral View

Underneath the brain, the frontal and temporal lobes are visible, as is the cerebellum. Like the dorsal view, the longitudinal fissure divides the cerebrum into right and left hemispheres. The pons and medulla (components of the brain stem) connect the cerebrum to the spinal cord.

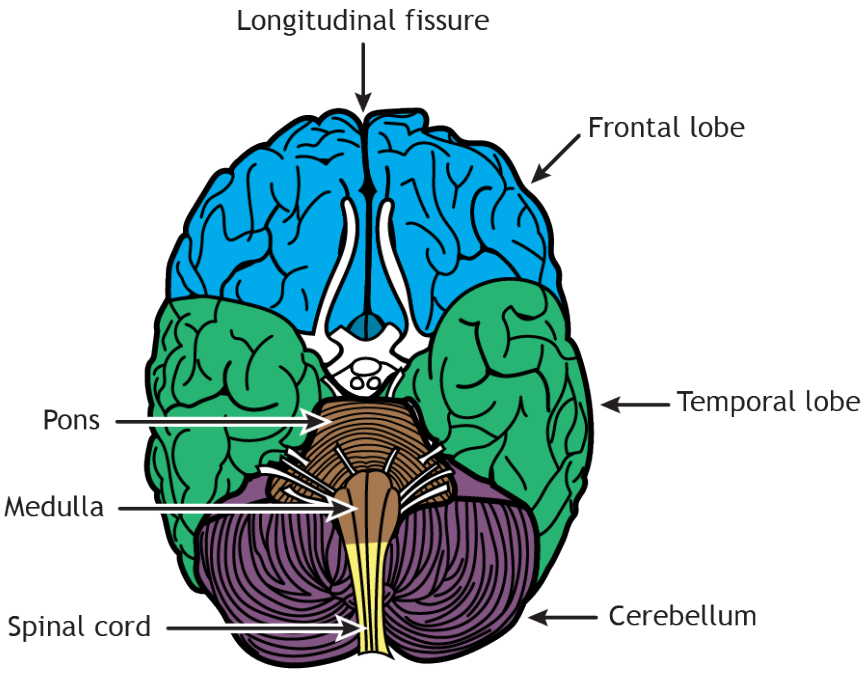

Fig 23.9. Ventral Surface of the Brain. The frontal lobe, temporal lobe, cerebellum, pons, medulla, spinal cord, and longitudinal fissure can be seen when viewing the bottom of the brain. "Ventral Surface of the Brain" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Cranial nerves are also visible on the ventral surface of the brain. The olfactory tract leads out to the olfactory bulb, which connects to the **olfactory nerve**. The optic tract crosses the midline at the optic chiasm, and then the **optic nerve** projects to the retina. Other cranial nerves enter or leave the brain at the level of the brainstem. The **hypothalamus** is located caudal to the pons and the mammillary bodies project out from the hypothalamus.

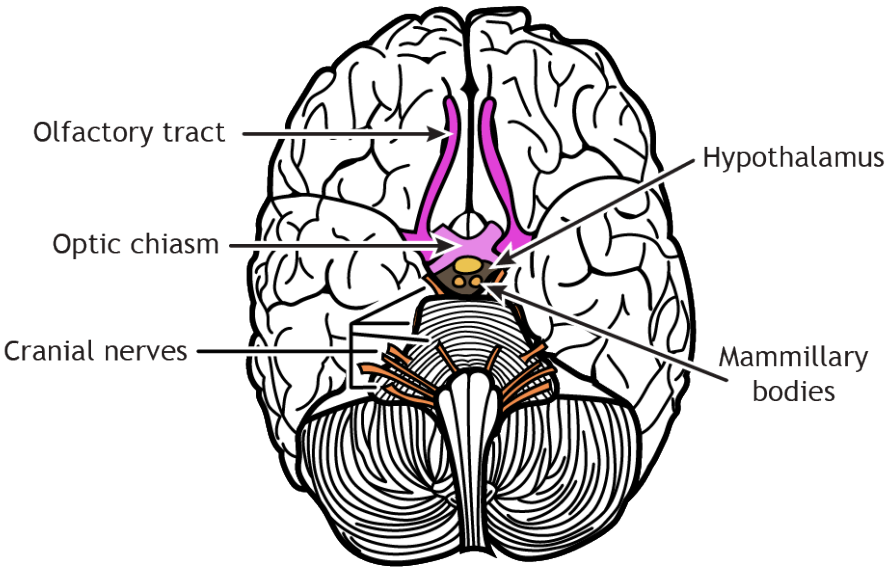

Figure 23.10. Cranial nerves, optic chiasm, and olfactory tract are visible on the bottom of the brain. In the center, the hypothalamus and mammillary bodies can also be seen. "Ventral Surface Cranial Nerves" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

There are twelve pairs of cranial nerves that are outlined in the table below.

Table 23.1. A table that defines each of the twelve cranial nerves by identifying their name, the type of nerve, and function.

Cranial Nerve	Type of Nerve	Function
CN I Olfactory nerve	Sensory	Sense of smell
CN II Optic nerve	Sensory	Sense of vision
CN III Oculomotor nerve	Motor	Control of extraocular muscles that allow movement of eyeballs; constriction of pupils; changing of lens shape
CN IV Trochlear nerve	Motor	Control of the superior oblique muscle of the eye that moves the eyeball down and lateral
CN V Trigeminal nerve	Sensory + Motor	Tactile and pain sensory information from the face and mouth; Control of muscles used in chewing
CN VI Abducens nerve	Motor	Control of the lateral rectus muscle of the eye that moves the eyeball outward laterally
CN VII Facial nerve	Sensory + Motor	Control of the muscles that allow for facial expressions; Taste sensation on the anterior two thirds of the tongue
CN VIII Vestibulocochlear nerve	Sensory	Detection of sound information and head positional (vestibular) information
CN IX Glossopharyngeal nerve	Sensory + Motor	Detection of somatic sensory in the middle ear and posterior third of the tongue; Taste sensation on the posterior third of the tongue; Controls the stylopharyngeal muscle that allows swallowing
CN X Vagus nerve	Sensory + Motor	Control of the internal organs by autonomic nervous system using parasympathetic activity
CN XI Accessory nerve	Motor	Control of the sternocleidomastoid and trapezius muscles of the neck and shoulders
CN XII Hypoglossal nerve	Motor	Control of the muscles of the tongue

Mid-Sagittal View

A mid-sagittal section slices the brain through the longitudinal fissure and separates the right hemisphere from the left. It also reveals more structures. In a mid-sagittal view, all four cortical lobes are visible. The frontal lobe is separated from the parietal lobe by the central sulcus, the occipital

lobe is in the posterior region of the brain, and the temporal lobe can be seen behind the brainstem. The cerebellum, pons, medulla, and spinal cord are seen caudal to the cerebrum, but in this view, the midbrain—which is made up of two regions: the tegmentum and tectum—is also visible superior to the pons. The corpus callosum is located in the center of the cerebrum and is a white matter bundle made up of axons crossing from one hemisphere to the other. Surrounding the corpus callosum is the cingulate gyrus, a region important for emotion.

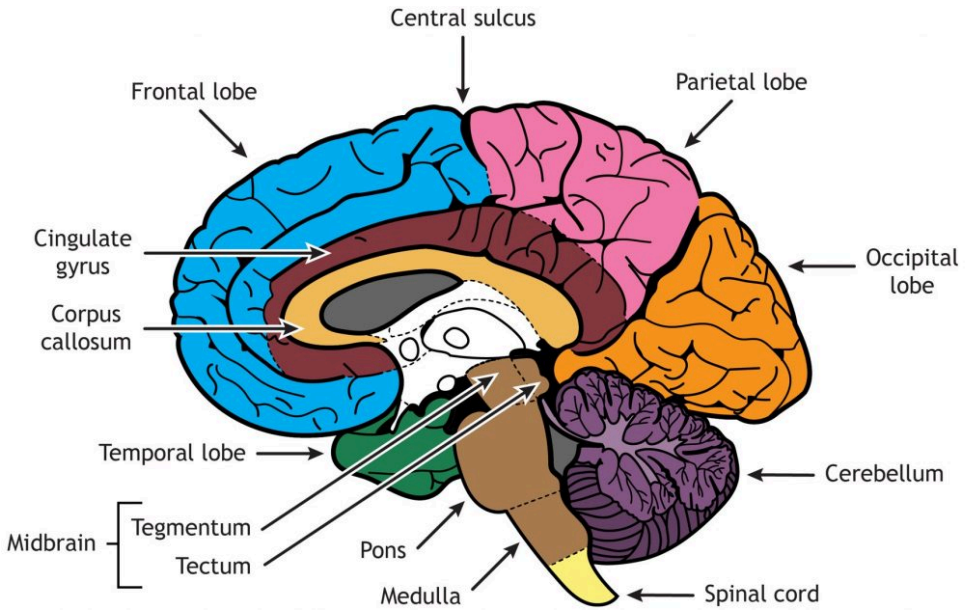

Figure 23.11. A midsagittal section of the brain. All four cerebral lobes are visible, as in the cingulate gyrus, which extends through the medial aspects of the frontal and parietal lobes. The corpus callosum sits beneath the cingulate gyrus. Below the cerebrum lies the midbrain, pons, medulla, and cerebellum. 'Internal Brain Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The diencephalon region of the brain consists of the region around the thalamus and hypothalamus.

It is located inferior to the fornix and lateral ventricle, posterior to the anterior commissure, and superior to the brainstem. The fornix is a nerve fiber bundle containing primarily output from the hippocampus. The anterior commissure sits above the hypothalamus and is a white matter tract (like the corpus callosum) that allows information to cross from one hemisphere to the other. The thalamus is best known for its role as a relay and processing location for the sensory and motor systems. The hypothalamus has a variety of functions including control of stress and the "fight or flight" response of the autonomic nervous system, reproduction, sleep, thirst, hunger, and other homeostatic functions. The mamillary bodies sit in the posterior part of the hypothalamus and are important for memory. The optic nerves from the retina cross at the optic chiasm and then the optic tracts continue back into the diencephalon.

In the brainstem, the tectum of the midbrain consists of the superior and inferior colliculi, which are important for vision and hearing, respectively. Finally, the reticular formation is located throughout the brainstem. Networks within the reticular formation are important for regulating sleep and consciousness, pain, and motor control.

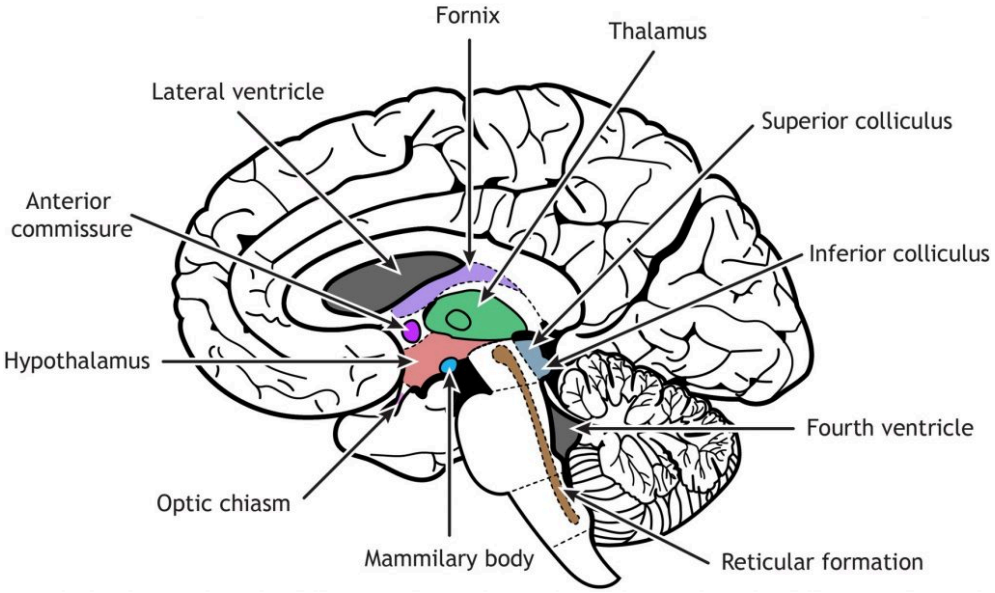

Figure 23.12. Regions of the diencephalon and brainstem in a midsagittal section. The thalamus, hypothalamus, and mammillary bodies are part of the diencephalon. The optic tracts leave the diencephalon, cross at the optic chiasm, and continue as the optic nerves out to the retina. The anterior commissure and fornix create the front and upper border of the diencephalon. The superior and inferior colliculi are part of the midbrain tectum, and the reticular formation is located throughout the brainstem. 'Midsagittal Diencephaon and Brainstem' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC

Coronal Section View

Coronal sections of the brain allow deep tissue structures to be visible. A cut through the anterior portion of the temporal lobe shows the amygdala, a region important for emotion, located in the medial temporal lobe. The regions of the basal ganglia are also visible: the striatum (which consists of the caudate and the putamen) and the globus pallidus. The basal ganglia has multiple functions, but is best known for its role in regulation of movement. The lateral ventricle sits medial to the basal ganglia and below the corpus callosum. The third ventricle is located in the middle of the brain, inferior to the lateral ventricle. The longitudinal fissure separates the left and right cerebral hemispheres and the lateral sulcus is the border between the frontal and temporal lobes.

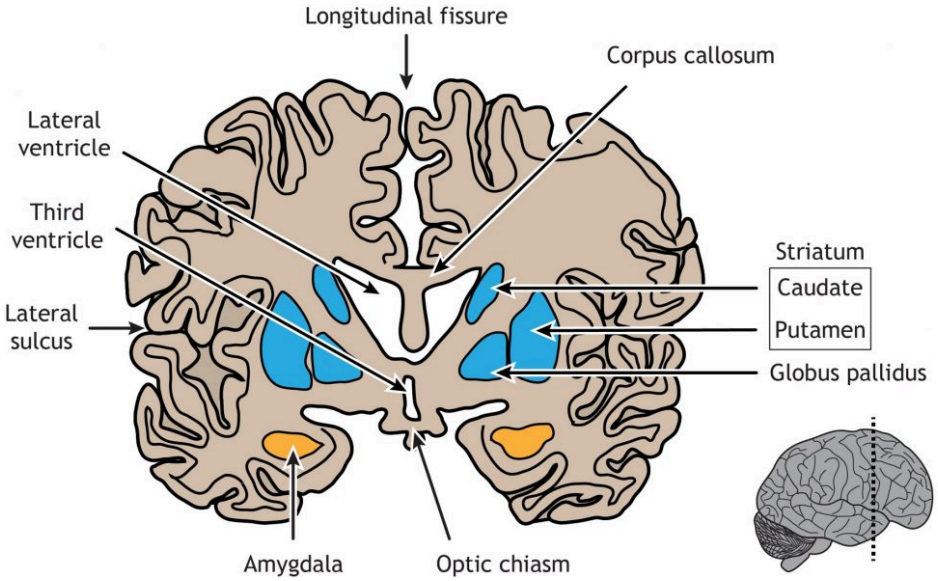

Figure 23.13 A coronal section at the location of the amygdala. The amygdala is located in the temporal lobe, and the basal ganglia is a subcortical structure located near the lateral ventricle. The corpus callosum, third ventricle, longitudinal fissure, and lateral sulcus can also be seen. 'Amygdala and Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

A coronal section taken closer to the central sulcus will make the hippocampus visible. The hippocampus is known for its role in memory and spatial awareness. At this location, the basal ganglia is more defined; the caudate and putamen are still present, but the two separate regions of the globus pallidus (the internal and external segments) can be seen, as well as the subthalamic nucleus and the substantia nigra. The thalamus is located on either side of the third ventricle. The corpus callosum is superior to the lateral ventricle. The cerebrum is divided in half by the longitudinal fissure and the lateral sulcus separates the temporal lobe from the frontal and parietal lobes.

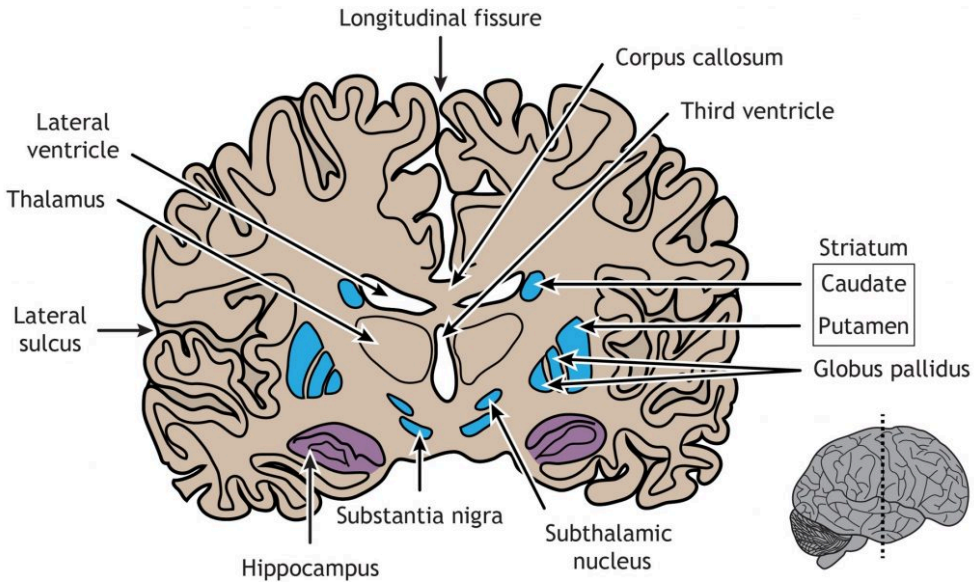

Figure 23.14. A coronal section at the location of the hippocampus. The hippocampus is located in the temporal lobe, and the basal ganglia is a subcortical structure located lateral to the thalamus and lateral ventricle. 'Hippocampus and Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The four lobes of the cerebral cortex each have specific functions
- The cerebral cortex has gyri and sulci to increase the surface area

- The cerebral cortex, underlying structures, cerebellum, brainstem, and spinal cord form the central nervous system
- Cranial nerves are visible on the ventral surface of the brain

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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- sagittal 2
- Amygdala and Basal Ganglia

- Hippocampus and Basal Ganglia

24.

ADDITIONAL STRUCTURES OF THE NERVOUS SYSTEM

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Although we mostly think about the neurons that make up the brain and spinal cord as being the main characters of the nervous system, there are many other anatomical features that play important supporting roles. These are often non-neuronal structures that are still critically important in allowing the nervous system to do what it needs to do.

Meninges

The brain is a soft and delicate internal organ housed inside the skull. If there weren't some protective buffer separating the soft brain matter from the rigid bone, the jelly-like brain would be smashed up against the inside of the skull and get injured as the head moves around.

The **meninges** are a series of protective membranes that minimize this kind of damage. They surround the brain and extend all the way down the spinal cord. Think of the meninges as an organic type of "bubble wrap" that encases a fragile nervous system.

There are three types of membranes that collectively make up the meninges. From the outermost to innermost layer, they are:

1. **Dura mater**. The dura is made of thick, fibrous material and can get to be 0.8 mm thick in the adult body (if you took a piece of printer paper and fold it in half four times, that should give you an idea of how thick the dura mater is in the adult human). The dura mater is physically attached to the inside of the skull with highly resilient connections found at the sutures between

the plates of the cranium. The name originates from Latin meaning “tough mother”.

2. **Arachnoid mater**. The arachnoid mater is the middle layer of the meninges. The fibers are very delicate and resemble a spider web, which is where the name comes from. Within this space, there are protrusions that allow for CSF to drain into sinuses, which allow for recycling of soluble substances. Most of the CSF in the brain exists underneath this layer in the subarachnoid space.
3. **Pia mater**. The pia mater is the third layer of the meninges. It is very fragile, is in direct contact with the surface of the brain, and closely follows the sulci and gyri. The name means “pious mother”.

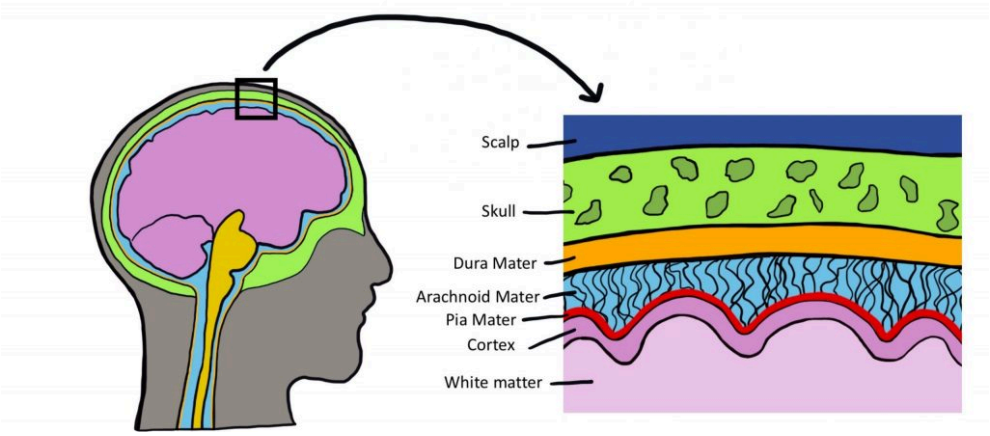

Figure 24.1. CNS Meninges. There are three meninges that cover both the brain and the spinal cord. The outermost layer beneath the skull is the dura mater (shown in orange). Below the dura mater is the spider-web like arachnoid mater (light blue and web-like). The innermost meninge is the pia mater. The pia mater (red) is in direct contact with the brain and has a greater surface area due to it following the gyri and sulci of the brain. 'Meninges' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Meningitis

Inflammation of the meninges is a potentially deadly condition called meningitis. Exposure to infectious agents like viruses or bacteria such as *Neisseria meningitidis* (that leaks from the blood into the meninges) is a common cause of the inflammation. When the meninges are inflamed, the brain gets compressed from all sides, increasing intracranial pressure, producing many of the same symptoms seen in hydrocephalus: fever, stiff neck, headache, seizures, and altered mental status. The *N. meningitidis* bacteria and the viruses are highly transmissible in close contact, but vaccinations are highly effective at minimizing the infection rate. As with bacterial infections, broad-spectrum antibiotics are effective at treating the infection.

Brain Circulation

Like every other organ in the body, the brain requires oxygen and nutrients to function. In humans, this function is accomplished by the blood that is pumped around the body using a network of blood vessels called the circulatory system. The brain has a very high demand for oxygen and nutrients: at only 2% of total body weight, it receives about 15% of total cardiac output.

Stroke

Stroke is an extremely common, life-threatening medical condition that results in a loss of blood flow to the brain. According to 2016 statistics from the World Health Organization, stroke is the second-highest cause of death worldwide. The number one risk factor for stroke is high blood pressure. There are two common types of strokes that a person may experience.

More than 80% of all strokes are **ischemic strokes** (pronounced is-keemik), which happens when normal blood flow is interrupted, causing cell death by deprivation of oxygen and nutrients to brain tissue. Generally, this type of injury can happen when a blood clot forms, travels through the circulatory system, and gets lodged in a tiny brain blood vessel, thus, blocking the passage of blood.

The other 20% of strokes are **hemorrhagic strokes**, which result from a burst blood vessel that causes bleeding into the brain. The presence of uncontrolled blood inside the brain causes an increase in intracranial pressure, which can be lethal. Many brain cells may die since they cannot take up oxygen directly from the blood. Additionally, blood has dramatically different properties than the normal solution brain cells live in, and this can cause the neurons to trigger a self-destruction program. Generally, hemorrhagic stroke is more deadly than ischemic stroke.

Because the different blood vessels of the brain's circulatory system are responsible for providing blood to specific areas of the brain, it is possible to diagnose the specific area where the stroke is happening based on the presentation of symptoms. For example, if the middle cerebral artery blood is occluded by an ischemic stroke, the left hemisphere motor cortex will lose blood flow. Because of the contralateral organization of the descending motor pathway, the patient may therefore present with **paralysis** or weakness in the right half of the body. It is vitally important to correctly diagnose and differentiate between the two types of strokes. An ischemic stroke may be treated with injection of a "clot-busting"

drug, a substance that helps the body break down the offending blockage. However, these clot-busters could make the bleeding from a hemorrhagic stroke even worse.

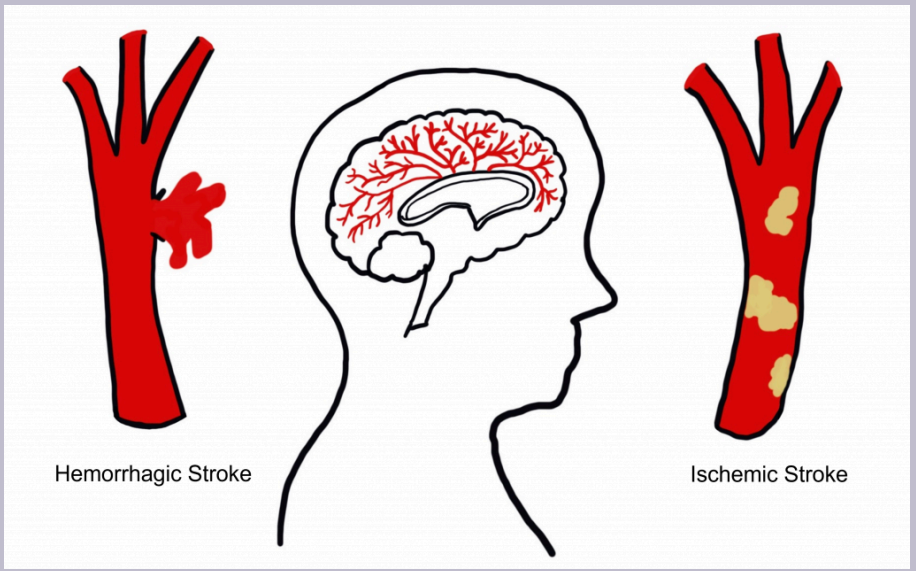

Figure 24.2. Types of Stroke. A hemorrhagic stroke is caused by a burst blood vessel that causes blood to leak into surrounding brain tissue. An ischemic stroke is caused by a blocked blood vessel that does not allow blood to perfuse to brain tissue. 'Stroke' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Blood–Brain Barrier

It is important for oxygen and nutrients to pass from the blood into the brain tissue. Small blood vessels outside of the brain, such as the capillaries in the fingertips, have very thin walls—sometimes the width of a single cell—and are, therefore, highly permeable to gases. These vessels can either contain tiny holes or large protein structures that physically transport substances across the blood vessel. On

the other hand, it is also advantageous to separate toxins and foreign pathogens in the bloodstream from getting into brain tissue.

The **blood–brain barrier (BBB)** is an anatomical adaptation that selectively transports substances necessary for normal biological function, while simultaneously excluding potentially harmful invaders from the brain. The BBB physically surrounds blood vessels in the brain. It is made up of endothelial cells and a type of glial cell called an **astrocyte**. The BBB is injured in a variety of medical disorders, ranging from **stroke**, **epilepsy**, and **Alzheimer's disease**, just to name a few. It is still unknown what role the disruption of the BBB plays in brain disorders.

The exclusive nature of the BBB can be a double-edged sword. It is difficult to deliver a drug into the brain from the blood stream if that drug is unable to pass through the BBB. For example, the current gold standard pharmaceutical treatment for **Parkinson's disease** is to increase the brain's levels of dopamine. However, dopamine does not pass through the BBB. To get around this, physicians give the BBB-permeable substance L-DOPA, which the brain is able to convert into dopamine. Many other therapeutic drugs do not cross the BBB, so researchers are developing methods using electromagnetic fields to temporarily weaken the barrier, or surround the drugs in nanoparticles so small that the body cannot identify them as foreign.

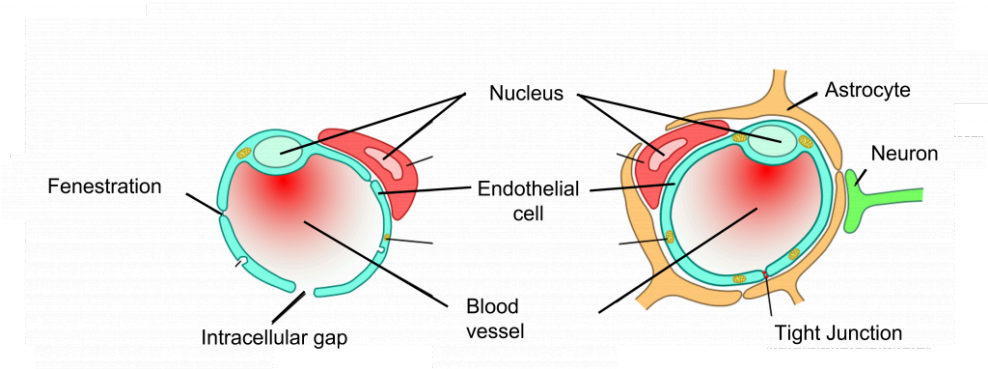

Figure 24.3. Blood–Brain Barrier. Endothelial cells in the body are typically leaky due to the presence of gaps and fenestrations surrounding blood vessels. The endothelial cells that surround blood vessels of the brain have astrocytes that create tight junctions that restrict the movement of many substances between the blood and the surrounding tissues.

Ventricles

There are hollow spaces within the brain called ventricles. The human brain has a total of four ventricles. The two very large, paired ventricles (one in each hemisphere) are the **lateral ventricles**. They are connected medially to the **third ventricle**, which extends to the **posterior** aspect of the brain. From here, the **cerebral aqueduct** that runs ventrally extends into the **fourth ventricle** before continuing into the **central canal:** a narrow space that runs all the way through the length of the spinal cord along the midline.

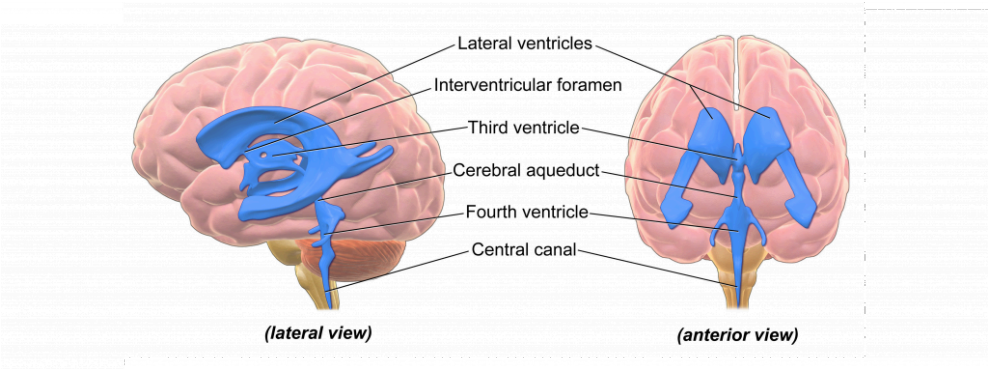

Figure 24.4. Image of brain ventricles. The brain ventricles (shown in blue) are hollow areas within the brain that are interconnected and filled with cerebrospinal fluid. The ventricles are connected to the central canal of the spinal cord. The ventricles are show in a lateral view (left) and anterior view (right).

The entire ventricular system is interconnected. The ventricles are filled with a liquid called **cerebrospinal fluid** (CSF). CSF is basically a high-salt water solution. Because of the high osmolarity of CSF, it is a very buoyant solution. Like a fully grown person who can float easily on the surface of the extremely salty Dead Sea, CSF allows the brain to remain "floating" inside the skull. Without CSF, the brain weighs almost 1.5 kg (~3 lbs). Cells and blood vessels at the **ventral** base of the brain would be crushed under the weight of the brain itself. But when the brain is surrounded by CSF, it weighs less than 50 grams, almost two orders of magnitude lighter!

CSF is also found within the **meninges** that encase the brain. In fact, more than 80% of the CSF in the body exists in this space outside the brain. This liquid serves as a form of "cushioning" that protects the brain from rapid head movements. If it weren't for this physical protection, the inertia of head movement may cause your brain to smash against the inside of the rigid skull if you move your head too quickly.

The CSF layer allows the head to withstand some sloshing of the brain, but a movement that is too abrupt can cause a **traumatic brain injury**. CSF can also function as a way to wash impurities out of the brain. The volume of CSF in the typical human body is about 150 mL, a little more than half a cup. Because there is frequent turnover of CSF, the material gets absorbed back into the body regularly.

Each day, the body produces about half a liter of CSF, so the brain cycles through the entire volume a few times.

Hydrocephalus

Hydrocephalus, historically called "water on the brain", is a common condition affecting the brain of about 1 in 200 newborns and a small number of adults. In patients with hydrocephalus, the volume of CSF increases, which elevates intracranial pressure, causing symptoms such as fever, stiff neck, headache, seizures, or altered mental status.

In adults, the skull is rigid and unmoving. But in newborns with hydrocephalus, the plates of the skull are not completely fused together. Often, these children will have a bulging parts on the skull and an expansion of the forehead.

Increased CSF volume can happen in a couple ways. The clearance of CSF may fail while production remains normal, or the entrance to the central canal in the spinal cord may be narrowed or blocked by a tumor, leading to an increase in the volume in the brain. A common treatment for hydrocephalus is to surgically implant a shunt (a hollow tube that runs from the ventricle down into the abdominal space) that allows for drainage, thus decreasing intracranial pressure.

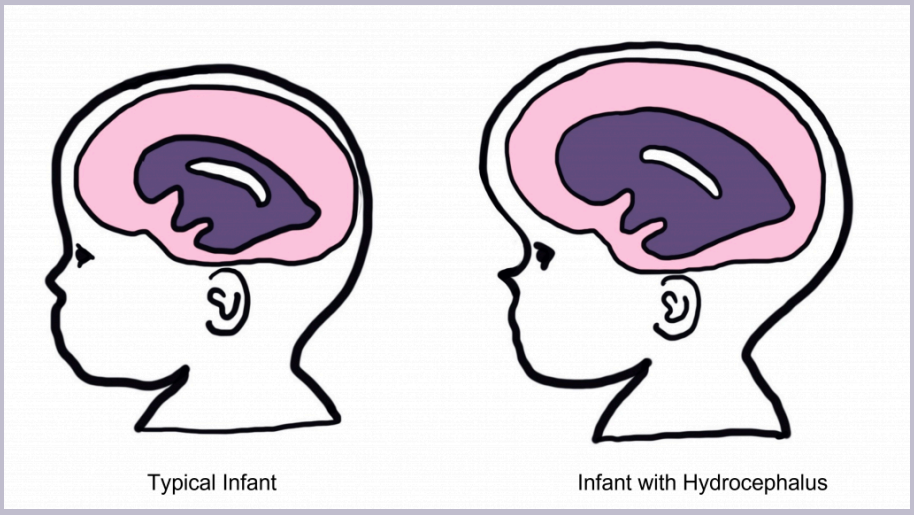

Figure 24.5. Hydrocephalus. The typical infant has normally sized ventricles (shown in dark purple) in the left image. The infant with hydrocephalus has enlarged ventricles and a bulging forehead (right image). 'Hydrocephalus' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- The meninges are protective coverings that cover central nervous system structures
- There are two types of stroke: ischemic (blocked blood vessel) and hemorrhagic (burst blood vessel)

- Ischemic strokes account for 80% of strokes and hemorrhagic strokes account for 20% of strokes
- The blood–brain barrier surrounds blood vessels of the brain to restrict the substances that can enter the brain
- Ventricles are hollow spaces in the brain that are filled with cerebral spinal fluid

Test Yourself!

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25.

IMAGING THE LIVING BRAIN

The earliest methods of analyzing nervous system anatomy were crude: manual dissection of the brain post-mortem (after death). The techniques discussed below were developed to allow scientists to see some aspect of the anatomy of the nervous system—either gross anatomical differences or connectivity. Additional techniques were developed to see how the living brain functions.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Studying Brain Structure

The following techniques are used to analyze brain structure.

CT Scan

Example questions answered:

"Does the patient have a brain tumor and where is the brain tumor located?"

"Are the meninges intact?"

The CT scan relies on X-ray technology. X-rays are high energy beams of electromagnetic radiation that are capable of passing through many physical objects. Traditional two-dimensional X-rays, such as those used to image a broken bone or tooth decay, use radiographic film to detect where the X-rays get blocked. When an X-ray passes unimpeded, it causes the film to darken. But, wherever the X-rays are blocked, the film remains white. Therefore, material that is more dense (such as bone) appears as white, less dense material (such as the air surrounding the body or CSF) appears dark. Other tissue are some shade of gray in between.

The CT scan is essentially a three-dimensional X-ray that revolves around the person as they move through the scanner. Instead of using radiographic film, the CT scan uses a computer that detects the passage of X-rays, located directly across the emission source of the X-ray. Instead of a flat, two dimensional-image, the CT scan uses an X-ray gun that revolves around the person's body as they advance slowly through a large circular hole. The computer is then able to compile the series of two-dimensional images and turn them into a three-dimensional reconstruction that can be used to see the brain from any projection. CT scans give us a spatial resolution of about 0.5 mm.

CT scans are generally used clinically to assess diagnostic changes over several days (such as before and after tumor removal or to determine if an intracranial bleed has healed), so temporal resolution is not a major consideration. As an anatomical analysis that can easily identify tissues of different density, it is great for identifying and diagnosing particular brain conditions. Brain tumors can be visualized in a CT scan, since they are identified by an increase in tissue density compared to normal brain tissue. **Hydrocephalus**, an abnormal and potentially deadly expansion of the CSF-filled ventricles, can be quickly identified by this analysis. **Meningitis**, an inflammation of the meninges, may present as increased contrast in the CT scan.

The big advantage of the CT scan is that it is noninvasive. You can use a CT scan in order to diagnose and identify the cause of a condition while a person is still alive, and hopefully work towards developing an intervention. It is also a relatively quick technique. A full-head CT scan takes only minutes, which allows for a rapid diagnosis of anatomical structures. However, X-rays are highly mutagenic. Prolonged exposure to X-rays dramatically increases the risk of developing various cancers, since X-rays interfere with the process of DNA replication. It is estimated that the radiation exposure in a single head CT scan is similar to the background exposure of X-rays in a few months. When a CT scan is prescribed, the diagnostic information gained from a CT scan is more important than the risks from increased radiation exposure.

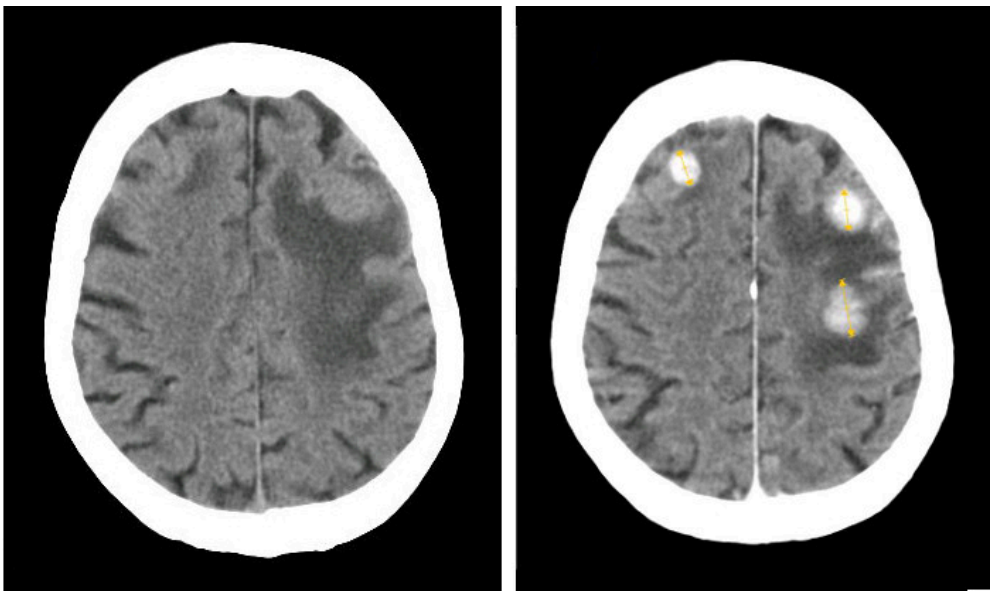

Figure 25.1. A CT scan (or CAT scan) uses X-ray technology to produce an image of brain structures. CT scans are non-invasive and are useful for visualization of the brain ventricles or brain tumors. In the above images are horizontal sections of a human brain with brain tumors that are shown as lightly-colored areas of tissue.

Magnetic Resonance Imaging (MRI)

Example questions answered:

"Are their structural abnormalities in a brain structure?"

"What are the measurements of a brain structure?"

Magnetic resonance imaging (MRI) is used for imaging brain structures. An MRI is able to more clearly differentiate between different types of tissues with high resolution. It can be used in place of CT scan for visualization of structures that are very small or need finer detail than can be seen with a CT scan.

The MRI machine is a circular tunnel through which a person on a table moves. As the person moves through the scanner, an extremely powerful magnet revolves around their head. The power of a typical magnet used in a hospital MRI may be as powerful as 10,000 gauss (1 Tesla)—strong enough to lift a car. The more powerful fMRI machines can be as powerful as 100,000 gauss (10 Tesla). The

stronger the magnets, the better the spatial resolution that the machine can produce (our current best spatial resolution is on the order of millimeters).

MRI technology detects and quantifies the movement of water molecules, which moves differently in gray matter than white matter. The movement of a water molecule in biological tissue is not completely random, largely because the brain is made up of heterogeneous tissue.

Although the technique has a great capacity for analyzing brain structure, the nature of the machine itself presents limitations. The machine can also be very loud, which is not trivial if you are interested in using this technology on younger patients. The use of a tremendously powerful magnetic field presents a different set of limitations. At the risk of severe injury or death, the patient entering the scanner cannot have any magnetosensitive implants, such as metallic aneurism clips, intrauterine devices, or shrapnel. Even older generation tattoos have trace amounts of metal that cause burns when exposed to the magnets of the MRI machine.

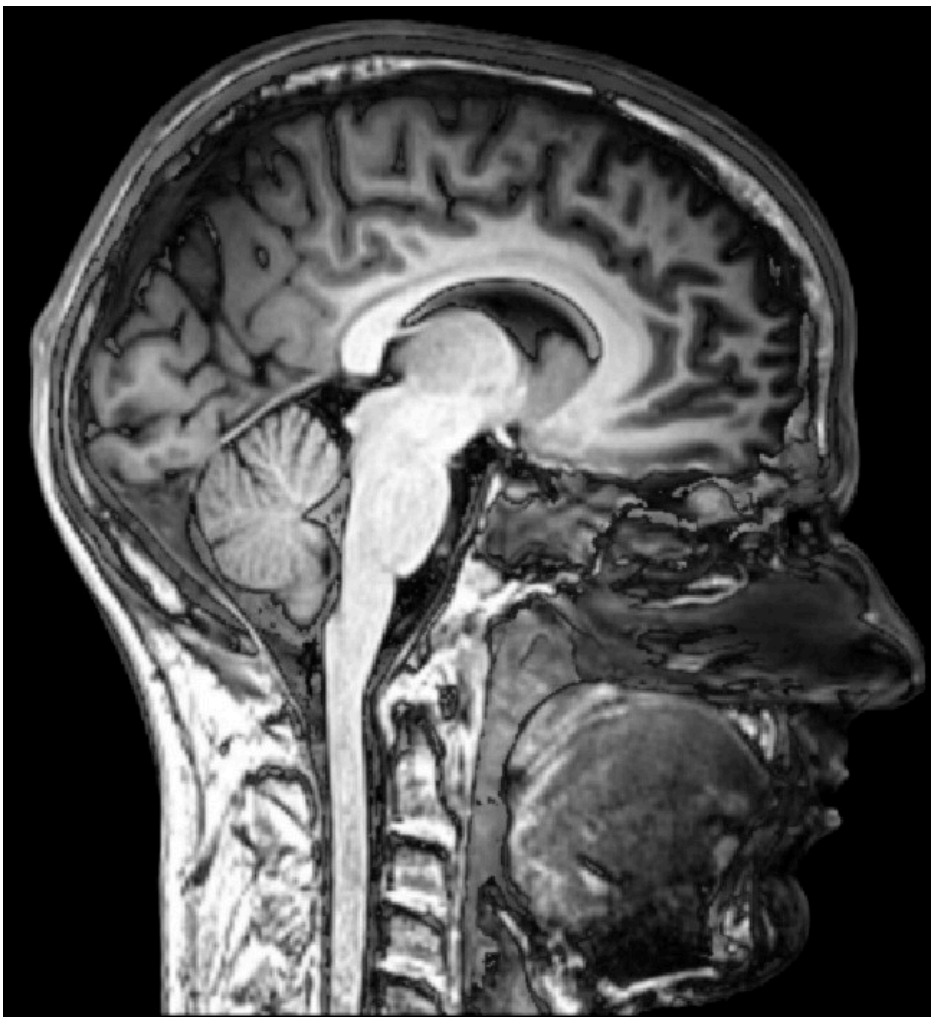

Figure 25.2. MRI Scan. An MRI scan uses high-powered magnets to produce high resolution images. MRI scans can clearly distinguish brain structures with higher resolution than other imaging techniques like CT scans. In this image of a midsagittal human brain fine details of brain structures can be visualized.

Diffusion tensor imaging (DTI)

Example questions answered:

"Is the volume of the white matter tract medial longitudinal fasciculus important for normal language processing?"

"Does spinal cord compression cause neurological deficits?"

While a CT scan is great for detecting gross anatomical anomalies like tumors or intracranial bleeding, it has a difficult time with subtle anatomical changes like differences between gray matter and white matter tracts. A technique for identifying these differences was proposed in 1994, called diffusion tensor imaging (DTI).

DTI quantifies white matter because of the morphological features of white matter. More specifically, DTI uses MRI technology to detect and quantify the movement of water molecules, which move differently in gray matter than white matter. The movement of a water molecule in biological tissue is not completely random, largely because the brain is made up of heterogeneous tissue. White matter is very different from gray matter. A water molecule is more easily able to diffuse along the same direction as a tract of white matter but has a difficult time moving perpendicularly across such tissue. When looking at DTI images, they will have coloring added to the figure to show the different white matter tracts.

Axonal projections are directional, with the soma at one end and the axon terminal at the other. One of the shortcomings of DTI is that it cannot give us information about the directionality of the axonal projections.

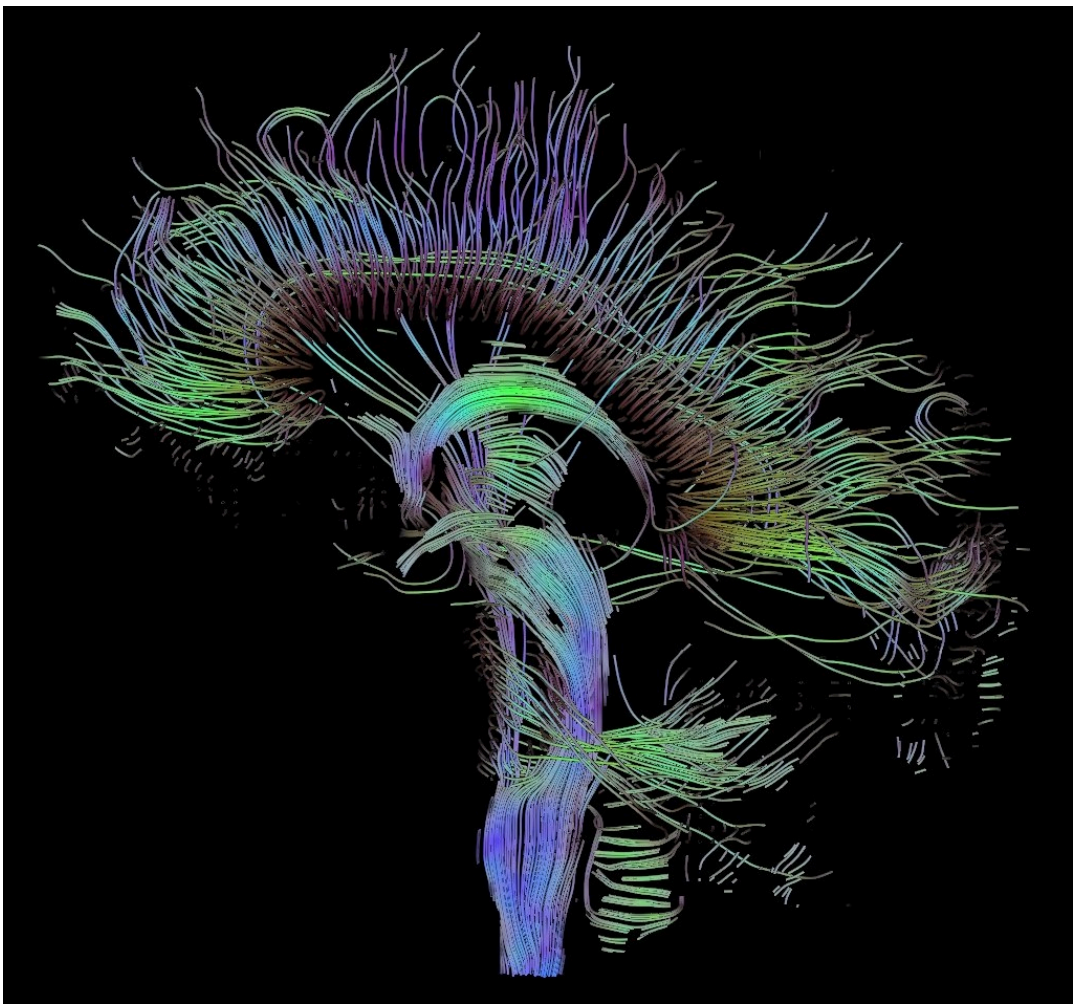

Figure 25.3. Diffusor Tensor Imaging. DTI imaging uses MRI technology to detect and quantify the movement of water molecules along tracts of white matter. This techniques allows for the visualization of white matter connections within the brain. The coloring is added to the image to show the different white matter tracts.

Studying Brain Function

The following techniques are used to study brain function.

Positron emission tomography (PET scan)

Example questions answered:

"Which areas of the brain decrease in activity when a person experiences mild cognitive impairment?"

"Do drug-dependent people have a high density of opioid receptors?"

The positron emission tomography (PET) scan is an application of nuclear medicine best known for its applications in the medical setting for the diagnosis of cancer. Before the PET scan, a radioactive compound called a tracer is injected into the bloodstream. The PET scanner itself is a large circular device that looks similar to the CT scanner. The tracer is chemically unstable, and it produces a signal within the body that can be detected by the PET scanner as the person moves through the machine. A common tracer is a radioactive analog of glucose. Areas of the brain that are active will metabolize glucose for energy. Therefore, when an area of the brain increases in energetic demand, that change can be detected by identifying the increase in glucose movement.

PET scans can be effective at diagnosing and identifying the location of tumors in the nervous system. It also provides an overall picture of brain activity, which may be useful in diagnosing disorders of cognitive deficits, like dementia associated with **Alzheimer's disease**. PET scans have also been used to image the activity of specific brain areas as a person performs behavioral tasks, but this use of PET scan has largely been replaced by functional magnetic resonance imaging. Another application of PET scanning is to visualize levels of receptors **in vivo**.

When looking at PET images, they will have coloring added to the figure to show where, anatomically, activity in the brain has increased or decreased. By convention, many times an increase in brain activity is depicted with warm colors (yellow, orange, red) whereas a decrease in brain activity is depicted with cool colors (blue, purple).

The downside of the PET scan as a diagnostic tool is similar to a limitation of the CT scan. A person is exposed to radioactive compounds and gamma wave radiation, which are potentially mutagenic. In images produced by a PET scan, it is often difficult to identify boundaries between tissue, even between dramatically different internal organs. To make up for this deficit, PET scans are frequently performed simultaneously with an anatomical analysis like a CT scan. PET scans generally have very poor spatial and temporal resolution.

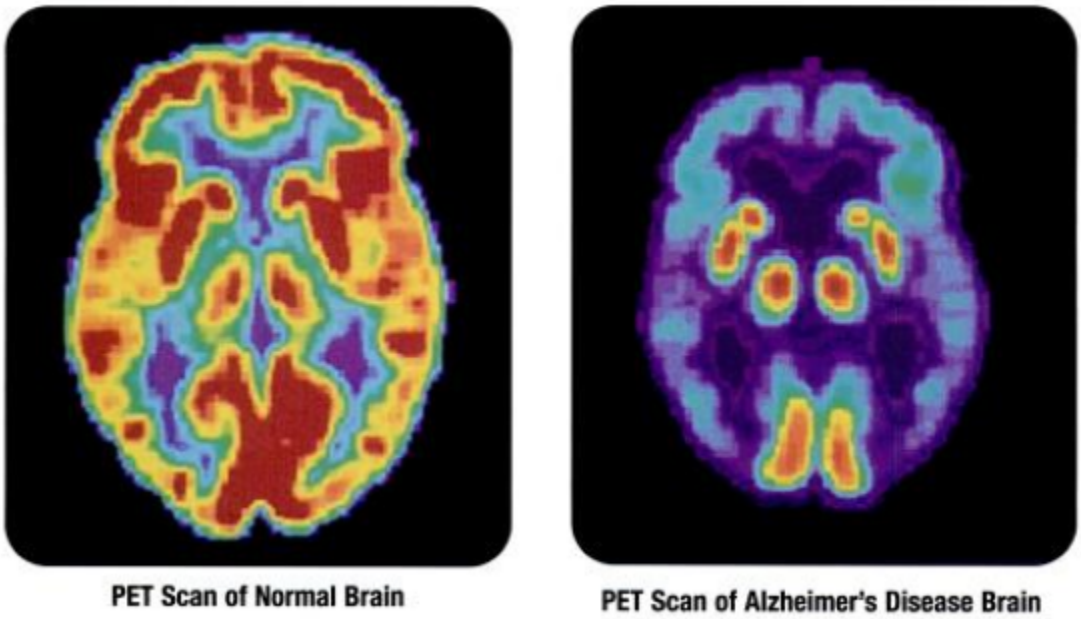

Figure 25.4. PET Scan Images. The positron emission tomography (PET) scan is used to visualize brain activity. A radioactive tracer is injected into the bloodstream prior to scanning that can be detected by the scanning machine. PET scans are colored to show where in the brain is experience increases or decreases in brain activity. Typically, increased brain activity is indicated with warm colors (yellow, orange, red) and decreased brain activity is depicted with cool colors (blue, purple).

Functional magnetic resonance imaging (fMRI)

Example questions answered:

"Do neurons in the right hemisphere cingulate gyrus increase in activity when a person sees their loved ones?"

"Which areas of the brain change in activity when a person is planning a motor action?"

The functional magnetic resonance imaging (fMRI) technique is probably the most well-known method of studying brain activity. Because fMRI can be performed while a person is engaged in a task, many research studies use fMRI as a means to correlate behavior with activity patterns in specific parts of the brain.

fMRI measures differences in blood flow and oxygen levels. Like the PET scan, the fMRI hinges on the idea that more active areas of the brain have different metabolic demands than less active areas of the brain. When there is more activity in one area of the brain, the neurons in that area need more

oxygen. This change in blood flow is detected by the fMRI. The main reason fMRI is useful in so many research applications is that you are able to visualize brain activity real-time during the performance of complex behavioral tasks. You can present specific visual stimuli to a person in an fMRI scan and evaluate which parts of the brain change in activity. For example, seeing pictures of faces causes increased blood flow into the fusiform face area. You can ask a person to perform a gambling task and evaluate the areas of the prefrontal lobe that are responsive to risk taking.

When looking at fMRI images, they will have coloring added to the figure to show anatomically where activity in the brain has increased or decreased. By convention, many times an increase in brain activity is depicted with warm colors (yellow, orange, red) whereas a decrease in brain activity is depicted with cool colors (blue, purple).

The limitations introduced with MRI earlier are the same for fMRI. In addition, due to the small tube, it can be difficult to study anxiety with endangering the patient. Further, the data collected by fMRI can be very difficult to analyze and are frequently subject to false positives. fMRI also assumes that increased blood flow is directly correlated with the amount of neural activity, which may not always be the case.

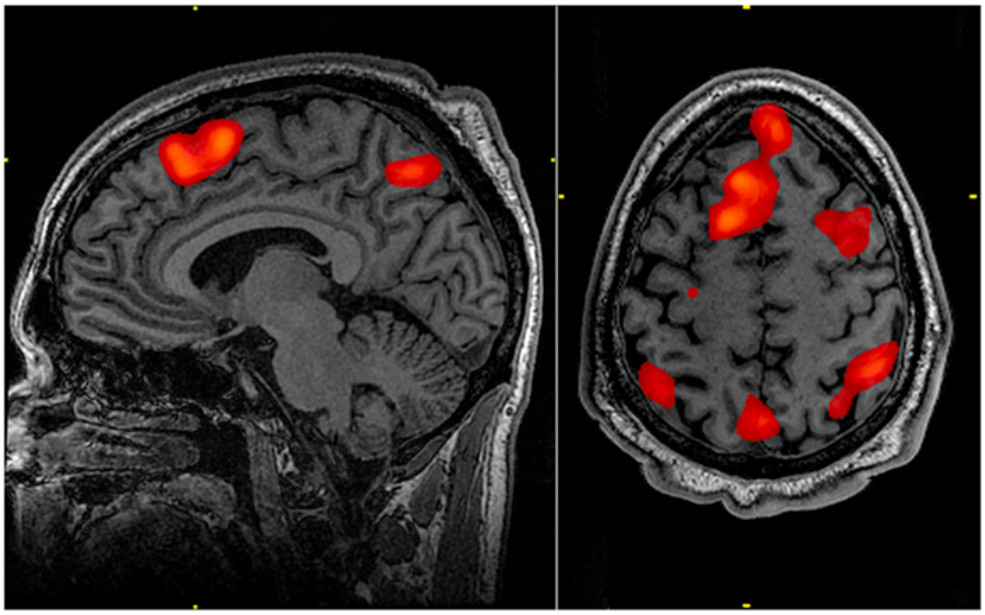

Figure 25.5. fMRI Scan Images. An fMRI scan measures differences in blood flow and oxygen levels, similarly to an MRI scan. An fMRI, however, can be used while an individual is performing a task to look at changes in brain activity over time. Coloring is added to fMRI images to show where within the brain there is increased or decreased brain activity. Similar to PET scans, increases in brain activity are depicted with warm colors (yellow, orange, red) whereas decreases in brain activity are depicted with cool colors (blue, purple).

Key Takeaways

- CT scans, MRI scans, DTI are used to visualize brain structures
- PET scans and fMRI scans are used to visualize brain function

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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26.

SPINAL CORD STRUCTURE

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

It is sometimes easy to think of neuroscience as a focused study of the brain: How does activity of the brain contribute to behavior? In what ways does the brain change in disease? Why do the cells of the brain behave the way they do?

The truth is there are many parts of the body that also fall under the broad study of neuroscience. For example, the automatic kneejerk reflex that a clinician examines when they tap on your patellar tendon is a test of the nervous system. The reflex is driven by sensory neurons that detect muscle stretch, motor neurons that cause the kicking response, and interneurons that prevent the opposing muscle from acting. We have neural circuits that provoke changes in the activity of our internal organs, from the beating of our heart to the digestion of food, and the study of these systems is certainly part of neuroscience as well.

Moving posterior from the brainstem is the other organ of the central nervous system: a long, thin structure of nervous tissue called the **spinal cord**. It functions to carry information both upwards towards the brain and downwards towards the body's other organs and muscles. It can also process sensations and form an appropriate motor response in the absence of brain input.

Spinal Column Anatomy

The spinal cord begins at the base of the brainstem and runs down to the small of your back, giving it a length around 44 cm (17.5 inches). The spinal cord is housed within a series of bones, called the vertebral column. Although the spinal cord itself is continuous, it can be divided based on the overlying

vertebrae. A combination of a letter and a number is used to identify each section of the spinal cord; the letter corresponds to the vertebral section and the number refers to the number of bones down from the previous section (the smaller numbers are more anterior, larger numbers more posterior). The diameter and shape of the spinal cord changes over the length of vertebral column, a result of the function of the spinal nerves. For example, the region where motor neurons are located (ventral horn) is larger in the cervical region of the spinal cord compared to other regions of the spinal cord with minimal motor output.

Branching off from each section of the spinal cord are two pairs of nerves, the **afferent** (incoming to the CNS) sensory nerve roots, which branch from the dorsal side of the spinal cord, and the **efferent** (outgoing from the CNS) motor nerve roots, which branch from the ventral side of the spinal cord. These two branches meet and extend away from the spinal cord. After merging, they are called the **spinal nerves**.

The vertebral column is divided into four main regions: cervical, thoracic, lumbar, and sacral. The spinal cord and spinal nerves that enter and exit the vertebral column are divided into these regions as well. Moving from **anterior** (top) to **posterior** (bottom), the four regions of the spinal cord are:

1. **Cervical**. The cervical region corresponds to C1 through C7. Nerves that exit through the cervical region innervate the muscles in the neck, shoulders, arms, and hands. Afferent nerves detect somatosensory inputs from these same areas. Sections C3 through C5 innervate the diaphragm, so an injury at this level or higher can quickly lead to death since the person may stop breathing. The spinal cord is at the widest diameter at the cervical area, as it has a swelling that corresponds to the many inputs and outputs to the arms.
2. **Thoracic**. The thoracic region corresponds to T1 through T12. These regions innervate the middle trunk area, the intercostal muscles between the ribs, and abdominal muscles. Branches of the spinal nerves in the thoracic areas are responsible for changing the activity of the various internal organs during a fight-or-flight response (more on the autonomic nervous system in Chapter 27).
3. **Lumbar**. The lumbar region corresponds to L1 through L5. These pathways carry motor command information to the hips, thighs, and knees. Afferent lumbar inputs detect sensory information from the ventral side of the legs, such as the top of the thigh or the shin bone. As in the cervical region, the lumbar region has a swelling that increases the diameter of this section of spinal cord compared to the thoracic or sacral areas.
4. **Sacral**. At the posterior-most end of the spinal cord is the sacral region, which corresponds to S1

through S5. Sacral spinal nerves control flexing of the toes. These nerves detect sensory information around the genital organs and the dorsal aspects of the legs, like the buttocks and the back of the thighs. There are also parasympathetic nerves that come from the sacral region and these innervate the colon, bladder, and genital organs (more on the autonomic nervous system in Chapter 27). Since information must pass through the anterior regions of the spinal cord to reach the posterior parts of the body, the more anterior an injury, the more parts of the body that are affected.

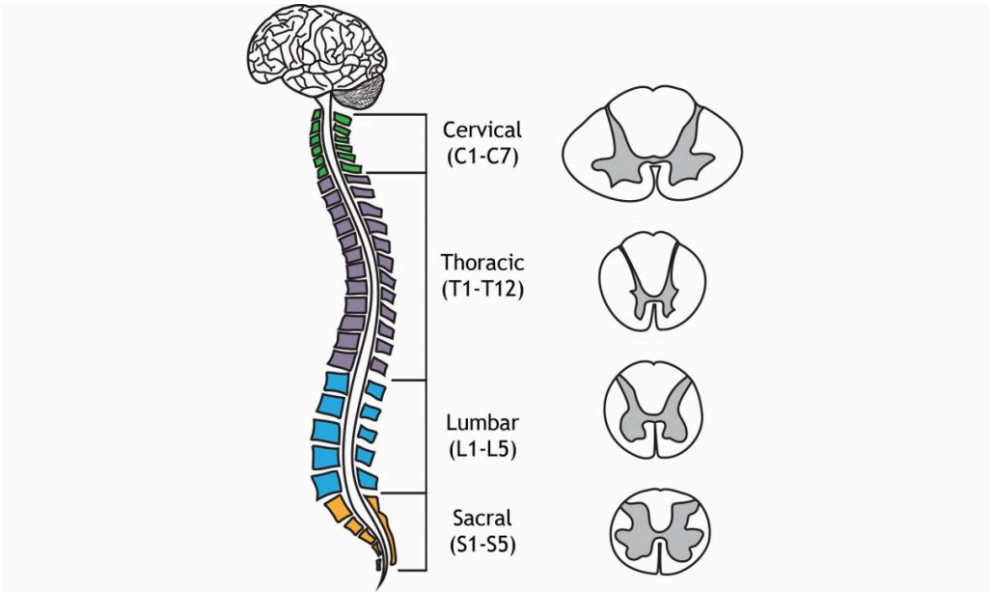

Figure 26.1. The vertebral column and representative spinal cord cross-sections. The vertebral column and corresponding spinal cord and spinal nerves are divided into four regions. The cervical division is the most rostral, starting at the base of the brainstem. The thoracic is the largest division, just caudal to the cervical. The lumbar is the next division, and the sacral is the most caudal. 'Spinal Cord' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

From L2 through S5, the spinal cord exists as the cauda equina, meaning "horse's tail" due to the appearance of the cord as individual nerves that branch from the main spinal cord. These nerves then innervate the pelvis area and lower limbs. This area of the spinal cord is where spinal tap and epidural procedures take place due to the decreased risk of spinal injury.

Figure 26.2. Cauda equina. The spinal cord at the L2-S5 levels is called the cauda equina. At the cauda equina, the spinal cord branches into individual nerves that innervate the pelvis area and the lower limbs.

The spinal cord is part of the central nervous system, but the fibers that leave and enter the spinal cord are located in the peripheral nervous system. These spinal nerves can then extend to or from target tissues throughout the body.

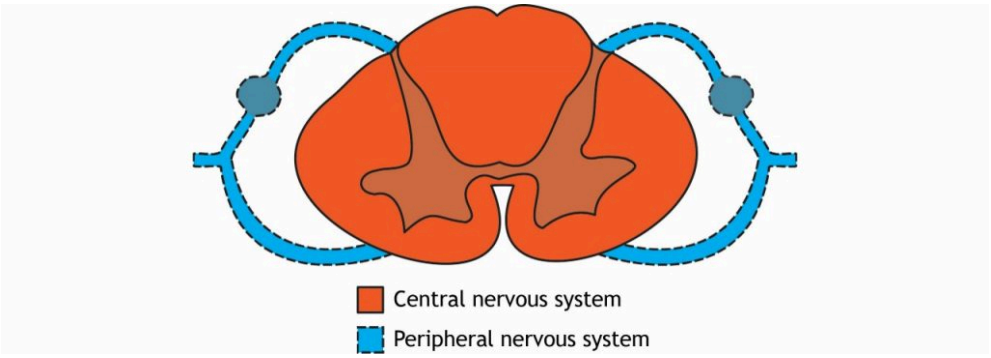

Figure 26.3. The spinal cord is part of the central nervous system, but the axons that exit and enter the spinal cord are in the peripheral nervous system. 'Spinal Cord CNS and PNS' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Nerves are collections of neuron axons found within the peripheral nervous system and can be classified as sensory, motor, or mixed nerves. The dorsal root is an example of a sensory (afferent) nerve that is responsible for carrying information toward the central nervous system. The ventral root is an example of a motor (efferent) nerve that is responsible for carrying information away from the central nervous system. Most nerves in the body are classified as mixed nerves that contain both sensory and motor fibers.

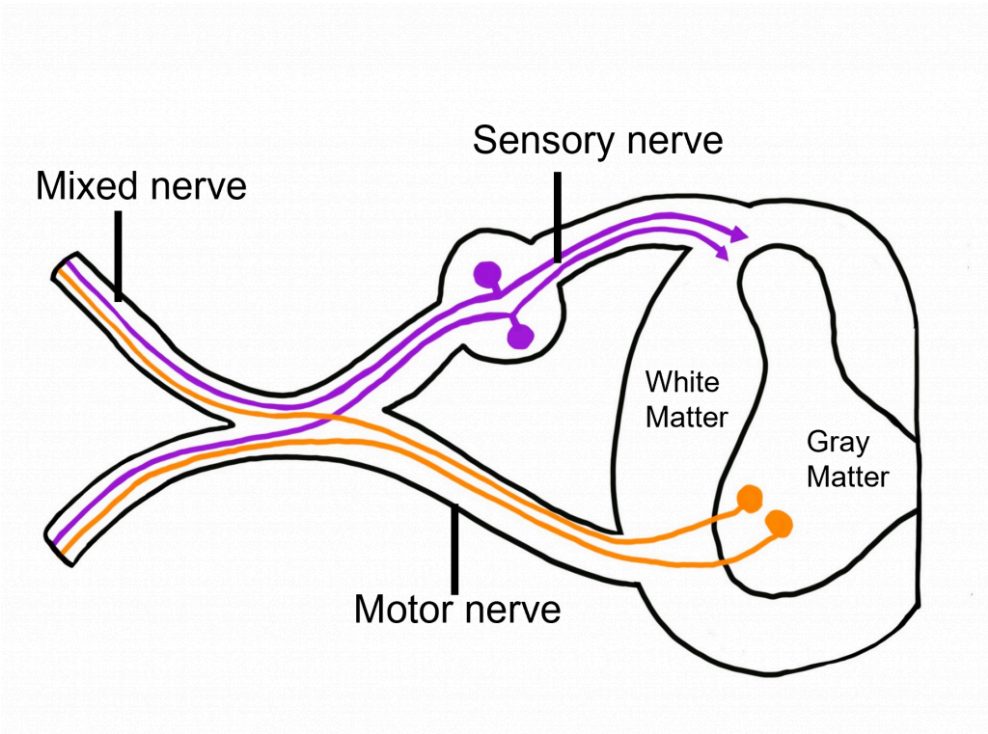

Figure 26.4. Sensory, or afferent nerves, contain only sensory axons, which can be found at the dorsal root. of the spinal cord. Motor, or efferent, nerves contain only motor axons and can be found at the ventral root of the spinal cord. Most nerves within the body contain both sensory and motor neurons and are referred to as mixed nerves. 'Nerve Classification' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Cross Section Anatomy of the Spinal Cord

Like the brain, the spinal cord is also made up of regions of white matter and gray matter. White matter regions are comprised of axons. It appears white due to the myelin sheath on the axons. Gray matter regions are comprised of cell bodies and dendrites. Gray matter is the location of most synapses.

In cross section, the gray matter of the spinal cord is found medially, and the white matter is found laterally. When referring to the spinal cord, we will typically use the directional terms "**dorsal**" and "**ventral**". By convention, when looking a cross section of the spinal cord (a horizontal cut through the cord), the dorsal portion of the spinal cord will be located at the top of the image and the ventral portion of the spinal cord will be located at the bottom of the image. There are a few structures to be aware of when examining the spinal cord in cross section.

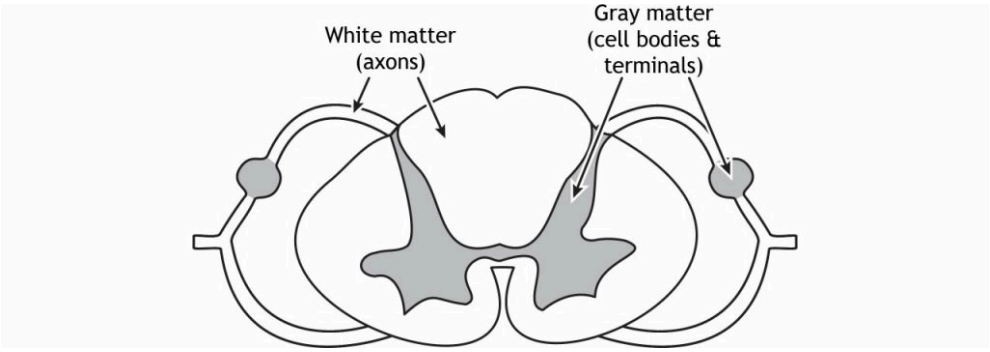

Figure 26.5. The spinal cord can be divided into white and gray matter. White matter is primarily myelinated axons. Gray matter is primarily neuronal cell bodies and dendrites. In the spinal cord, the inner part is gray matter, whereas the surround tissue is white matter. The regions that extend from the central nervous system and into the peripheral nervous system primarily contains axons traveling to or from peripheral targets and, therefore, are mainly white matter except for ganglia, which are clusters of cell bodies in the periphery. 'Spinal Cord White and Gray Matter' by Casey Henley is licensed under a Creative Commons Attribution

The white matter in the spinal cord is divided into structures called columns because the axons in these regions are either ascending toward the brain or descending toward the appropriate spinal nerve. The **dorsal column** is on the dorsal or posterior side of the spinal cord, the **ventral horn** is on the ventral or anterior side of the spinal cord, and the **lateral column** lies between them. The gray matter is likewise divided into regions called horns. The **dorsal horn** is the location of sensory synapses, the **ventral horn** is the location of motor neuron cell bodies, and the **lateral horn** is the location of cell bodies of the autonomic nervous system. The **dorsal root** and **ventral root** consist of the axons of afferent (dorsal) and efferent (ventral) fibers. They combine to form the spinal nerves. Sensory neuron cell bodies are located in the dorsal root ganglion, a gray matter region of the dorsal root.

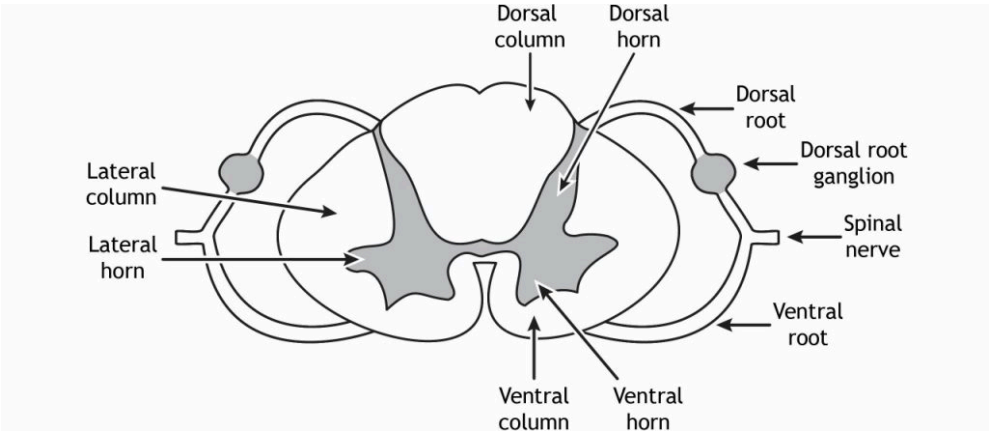

Figure 26.6. The spinal cord is comprised of white and gray matter. The dorsal column and dorsal horn are on the posterior side of the spinal cord. The ventral column and ventral horn are located on the anterior side of the spinal cord. The lateral column and lateral horn are located in the middle. The spinal nerves that extend into the periphery consist of fibers that split into the dorsal root and the ventral root to enter (dorsal) or exit (ventral) the spinal cord. The dorsal root ganglion is a gray matter region of the dorsal root. 'Spinal Cord Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0

All somatosensory receptor neurons have their cell bodies located in the **dorsal root ganglion**; a structure found just outside the dorsal aspect of the spinal cord. The receptor neurons (also called primary afferent fibers) of the somatosensory system are bipolar neurons, meaning they have one process from the cell body that splits into two branches. Afferent fibers coming from the periphery through the spinal nerves enter the spinal cord via the dorsal root. The cell bodies of sensory neurons are located in the dorsal root ganglion. The axons continue into the spinal cord and typically synapse in the dorsal horn. Interneurons are very short neurons that are a communication link between cell types in the spinal cord. They can be either excitatory or inhibitory depending on their role. They can also cross the midline of the spinal cord. The cell bodies of motor neurons that innervate skeletal muscles are located in the ventral horn. The efferent axons of these neurons leave the spinal cord via the ventral root and then enter the spinal nerve on their way to their target tissue.

The ventral portion of the spinal cord is concerned with motor output, or efferent signals. Muscle fibers are innervated by alpha motor neurons that have their cell bodies in the ventral horn of the spinal cord. Their axons leave the spinal cord via the ventral roots and travel to the muscle via efferent peripheral spinal nerves.

In summary, sensory information is concerned with the dorsal portion of the spinal cord whereas motor information is concerned with the ventral portion of the spinal cord.

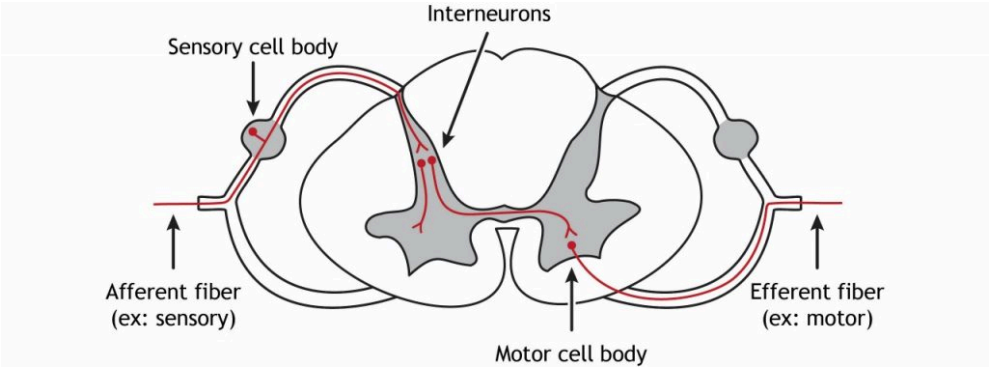

Figure 26.7. Afferent axons coming from the periphery travel through the dorsal root to enter the spinal cord. These axons can synapse on interneurons, cells with short axons that communicate with other cell types. Efferent fibers, like those of the skeletal muscle motor neurons located in the ventral horn, leave the spinal cord through the ventral root. ‘Spinal Cord Fibers” 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.

- There are four regions of the spinal cord
- There are gray matter and white matter areas of the spinal cord
- Sensory information enters into the spinal cord via the dorsal root ganglion to the dorsal horn
- Sensory cell bodies are located within the dorsal root ganglion
- Motor information exits the spinal cord from the ventral horn then through the ventral root out to the body

Test Yourself!

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- Nerve Classifications
- Spinal Cord White and Gray Matter
- Spinal Cord Anatomy
- Spinal Cord Fibers

27.

PERIPHERAL NERVOUS SYSTEM

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

The **Peripheral Nervous System** (PNS) functions as the intermediary between the **central nervous system** (CNS) and the rest of the body, including the skin, internal organs, and muscles of our limbs. The PNS can be divided into three main branches:

1. Somatic nervous system
2. Autonomic nervous system
3. Enteric nervous system

In this chapter, the somatic and autonomic nervous systems will be compared and contrasted. An overview of the enteric nervous system will also be provided.

Somatic vs. Autonomic Nervous System

The somatic and autonomic nervous system differ in their:

- Target/effector organs
- **Efferent** pathways and the neurotransmitters that are used
- How the target/effector organ responds to the neurotransmitter

Peripheral Nervous System: Somatic Nervous System

The **somatic nervous system** represents all the parts of the **PNS** that are involved with the outside environment, either in sensing the environment or acting on it. For example, the nerves that detect pressure or pain on the foot are part of the **afferent** somatic nervous system. We also think of the somatic nervous system as the branch that sends signals to our skeletal muscles. The nerves that innervate the muscles of the legs as we run are part of the efferent somatic nervous system. The somatic nervous system is also called the "voluntary nervous system" since it is used to cause muscle movement related to intentional actions.

The somatic nervous system has an efferent path from the central nervous system to the target / effector organ that is made up of one neuron. The axon of this neuron is heavily **myelinated**, which allows for fast delivery of messages. This somatic motor neuron has its cell body in the central nervous system and has an axon that extends all the way to the target/effector organ, which—for the somatic nervous system—will be a **skeletal muscle**.

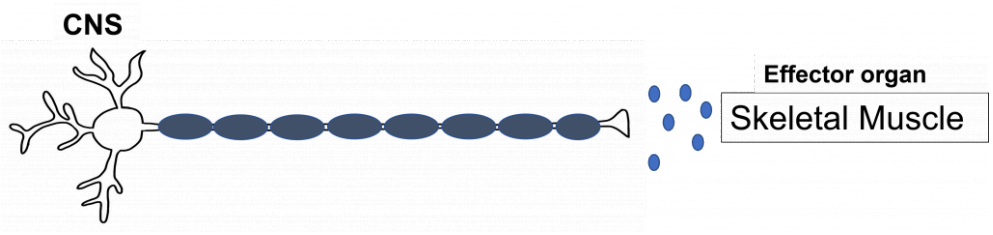

Figure 27.1. Somatic nervous system efferent pathway. The somatic nervous system efferent path consists of a neuron that has a cell body within the central nervous system that extends all the way to the target tissue: skeletal muscles. The neurotransmitter released onto the skeletal muscle is acetylcholine. 'Somatic Nervous System' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Synapse: Neuromuscular Junction

All somatic motor neurons release the same neurotransmitter, **acetylcholine**, onto the skeletal muscle target/effector organ at the **neuromuscular junction** (NMJ). The NMJ 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 NMJ and it acts upon **ligand-gated**, non-selective **cation** channels called nicotinic acetylcholine receptors that are present in postjunctional folds 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.

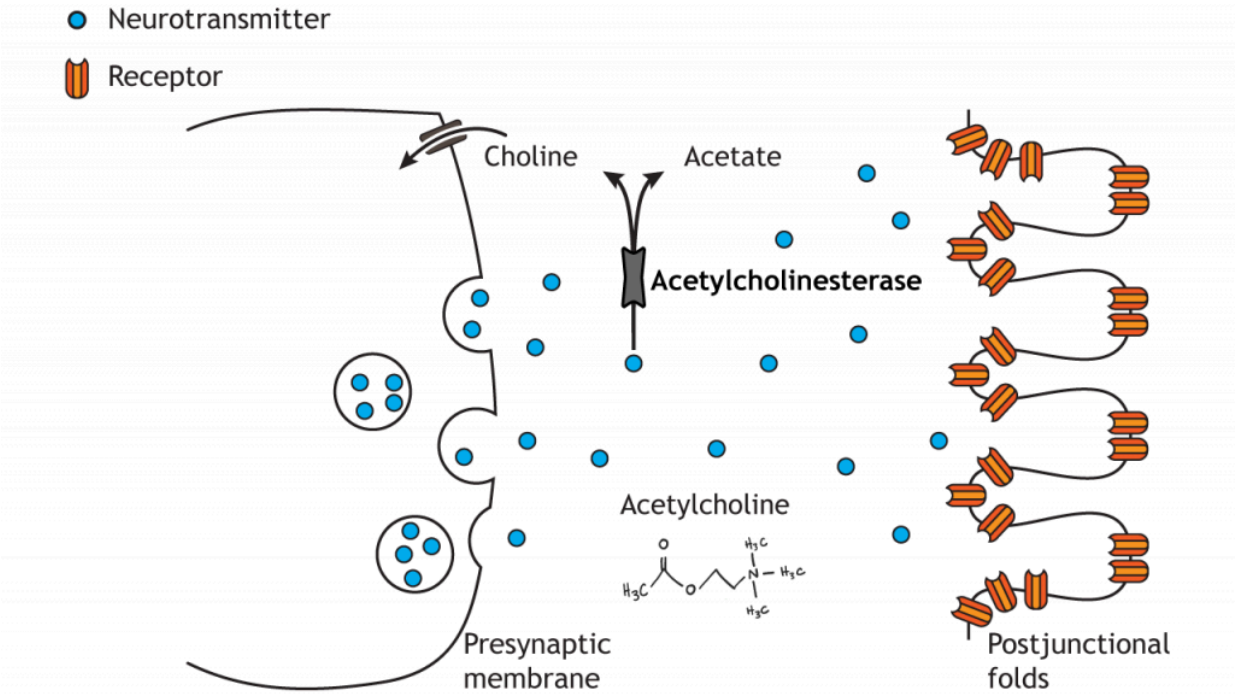

Figure 27.2. The neuromuscular junction (NMJ) is the synapse between a motor neuron and a muscle fiber. Acetylcholine is released at the NMJ and acts on nicotinic acetylcholine receptors located in the postjunctional folds of the muscle fiber. Neurotransmitter action is terminated through breakdown by 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.

Nicotinic acetylcholine receptors allow for the influx of sodium ions into the muscle cell. The depolarization will cause nearby **voltage-gated channels** to open and fire an action potential in the muscle fiber. 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.

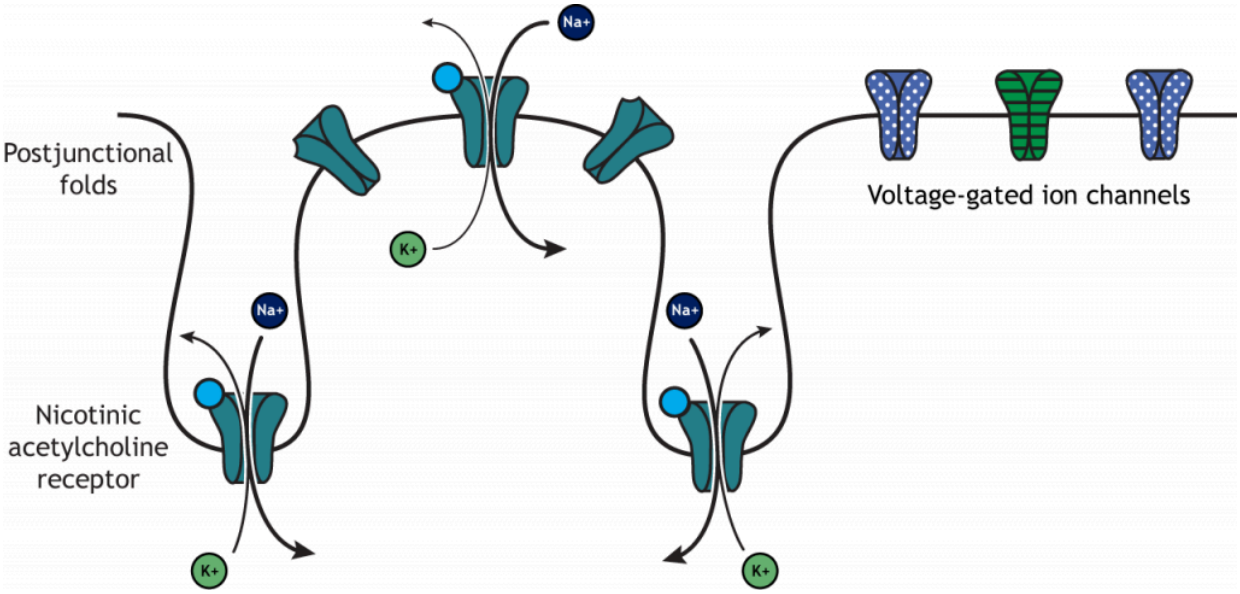

Figure 27.3. The ionotropic nicotinic acetylcholine receptors in the postjunctional folds of the muscle fiber are non-selective cation channels that allow the influx of sodium and the efflux of potassium. The depolarization of the cell by the sodium influx will activate nearby voltage-gated ion channels. 'NMJ Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Peripheral Nervous System: Autonomic Nervous System

The **autonomic nervous system** encompasses all the branches of the peripheral nervous system that deal with the internal environment. As with the somatic nervous system, the autonomic nervous system is comprised of nerves that detect the internal state as well as nerves that influence the internal organs. The body carries out all sorts of functions and responses unconsciously without any intentional control. It can do so by sending signals to smooth muscles and glands. The signals that cause us to sweat when it is hot, our pupils to dilate when it is dark, and our blood pressure to adjust when we stand up too quickly are all driven by the nerves of the autonomic nervous system.

The autonomic nervous system has an efferent path from the central nervous system to the target/effector organ that is made up of a chain of two neurons with a ganglion in the middle. Recall that a **ganglion** is a collection of neuron cell bodies in the periphery.

The neuron that has its cell body in the central nervous system is called the **preganglionic neuron**. The preganglionic cell axon is lightly myelinated and extends to a ganglion in the periphery where it synapses on the second neuron in the chain called the **postganglionic neuron**. The postganglionic neuron has its cell body in the ganglion and its unmyelinated axon extends from the ganglion to the target/effector organ, which for the autonomic nervous system will be: smooth muscle, cardiac muscle, glands, or organs.

The first synapse happens at the site of the ganglion. All preganglionic cells release **acetylcholine** onto the postganglionic cells. The acetylcholine binds to nicotinic acetylcholine receptors, which results in the generation of an **excitatory postsynaptic potential** for the postganglionic cell body. This effectively passes the message between the preganglionic and postganglionic cells.

The second synapse occurs between the postganglionic cell and the target/effector organ. Postganglionic neurons in the autonomic nervous system release either norepinephrine or acetylcholine (more on this later). These neurotransmitters can have either stimulatory or inhibitory activity at the target organs, dependent on the properties of the postsynaptic receptor that they bind to.

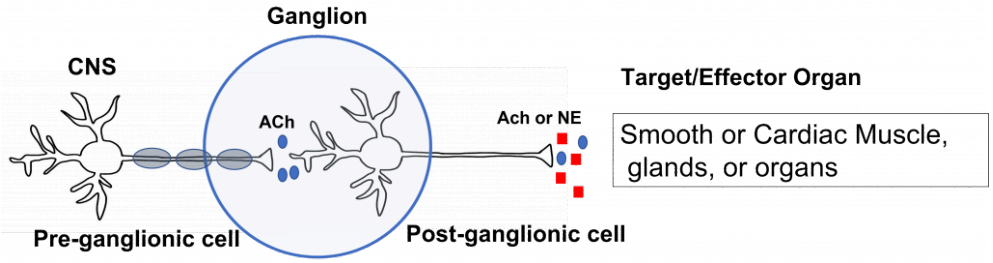

Fig 27.4. Autonomic nervous system efferent path. The efferent path for the autonomic nervous system consists of two neurons. The first neuron is called the preganglionic neuron and it starts in the central nervous system and extends to a ganglion in the periphery where it releases acetylcholine onto the postganglionic neuron. The postganglionic neuron extends to the target tissue where it releases either acetylcholine or norepinephrine. Target tissues include smooth muscle, cardiac muscle, glands, and organs. 'Autonomic two neuron chain' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike

Autonomic Effector Synapse

Within the autonomic nervous system, synapses have a different structure than what is observed at the **NMJ** of the somatic nervous system. Instead, autonomic axons are highly branched and have enlarged **varicosities** that are spread along the axon. These varicosities contain synaptic vesicles that are filled with neurotransmitters. The varicosities form synapses **'en passant'** (literally meaning 'in passage') with the target organ. These axon branches with varicosities drape over the cells of the target tissue, allowing a single axon branch to affect change over a greater area of the target tissue and better distribute autonomic activation at the target tissue.

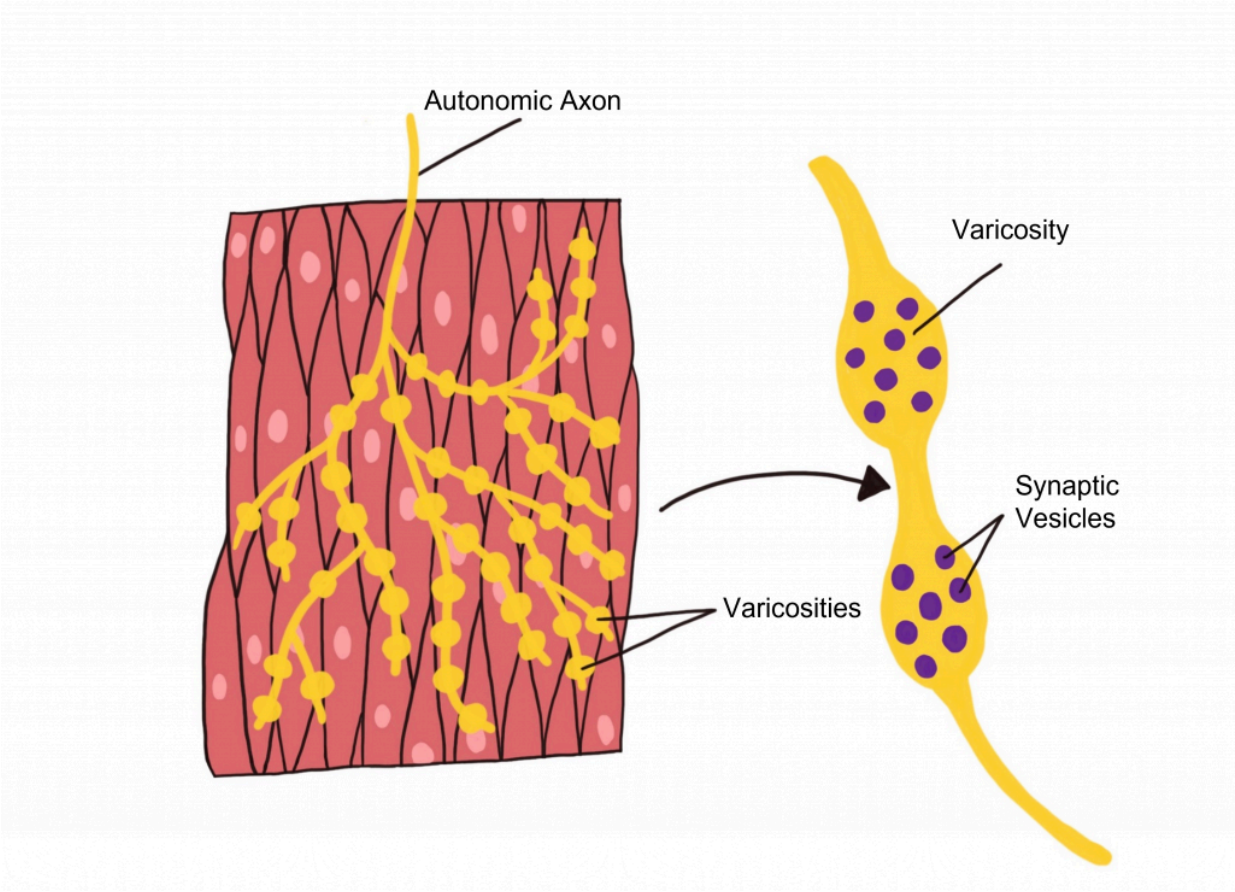

Figure 27.5. An autonomic axon branches extensively to cover effector tissues like a net. Multiple varicosities have synaptic vesicles that release neurotransmitters onto effector cells. 'Synapse en passant' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Comparing Somatic to Autonomic Nervous System

In summary, the somatic nervous system has a one neuron path that originates in the central nervous system. That neuron extends all the way to the skeletal muscle (target tissue) where it releases acetylcholine. The acetylcholine binds to nicotinic acetylcholine receptors that cause EPSPs in the muscle fibers and giving a stimulatory effect. The autonomic nervous system (both branches) use a two neuron pathway between the CNS and the target tissues that are smooth muscle, cardiac muscle, glands, and organs. The sympathetic division consists of short presynaptic neurons that synapse on

longer postsynaptic neurons in peripheral ganglia that are situated close to the spinal cord. The parasympathetic division consists of long presynaptic neurons that synapse on shorter postsynaptic neurons in peripheral ganglia that are situated close to the target organ. Like the somatic motor system, the primary neurotransmitter in the parasympathetic division is acetylcholine. In the sympathetic division, the preganglionic neuron releases acetylcholine, but the postganglionic neuron releases norepinephrine. The effects of these neurotransmitters at the target tissue can be either stimulatory or inhibitory depending on the properties of the postsynaptic receptor. This information is summarized in the figure and table below.

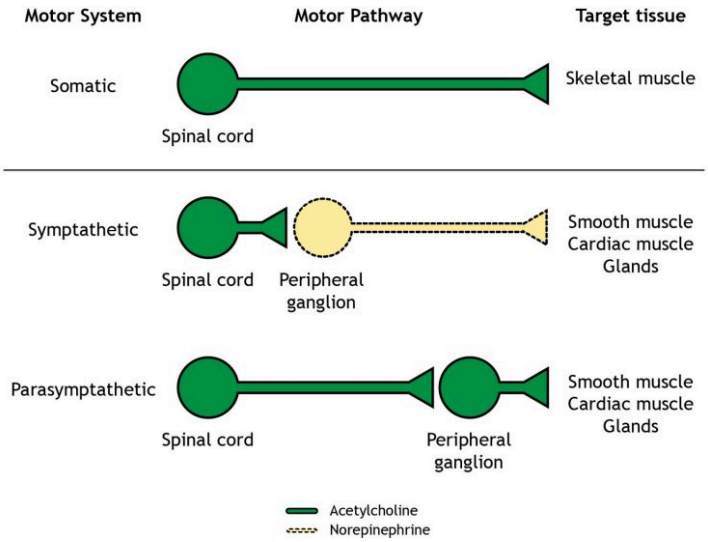

Figure 27.6. The somatic motor system consists of single neuron that extends from the central nervous system directly to skeletal muscle where it releases acetylcholine. The autonomic nervous system uses a two-neuron pathway. The preganglionic cell extends from the central nervous system to a peripheral ganglion where it synapses on the postganglionic cell body and releases acetylcholine. The postganglionic neuron then innervates the target tissue, which could be smooth muscle, cardiac muscle, or a gland. In the sympathetic division, the postganglionic neuron releases norepinephrine onto the target tissue, whereas in the parasympathetic

system, the postganglionic neuron releases acetylcholine onto the target tissue. 'Somatic vs SNS and PNS Motor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Table 27.1. Table comparing the somatic nervous system to the autonomic nervous system specifically identifying the efferent path, the target / effector organ, the neurotransmitter released at the ganglion and effect, the neurotransmitter released at the target organ, and the response of the target organ to the neurotransmitter.

Branch of PNS	Efferent Path	Target / Effector Organ	Neurotransmitter Released at Ganglion and Effect	Neurotransmitter Released at Target Organ	Target Organ Response to Neurotransmitter
Somatic	1 Neuron	Skeletal Muscle	None- No Ganglion	Acetylcholine	Stimulatory
Autonomic	2 Neuron Chain	Smooth / Cardiac Muscle, Glands, Organs	Acetylcholine, excitatory	Acetylcholine or Norepinephrine	Can be stimulatory or inhibitory

Two Branches of the Autonomic Nervous System

There are two branches of the autonomic nervous system, called the sympathetic nervous system and the parasympathetic nervous system, that typically have opposite effects at target tissues.

Consider a scenario in which you encounter a bear on hike through Yellowstone National Park.

Your heartrate would likely increase and your breathing rate would increase as you contemplate how to survive your encounter. This complex set of physiological reactions are due to activation of one of the branches of the autonomic nervous system: **the sympathetic nervous system**. The sympathetic nervous system mobilizes a set of physiological changes to a threat that is sometimes called the fight-or-flight response, which is activated when we are faced with a threat, either perceived or real. All of these rapid bodily responses result in the body preparing to attack or defend itself. Increased respiration allows the body to take in more oxygen, and dilation of blood vessels in the muscles allows that oxygen to get to the muscles, which is needed for muscle activation.

Now, consider a completely opposite scenario. You've just eaten a large meal and you are spending the evening watching television on your couch. You would probably feel relaxed, satisfied, and more than a little sluggish. A different physiological response is happening, a behavior called the rest-and-digest response. These physiological changes are driven by the other main branch of the autonomic nervous system, called the **parasympathetic nervous system**.

Targets and Effects of the 2 Branches of the Autonomic Nervous System

The sympathetic nervous system and the parasympathetic nervous system are referred to as antagonistic. These branches are called 'antagonistic' because they typically have opposite effects at target tissues.

There is dual innervation at many target organs of the autonomic nervous system. This means that target organs receive connections from both sympathetic and parasympathetic neurons. In a sense, this dual innervation provides both a 'break' and an 'accelerator' for changing the activity of our internal organs, offering a good amount of control.

Both the sympathetic nervous system and parasympathetic nervous systems influence the internal organs simultaneously. At all times, the heart is getting signals from the sympathetic nervous system which increase heart rate, and signals from the parasympathetic nervous system which decreases heart rate. However, this seesaw-like balance can shift quickly in either direction, such as inducing a sympathetic response if a fearful stimulus is encountered.

Table 27.2. Comparison between sympathetic and parasympathetic action at various target organs.

Target Organ	Sympathetic Action	Parasympathetic Action
Eye	Pupil dilation	Pupil constriction
Salivary glands	Prevents saliva secretion	Increases saliva secretion
Lungs	Airway dilation	Airway constriction
Heart	Increases heart rate	Decreases heart rate
Blood vessels	Constriction	No innervation
Stomach, liver, intestines, pancreas	Decreases digestion	Increases digestion
Kidneys	Sodium and water retention	No innervation
Adrenal gland	Increases epinephrine and norepinephrine secretion	No innervation
Reproductive organs	Orgasm and ejaculation	Blood vessel dilation leading to erection

Anatomical Differences between 2 Branches of Autonomic Nervous System

The sympathetic and parasympathetic nervous systems differ anatomically as well. The sympathetic preganglionic neurons are short and the sympathetic postganglionic neurons are long. The parasympathetic preganglionic neurons are long and the parasympathetic postganglionic neurons are short.

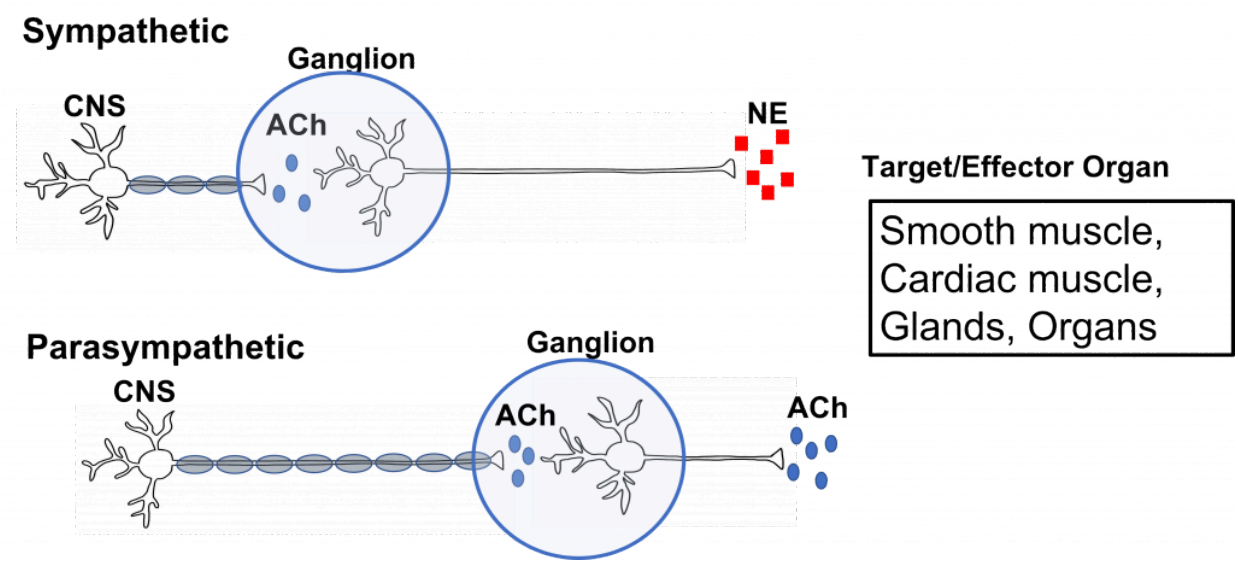

Figure 27.7. Anatomical differences between the sympathetic and parasympathetic nervous system. The sympathetic nervous system has short preganglionic neurons due to the proximity of the ganglion to the spinal cord (central nervous system). The sympathetic nervous system has long postganglionic neurons that release norepinephrine (red squares) onto target tissues. The parasympathetic nervous system has long preganglionic neurons due to the ganglions being close to target tissues. The postganglionic neurons of the parasympathetic nervous system are short and release acetylcholine (blue ovals) onto target tissues. 'Anatomical differences between sympathetic and parasympathetic nervous systems' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Sympathetic Anatomy

The cell bodies of the preganglionic neurons of the sympathetic nervous system are located in the thoracic and lumbar sections of the spinal cord, so we can use thoracolumbar to describe the site of origin. The axons leave the central nervous system and travel only a short distance to the peripheral ganglion. In the sympathetic system, most of the ganglia are located along the spinal cord in the sympathetic paravertebral chain. A few sympathetic ganglia, called prevertebral, are located slightly more laterally. The preganglionic neurons synapse on the postganglionic neurons in the sympathetic ganglia. The postganglionic neurons then travel the rest of the distance to synapse on the target organs.

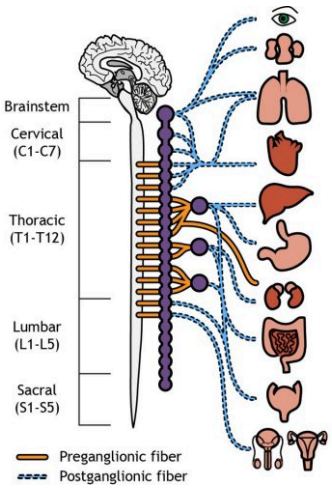

Figure 27.8. The preganglionic neurons of the sympathetic nervous system arise from the thoracic and lumbar sections of the spinal cord and terminate in paravertebral and prevertebral ganglia. The preganglionic neurons synapse on postganglionic neurons, which then extend to the target organ tissue and innervate the muscle and gland cells. 'Sympathetic nervous system' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

One exception to this structure is the innervation of the adrenal medulla. The adrenal gland is a structure located at the top of each kidney. The gland has an outer portion called the **cortex** and an inner portion called the **adrenal medulla**, which is made up of cells called **chromaffin cells**. The sympathetic preganglionic cell releases acetylcholine at the synapse with the chromaffin cells of the medulla and releases acetylcholine onto the chromaffin cell that is serving as a modified post-ganglionic

neuron. Then the chromaffin cells of the adrenal medulla release epinephrine and norepinephrine into the bloodstream. Within the bloodstream these neurotransmitters can act as hormones affecting change throughout the body leading to a rapid onset of sympathetic activity and sustained activation.

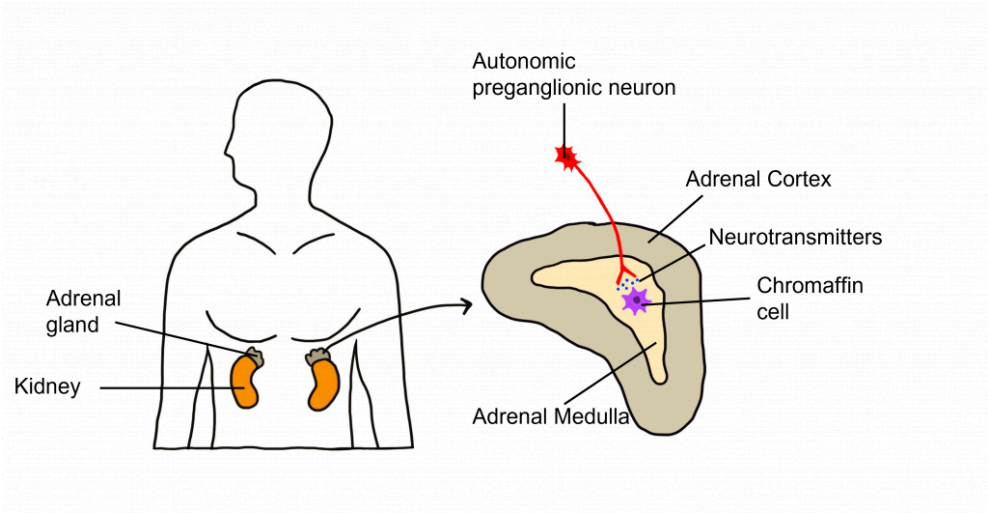

Figure 27.9. Autonomic control of the adrenal medulla. The adrenal glands are located on top of the kidneys and consist of outer cortex and an inner medulla. Sympathetic preganglionic neurons release acetylcholine onto chromaffin cells that serve as modified postganglionic neurons. The chromaffin cells of the adrenal medulla release epinephrine and norepinephrine into the blood stream. 'Sympathetic control of the adrenal medulla' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

The sympathetic preganglionic cell bodies are located in the intermediolateral cell columns in the lateral horn of the spinal cord, a gray matter region between the dorsal and ventral horns. The neurons send their axons out through the ventral root, and then can take one of multiple pathways. The axon can terminate in the paravertebral ganglion at the same spinal level as the cell body, or the axon can extend up or down the sympathetic chain to synapse on a postganglionic fiber at a different spinal level. Another possible pathway is to enter and exit the sympathetic chain without synapsing and continue on to terminate in a prevertebral ganglion located closer to the target organ.

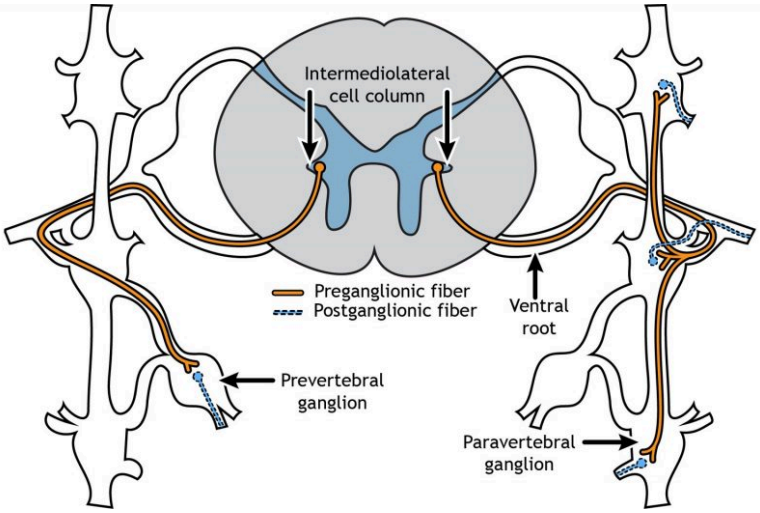

Figure 27.10. The cell bodies of the sympathetic preganglionic neurons are located in the intermediolateral cell column of the spinal cord. The preganglionic neurons leave the spinal cord via the ventral root and can synapse in paravertebral ganglion at the same spinal level as the cell body location or can travel rostrally or caudally along the sympathetic chain to a different spinal level (right side of image). Preganglionic neurons can also leave the spinal cord, pass through the paravertebral ganglia without synapsing and instead synapse on a postganglionic neuron in a prevertebral ganglion (left side of image). 'Sympathetic Preganglionic Fibers' by Casey

Parasympathetic Anatomy

On the other hand, parasympathetic neurons originates predominantly in the cervical spinal cord (near the neck), with some signals originating in the sacral areas (near the tail bone). The parasympathetic nervous system usually receives signals from several cranial nerves. Cranial nerve X, also called the vagus nerve innervates multiple bodily organs in the midsection of the body. For the parasympathetic nervous system, the ganglia are located very close to the target tissues. Therefore, the preganglionic neuron must be very long to reach all the way to the ganglion to makes its first synapse. But due to the proximity of the ganglion to the target tissue, the postganglionic neuron is very short.

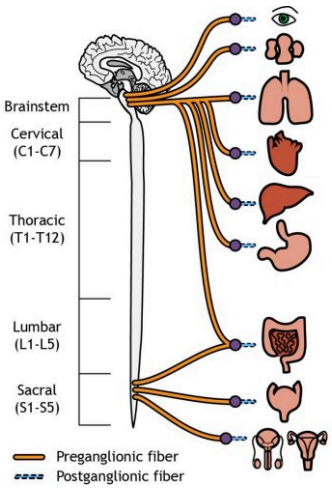

Figure 27.11. The preganglionic neurons of the parasympathetic nervous system arise from the brainstem and sacral sections of the spinal cord and terminate in ganglia located on or near the target organs. The preganglionic neurons synapse on postganglionic neurons, which then innervate the muscle and gland cells. 'Parasympathetic nervous system' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Neurotransmitters of the Autonomic Nervous System

We have already established that at the first synapse in the chain of autonomic neurons, all preganglionic neurons release acetylcholine, which binds to excitatory nicotinic receptors on the postganglionic neurons. This is true of both the sympathetic and parasympathetic nervous system. However, the two branches of the autonomic nervous system have different effects at target tissues

because they use different neurotransmitters that produce either stimulatory or inhibitory effects at target tissues.

The sympathetic postganglionic neurons release norepinephrine at target tissues. Norepinephrine (and epinephrine) binds two major classes of adrenergic receptors: alpha adrenergic receptors and beta adrenergic receptors. The effects of norepinephrine (and epinephrine) can be either excitatory or inhibitory depending on the properties of the postsynaptic receptor.

The parasympathetic postganglionic neurons release acetylcholine at target tissues. The target tissues express muscarinic acetylcholine receptors. The effect of the acetylcholine can be either excitatory or inhibitory depending on the subtype of muscarinic (metabotropic) receptors. The location of function of these transmitters and receptors are critical for clinical use, for example, when treating high blood pressure or sexual dysfunction.

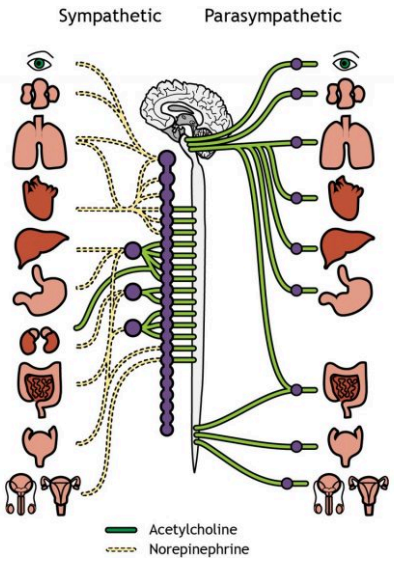

Figure 27.12. Acetylcholine is the primary neurotransmitter in both the pre- and postganglionic fibers of the parasympathetic nervous system and in the preganglionic neurons in sympathetic system. The sympathetic postganglionic fibers release norepinephrine onto their targets. 'Autonomic Neurotransmitters' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Autonomic Control Centers in the Brain

Visceral functions are regulated through a number of autonomic reflexes, but they can be directly controlled by higher brain areas. Within the brain stem, the medulla most directly controls autonomic activity. The medulla receives most of its information via the vagus nerve (a mixed nerve that contains both sensory and motor fibers). Within the medulla are a variety of control centers that regulate

functions such as cardiovascular activity, respiratory rate, vomiting, and swallowing. The pons, another brain stem structure also serves as an autonomic control center for respiration.

In addition to brain stem structures, there are also higher order brain areas that are important for autonomic control. The hypothalamus can directly regulate the medulla, and is also critical for the regulation of water balance, temperature control, and hunger. The Limbic System, made up of a number of structures including the the hippocampus and amygdala, functions in our expression of emotion. The limbic system structures are responsible for visceral responses associated with emotional states, including blushing, fainting, pallor, nervous cold sweats, racing heart rate, and uneasy feelings in the stomach.

Further, the cerebral cortex and cerebellum also function in autonomic control. The cerebral cortex has been shown to regulate lower brain structures especially in autonomic control associated with emotion and personality. The cerebellum has connections to the medulla that are critical for the control of autonomic functions such as sweating and nausea.

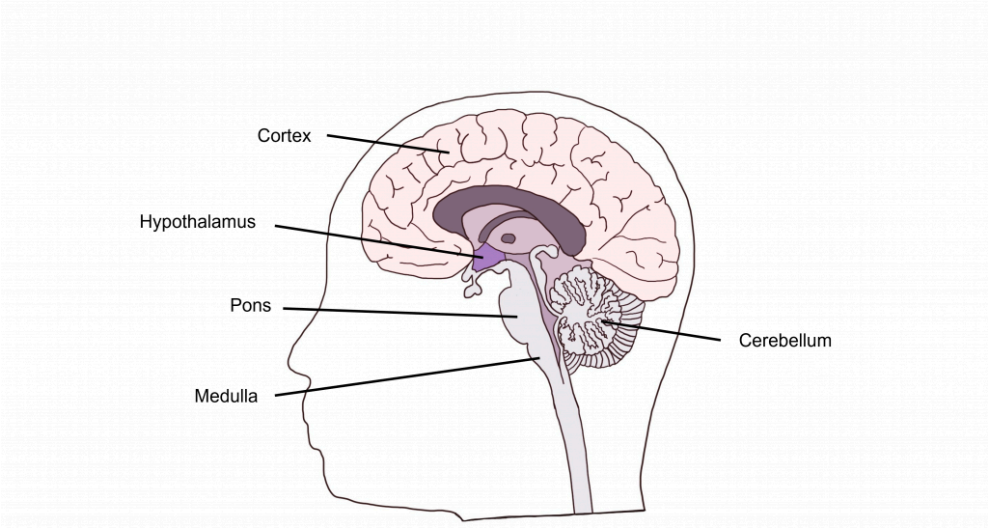

Figure 27.13. Autonomic control centers of the brain. Various higher order brain structures control autonomic nervous system function including the medulla and pons within the brain stem, the hypothalamus, the limbic system, cortex, and cerebellum. 'Autonomic control centers of the brain' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Enteric Nervous System

The internal organs that carry out digestive functions, such as the esophagus, stomach, and intestines, are surrounded by a dense mesh of neurons that regulate their activity. Consisting of half a billion nerve cells, this net of neurons cause the digestive tract to increase or decrease the rate of these processes depending on the body's demands The enteric nervous system receives signals from both the sympathetic and parasympathetic nervous systems, and functions without our conscious knowledge. Historically, these digestive functions have been classified as part of the autonomic nervous system,

but these responses do not share the same reflex pathway, and the enteric signals can work entirely independent of the vagus nerve, for example.

Key Takeaways

- There are 3 main divisions of the peripheral nervous system: the somatic nervous system, the autonomic nervous system and the enteric nervous system.
- The somatic and autonomic nervous systems different in their efferent path, how they synapse on target tissues, the neurotransmitters that are used, and the action of those neurotransmitters at target tissues.
- The autonomic nervous system can be subdivided into the sympathetic and parasympathetic nervous systems.
- The sympathetic nervous system is the "fight or flight" system and the parasympathetic nervous system is the "rest and digest" system.
- There are anatomical differences between the sympathetic and parasympathetic nervous system.
- Several brain areas serve as autonomic control centers.
- The enteric nervous system controls the gut and receives connections from both autonomic nervous system branches.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can

view it online here:
https://openbooks.lib.msu.edu/intronеuroscience1/?p=619#h5p-38

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PART V

SENSORY SYSTEMS

28.

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.

Sensory receptors

Sensory transduction begins at the sensory receptors. Each sensory system has specialized cells that are able to detect the environmental stimuli. Photoreceptors detect light, chemical receptors in the tongue and nose detect odors and taste, mechanoreceptors detect touch, and hair cells detect sound.

Receptor Potentials

We have learned about postsynaptic potentials in neurons, receptor potentials are similar membrane potential changes that happen in sensory receptors in response to a stimulus.

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.

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29.

VISUAL SYSTEM: THE EYE

Humans are remarkably dependent on the visual system to gain information about our surroundings. Consider how tentatively you walk from the light switch to your bed right after turning off the lights!

The visual system is complex and consists of several interacting anatomical structures. Here, we will describe the process of how photons of light from our surroundings become signals that the brain turns into representations of our surroundings.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself
- Additional Review

Properties of Light

Visual sensation starts at the level of the eye. The eye is an organ that has evolved to capture photons, the elementary particle of light. Photons are unusual because they behave as both particles and as waves, but neuroscientists mostly focus on the wave-like properties. Because photons travel as waves, they oscillate at different frequencies. The frequency at which a photon oscillates is directly related to the color that we perceive.

The human visual system is capable of seeing light in a very narrow range of frequencies on the **electromagnetic spectrum**. On the short end, 400 nm wavelengths are observed as violet, while on the long end, 700 nm wavelengths are red. Ultraviolet light oscillates at a wavelength shorter than 400 nm, while infrared light oscillates at a wavelength longer than 700 nm. Neither ultraviolet nor infrared light can be detected with our eyes.

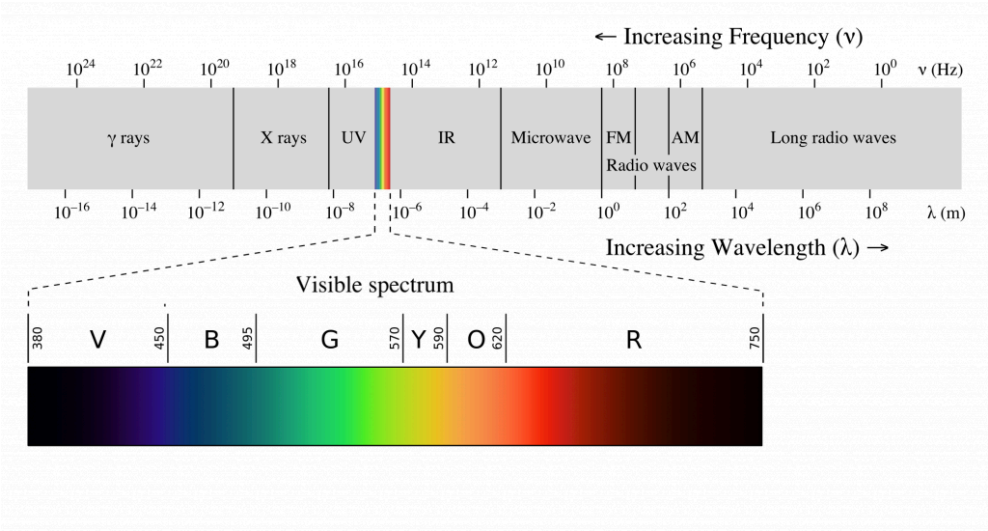

Figure 29.1. Electromagnetic spectrum. Humans are only able to perceive wavelengths of light between 400nm and 700nm. The wavelength is directly related to the perceived color that is seen. Shorter wavelengths are perceived as violet, where are longer wavelengths are perceived as red.

Anatomy of the Eye

Photons pass through several anatomical structures before the nervous system processes and interprets them. The front of the eye consists of the cornea, pupil, iris, and lens. The **cornea** is the transparent, external part of the eye. The cornea refracts, or bends, the incoming rays of light so that they converge precisely at the **retina**, the posterior most part of the eye. If the light rays fail to properly converge, a person would be near-sighted or far-sighted, and this would result in blurry vision. Glasses or contact lenses bend light before it reaches the cornea to compensate the cornea's shape.

After passing through the cornea, light enters through a hole in the opening in the **iris** at the center of the eye called the **pupil**. The iris is the colored portion of the eye that surrounds the pupil and along with local muscles that can control the size of the pupil to allow for an appropriate amount of light to enter the eye. The diameter of the pupil can change depending on ambient light conditions. In the dark, the pupil dilates, or gets bigger, which allows the eye to capture more light. In bright conditions, the pupils constricts, or gets smaller, which decreases the amount of light that enters the eye.

The next structure that light passes through is the lens. The **lens** is located behind the pupil and iris. Like the cornea, the lens refracts light so that the rays converge on the retina. Proper focusing requires

the lens to stretch or relax, a process called **accommodation**. A circular muscle that surrounds the lens, called the **ciliary muscle**, changes the shape of the lens depending on the distance of the object of focus.

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 bowl. In the middle of the bowl is the **fovea**, the region of highest visual acuity, meaning the area that can form the sharpest images. The **optic nerve** projects to the brain from the back of the eye, carrying information from the retinal cells. Where the optic nerve leaves, there are no photoreceptors since the axons from the neurons are coming together. This region is called the **optic disc** and is the location of the blind spot in our visual field.

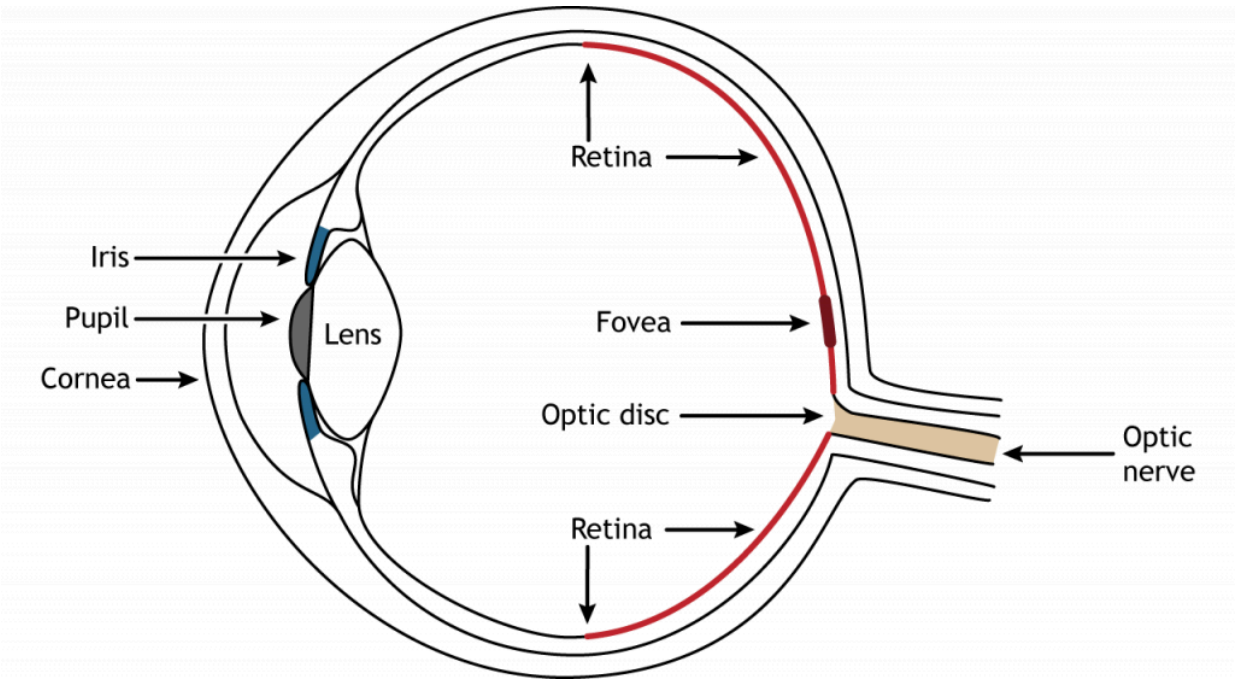

Figure 29.2. Cross section of the eye. The visible regions of the eye include the cornea, pupil (gray region), and iris (blue region). The lens sits behind the pupil and iris. The retina (red line) is located along the back of the eye. The fovea (dark red section) is a small portion of the retina where visual acuity is highest, and the optic disc is located where the optic nerve (tan region) leaves the eye. Details about the functions of each region are in the text. 'Eye Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Retinal Cells

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 neuron layers.

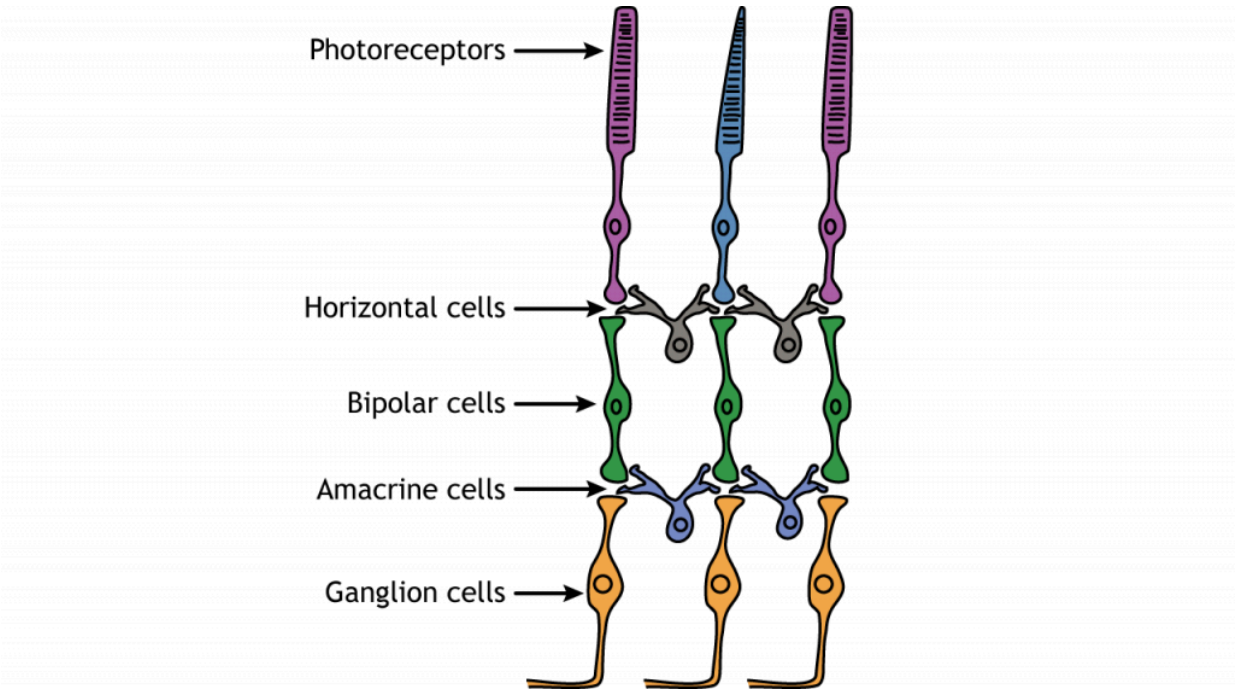

Figure 29.3. There are five cell types in the retina. The photoreceptors synapse on bipolar cells, and the bipolar cells synapse on ganglion cells. The horizonal cells allow for communication between photoreceptors by interacting with the photoreceptor-bipolar cell synapse, and the amacrine cells allow for communication between bipolar cells by interacting at the bipolar cell-ganglion cell synapse. '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 enters the eye and strikes the retina, it must pass through all the neuronal cell layers before reaching and activating the photoreceptors. The photoreceptors then initiate the synaptic communication back toward the ganglion cells.

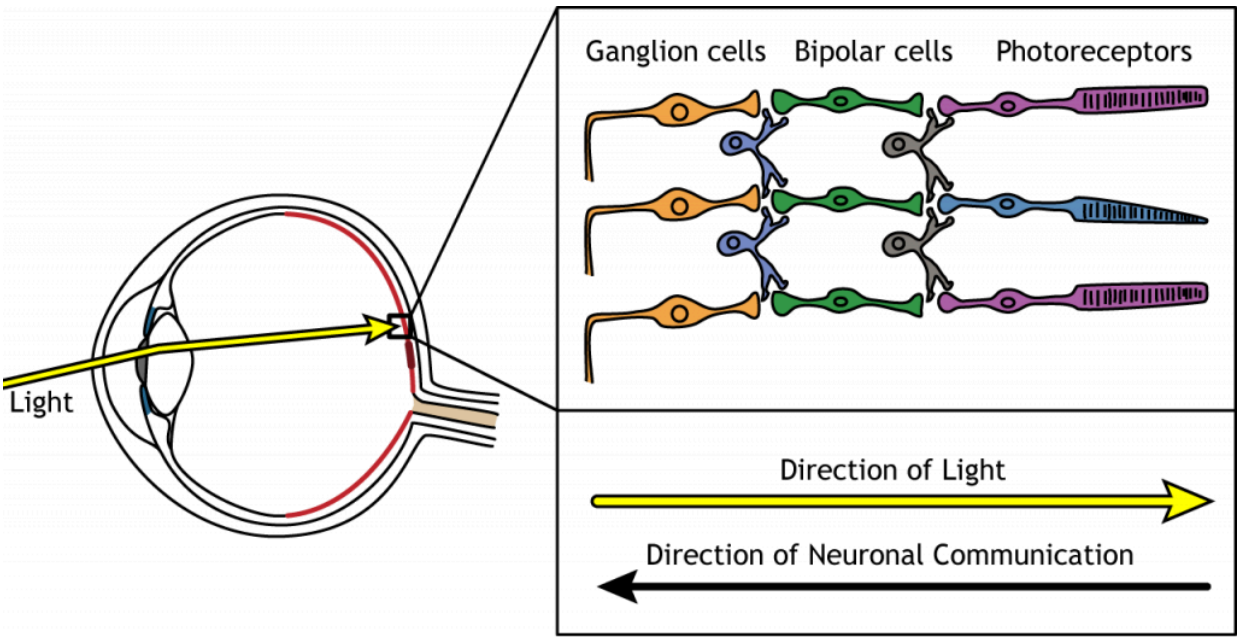

Figure 29.4. When light enters the eye, it must pass through the ganglion and bipolar cell layers before reaching the photoreceptors. The neuronal communication travels in the opposite direction from the photoreceptors toward the ganglion cells. 'Light in the Retina' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Photoreceptors

Photoreceptors are the first cells in the neuronal visual perception pathway. The photoreceptors are the specialized receptors that respond to light. They are the cells that detect photons of light and convert them into neurotransmitter release, a process called **phototransduction**.

Morphologically, photoreceptor cells have two parts, an outer segment and inner segment. The outer segment contains stacks of **membranous disks** bounded within the neuronal membrane. These membranous disks contain molecules called **photopigments**, which are the light-sensing components of the photoreceptors. Hundreds of billions of these photopigments can be found in a single photoreceptor cell. The inner segment contains the nucleus and other organelles. Extending from the inner segment is the axon terminal.

Photoreceptors are classified into two categories, named because of their appearance and shape: **rods and cones**. Rod photoreceptors have a long cylindrical outer segment that holds many membranous

disks. The presence of more membranous disks means that rod photoreceptors contain more photopigments and thus are capable of greater light sensitivity.

Cone photoreceptors have a short, tapered c, and cylindrical outer segment that holds fewer membranous disks than rod photoreceptors. The presence of less membranous disks means that cone photoreceptors contain less photopigments and thus are not as sensitive to light as rod photoreceptors. Cone photoreceptors are responsible for processing our sensation of color (the easiest way to remember this is cones = color). The typical human has three different types of cone photoreceptors cells, with each of these three types tuned to specific wavelengths of light. The short wavelength cones (S-cones) respond most robustly to 420 nm violet light. The middle wavelength cones (M-cones) exhibit peak responding at 530 nm green light, and the long wavelength cones (L-cones) are most responsive in 560 nm red light. Each of these cones is activated by other wavelengths of light too, but to a lesser degree. Every color on the visible spectrum is represented by some combination of activity of these three cone photoreceptors.

The idea that we have two different cellular populations and circuits that are used in visual perception is called the **duplicity theory of vision** and is our current understanding of how the visual system perceives light. It suggests that both the rods and cones are used simultaneously and complement each other. The **photopic vision**, uses cone photoreceptors of the retina, and is responsible for high-acuity sight and color vision in daytime. Its counterpart, called **scotopic vision**, uses rod photoreceptors and is best for seeing in low-light conditions, such as at night. Both rods and cones are used for **mesopic vision**, when there are intermediate lighting conditions, such as indoor lighting or outdoor traffic lighting at night.

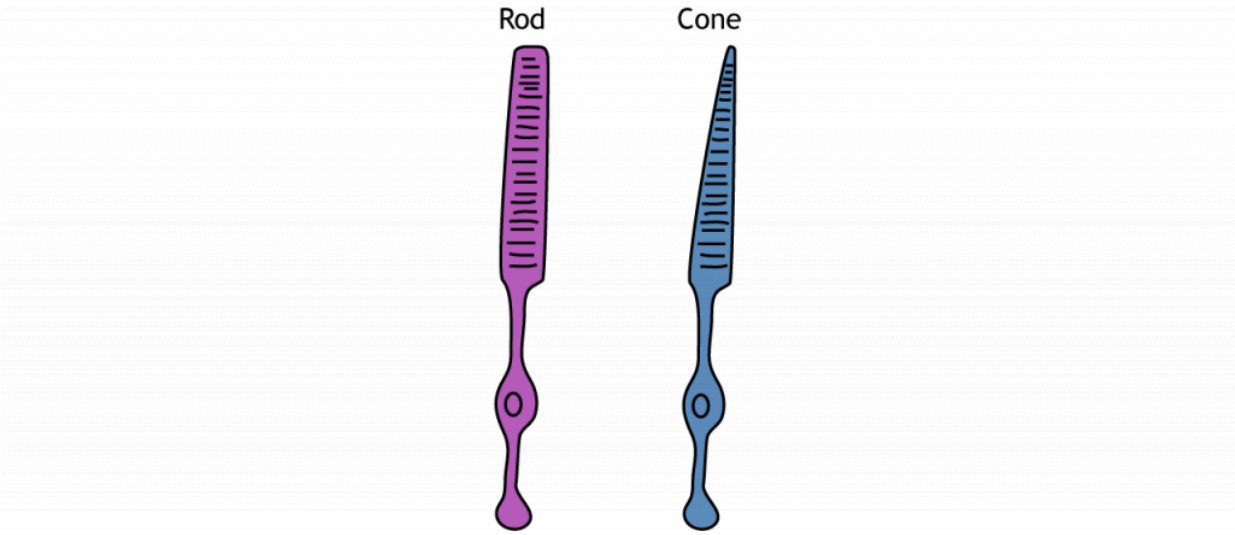

Figure 29.5. The rods and cones have different physical appearances and play separate roles in visual processing. 'Rod and Cone' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Photoreceptor Density

In addition to having different visual functions, the rods and cones are also distributed across the retina in different densities. Visual information from our peripheral vision is generally detected by our rod cells, which are most densely concentrated outside the fovea. Cone photoreceptor cells allow for high-acuity vision. They are most densely packed at the fovea, corresponding to the very center of your visual field. Despite being the cell population that we use for our best vision, cone cells make up the minority of photoreceptors in the human retina, outnumbered by about 20-times more rod cells.

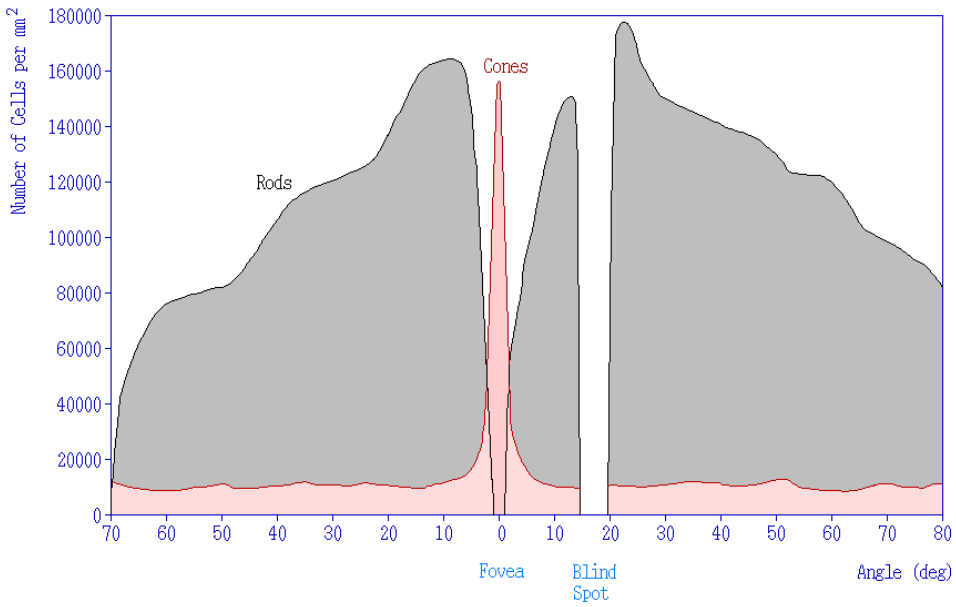

Figure 29.6. Graph depicting the number of cells in (mm2) across the retina. Cones are concentrated at the center of the retina (0 degrees) in the fovea. There are many more rods than there are cones. The rods are located in the periphery, but not at the center of the retina. There are neither cones nor rods at the blind spot, which is where the retinal ganglion cells exit the retina.

Synaptic Convergence of Photoreceptors

Rod cells are organized to have high **synaptic convergence**, where several rod cells (up to 30) feed into a single downstream route of communication (the bipolar cells, to be specific). An advantage of a high-convergence network is the ability to add many small signals together to create a seemingly larger signal. Consider stargazing at night, for example. Each rod is able to detect low levels of light, but signals from multiple rod cells, when summed together, allows you to recognize faint light sources such as a star. A disadvantage of this type of organization is that it is difficult to identify exactly which photoreceptor is activated by the incoming light, which is why accuracy is poor when seeing stimuli in our peripheral vision. This is one of the reasons that we cannot actually read text in our peripheral vision or see the distinct edges of a star. Rod photoreceptors are maximally active in low-light conditions.

Unlike rod cells, cone cells have very low synaptic convergence. In fact, at the point of highest visual acuity, a single cone photoreceptor communicates with a single pathway to the brain. The signaling

from low-convergence networks is not additive, so they are less effective at low light conditions. However, because of this low-convergence organization, cone cells are highly effective at precisely identifying the location of incoming light.

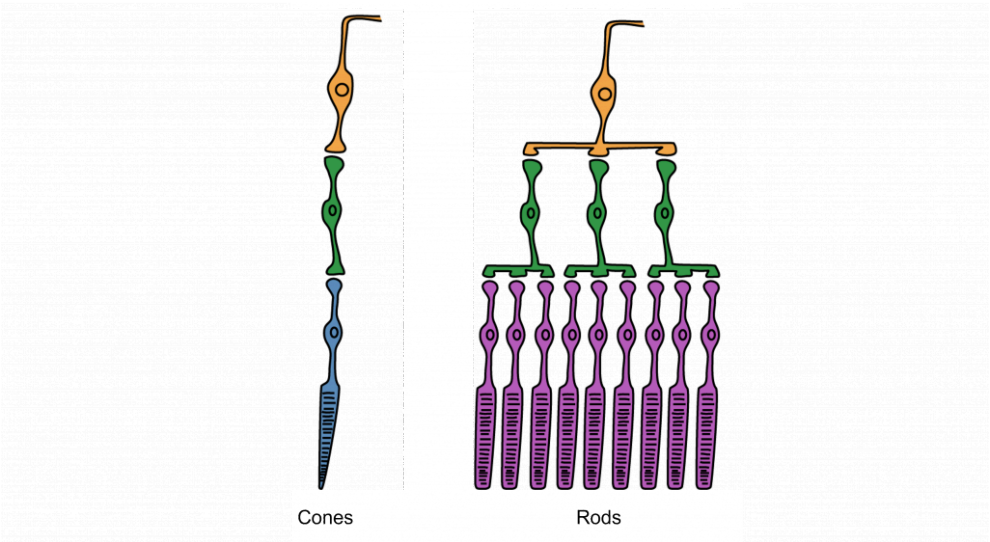

Figure 29.7. Photoreceptor Convergence. Cones have very low synaptic convergence, meaning that single cone photoreceptors ultimately signal to a single retinal ganglion cell, providing high visual acuity in cones. Rods, however, have high synaptic convergence, meaning many rod photoreceptors ultimately signal to a single retinal ganglion cell. This gives rods the ability to better see objects in low light.

Retina: Fovea and Optic Disk

The retina is not completely uniform across the entire back of the eye. There are a few spots of particular interest along the retina where the cellular morphology is different: the **fovea** and the **optic disk**.

There are two cellular differences that explain why the fovea is the site of our best visual acuity. For one, the neurons found at the fovea are "swept" away from the center, which explains why the fovea looks like a pit. Cell membranes are made up mostly of lipids, which distort the passage of

light. Because there are fewer cell bodies present here, the photons of light that reach the fovea are not refracted by the presence of other neurons. Secondly, the distribution of photoreceptors at the fovea heavily leans toward cone type photoreceptors. Because the cone cells at the fovea exhibit low convergence, they are most accurately able to pinpoint the exact location of incoming light. On the other hand, most of the photoreceptors in the periphery are rod cells. With their high-convergence circuitry, the periphery of the retina is suited for detecting small amounts of light, though location and detail information is reduced.

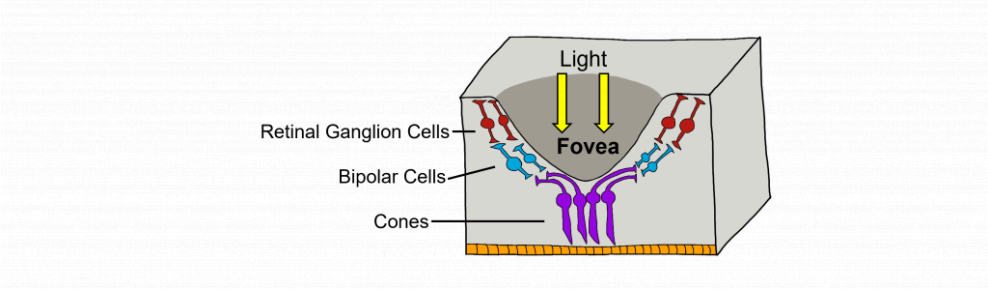

Figure 29.8. Fovea. The fovea is a pit at the center of the retina and provides the most visual acuity. This is due to the cells of the retina (photoreceptors, bipolar cells, retinal ganglion cells) being pushed to the side of the fovea, leaving no cells to distort the light as it reaches the photoreceptors. 'Fovea' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Another anatomically interesting area of the retina is an elliptical spot called the **optic disk**. This is

where the optic nerve exits the eye. At this part of the retina, there is an absence of photoreceptor cells. Because of this, we are unable to perceive light that falls onto the optic disk. This spot in our vision is called the **blind spot**.

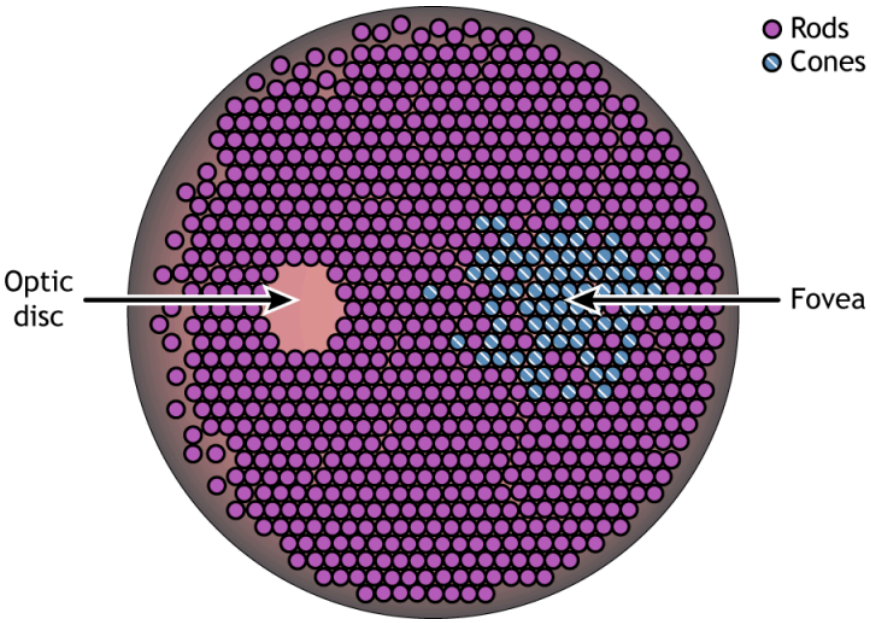

Figure 29.9. Rods and cones are distributed across the retina in different densities. Cones are located at the fovea. Rods are located everywhere else. The optic disc lacks all photoreceptors since the optic nerve fibers are exiting the eye at this location. 'Retinal Receptor Density' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Phototransduction

The photoreceptors are responsible for sensory transduction in the visual system, converting light into electrical signals in the neurons. For our purposes, to examine the function of the photoreceptors, we will A) focus on black and white light (not color vision) and B) assume the cells are moving from either an area of dark to an area of light or vice versa.

Photoreceptors do not fire action potentials; they respond to light changes with graded receptor 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. Photoreceptors hyperpolarize in light and depolarize in dark. In the graphs used in this lesson, the starting membrane potential will depend on the initial lighting condition.

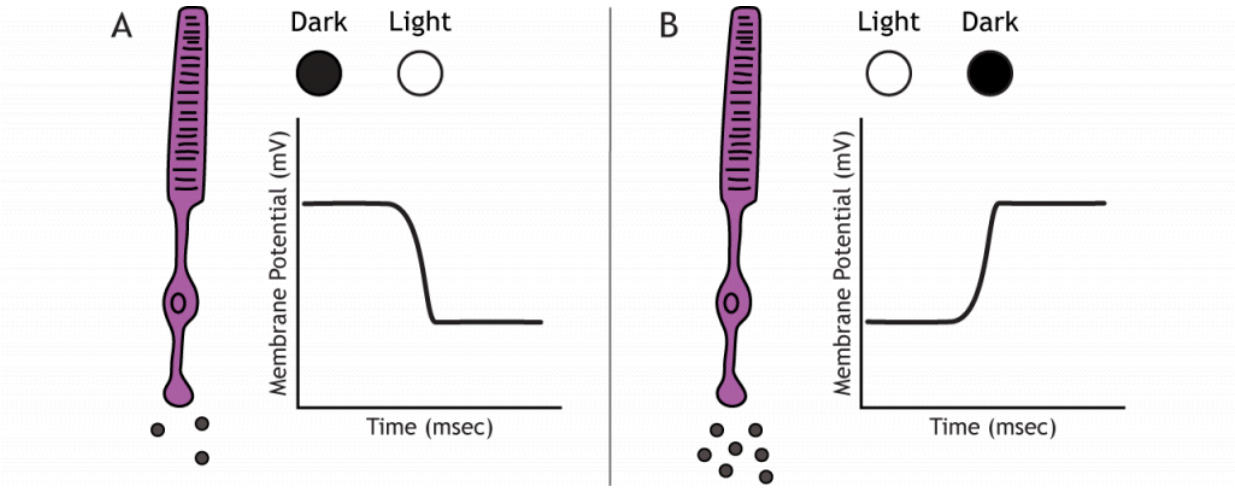

Figure 29.10. Photoreceptors respond with graded potentials when moving from light to dark or vice versa. A) When moving from dark to light, the photoreceptor will hyperpolarize, and glutamate release will decrease. B) When moving from light to dark, the photoreceptor will depolarize, and glutamate release will increase. 'Photoreceptor Receptor Potentials' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

When the photoreceptor moves into the light, the cell hyperpolarizes. Light enters the eye, reaches the photoreceptors, and causes a conformational change in a special receptor protein called an **opsin**. The opsin receptor has a pre-bound chemical agonist called **retinal**. Together, the opsin + retinal makes up the photopigment **rhodopsin**.

When rhodopsin absorbs light, it causes a conformational change in the pre-bound retinal, in a process called "bleaching". The bleaching of rhodopsin activates an associated G-protein called **transducin**, which then activates an effector enzyme called **phosphodiesterase (PDE)**. PDE breaks down **cGMP** in the cell to GMP. As a result, the cGMP-gated ion channels close. The decrease in cation flow into the cell causes the photoreceptor to hyperpolarize.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://openbooks.lib.msu.edu/introneuroscience1/?p=159#video-159-1

Animation 29.1. Light reaching the photoreceptor causes a conformational change in the opsin protein, which activates the G-protein transducing. Transducin activates phosphodiesterase (PDE), which converts cGMP to GMP. Without cGMP, the cation channels close, stopping the influx of positive ions. This results in a hyperpolarization of 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. View static image of animation.

In the dark, the photoreceptor has a membrane potential that is more depolarized than the "typical" neuron we examined in previous chapters; the photoreceptor membrane potential is approximately -40 mV.

Rhodopsin is not bleached, thus the associated G-protein, transducin, remains inactive. As a result, there is no activation of the PDE enzyme, and levels of cGMP within the cell remain high. cGMP binds to cGMP-gated sodium ion channels, causing them to open. The open cation channels allow the influx of sodium and calcium, which depolarize the cell in the dark.

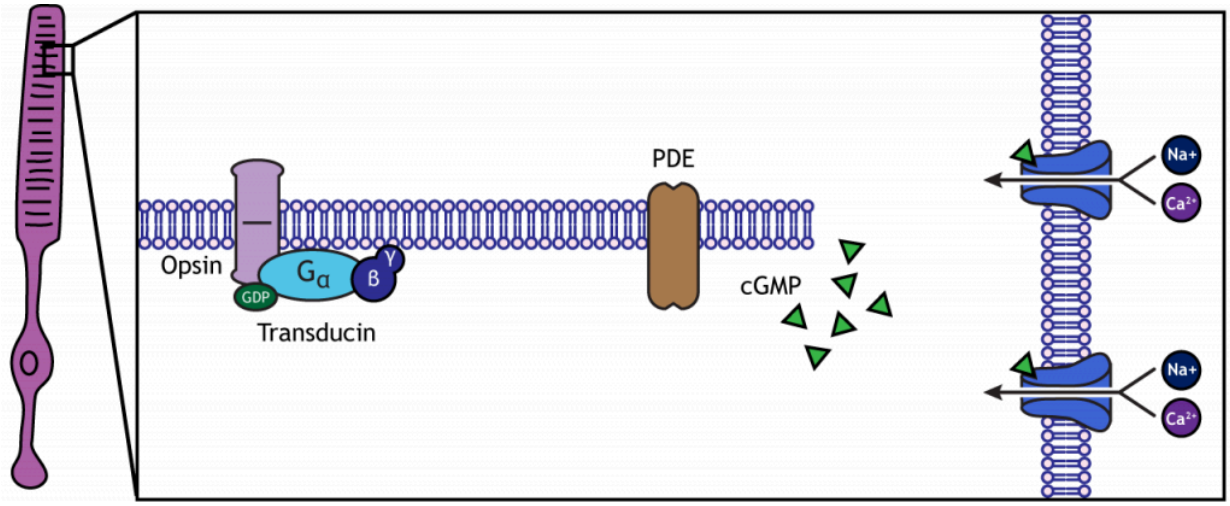

Figure 29.11. In the dark, the photoreceptor is depolarized due to an influx of sodium and calcium through open ion channels that are gated by cGMP. The photoreceptor has high levels of cGMP when it is in the dark. Additionally, the opsin proteins, the G-protein transducin, and phosphodiesterase (PDE) are all inactivated. 'Retinal Dark Current' 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

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

OFF-center Bipolar Cells

In OFF-center bipolar cells, the glutamate released by the photoreceptor is *excitatory*. OFF-center bipolar cells express **ionotropic** glutamate receptors. In the dark, the photoreceptor is depolarized, and thus releases more glutamate. The glutamate released by the photoreceptor activates the ionotropic receptors, and sodium can flow into the cell, depolarizing the membrane potential. In the light, the photoreceptor is hyperpolarized, and thus does not release glutamate. This lack of glutamate causes the

ionotropic receptors to close, preventing sodium influx, hyperpolarizing the membrane potential of the OFF-center bipolar cell. One way to remember this is that OFF-center bipolar cells are excited by the dark (when the lights are OFF).

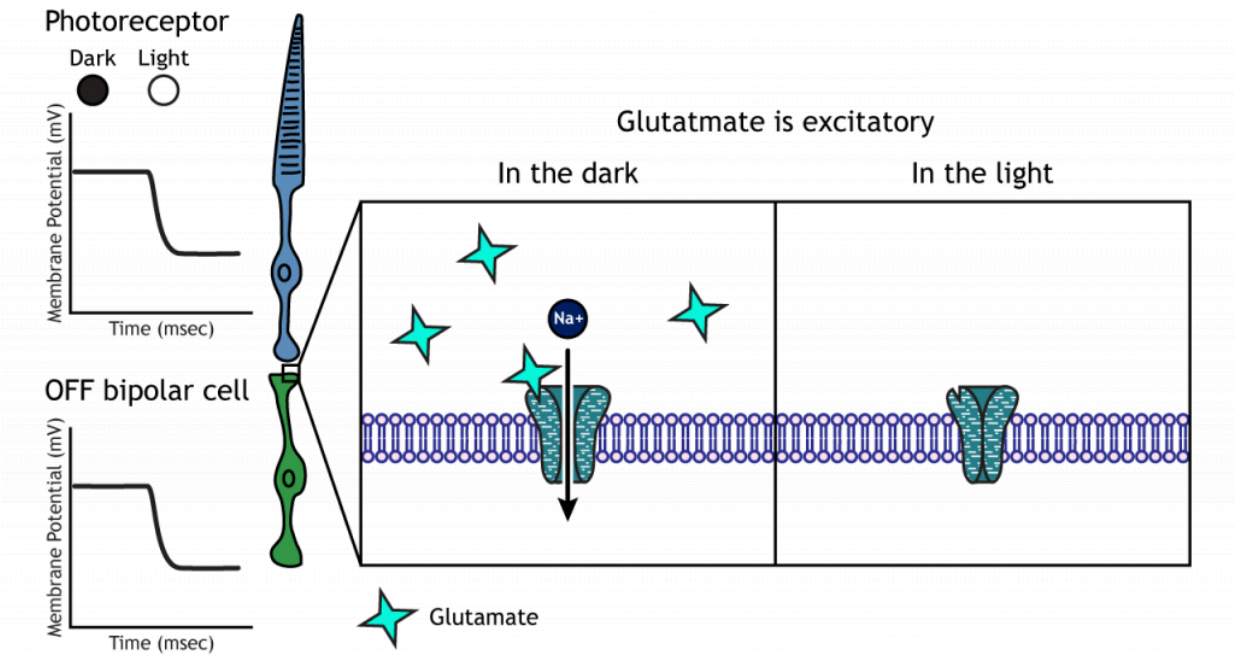

Figure 29.12. Photoreceptors hyperpolarize in light and decrease the amount of released glutamate. Glutamate is excitatory in OFF bipolar cells, opening ionotropic receptors and allowing sodium influx. In the dark, the OFF bipolar cells are depolarized, and in the light the OFF bipolar cells are hyperpolarized. 'Off Bipolar Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

ON-center Bipolar Cells

In ON-center bipolar cells, the glutamate released by the photoreceptor is *inhibitory*. ON-center bipolar cells express **metabotropic** glutamate receptors. In the dark, the photoreceptor is depolarized, and thus releases more glutamate. The glutamate released by the photoreceptor binds to the metabotropic receptors on ON-center bipolar cells, and the G-proteins close cation channels in the membrane, stopping the influx of sodium and calcium, hyperpolarizing the membrane potential. In the light, the photoreceptor is hyperpolarized, and thus does not release glutamate. The absence of glutamate results in the ion channels being open and allowing cation influx, depolarizing the

membrane potential. You can remember that ON-center bipolar cells are excited by the light (when the lights are ON).

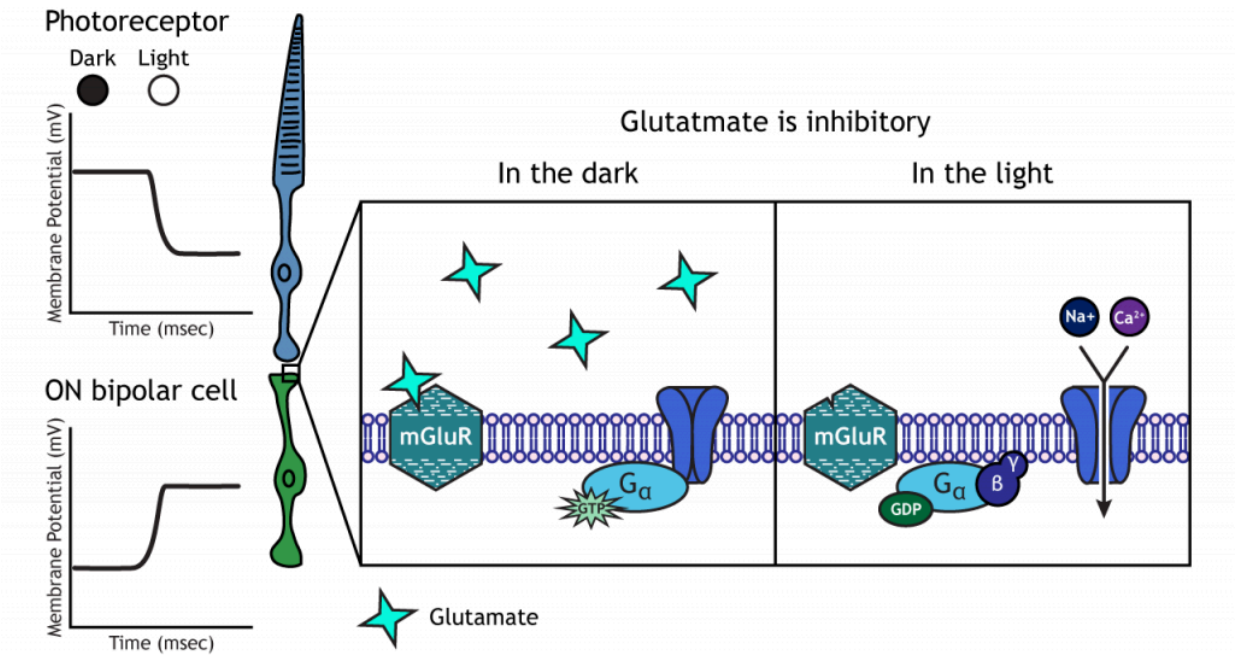

Figure 29.13. Photoreceptors hyperpolarize in light and decrease the amount of released glutamate. Glutamate is inhibitory in ON bipolar cells, activating metabotropic receptors, which closes cation channels. In the dark, the ON bipolar cells are hyperpolarized, and in the light the ON bipolar cells are depolarized. 'ON Bipolar Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Retinal Ganglion Cells

Retinal ganglion cells are the third and last cell type that directly conveys visual sensory information, receiving inputs from the bipolar cells. OFF-center and ON-center bipolar cells synapse on OFF-center and ON-center ganglion cells, respectively. The axons of the retinal ganglion cells bundle together and form the optic nerve, which then exits the eye through the optic disk. Retinal 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. A move from dark to light will cause OFF-center ganglion cells to decrease their firing rate and ON-center ganglion cells to increase their firing rate.

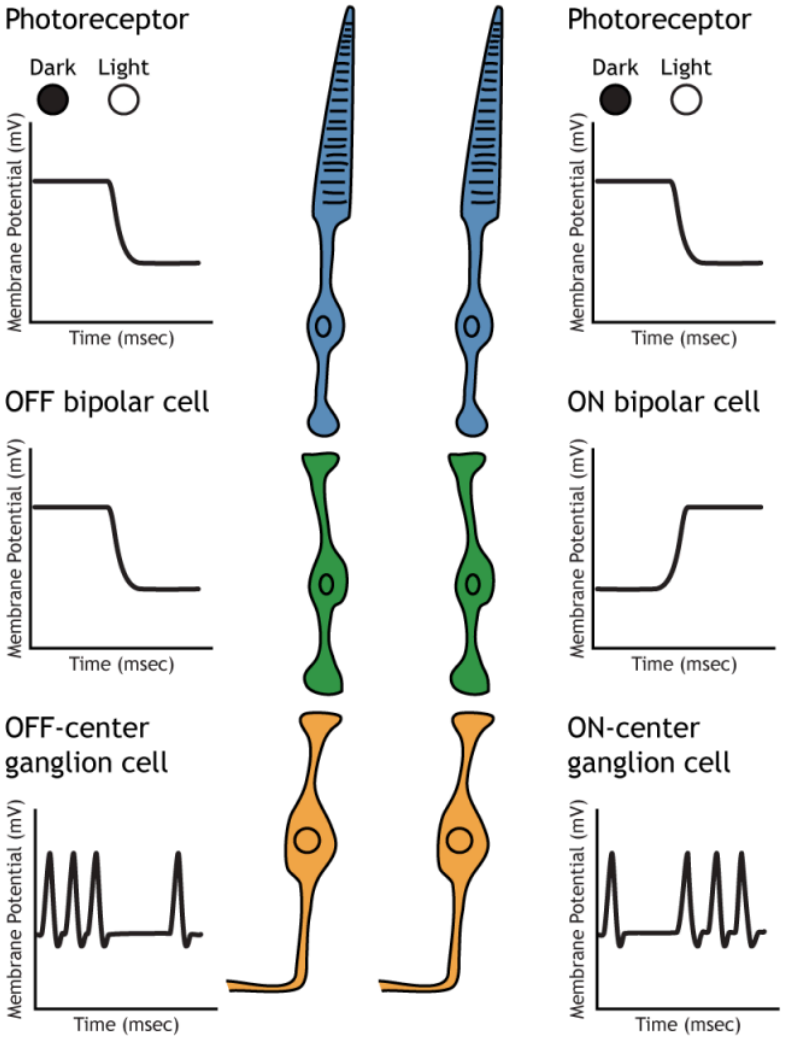

Figure 29.14. A move from dark to light will hyperpolarize all photoreceptors. OFF bipolar cells will also hyperpolarize in light, which will lead to a decreased firing rate in OFF-center ganglion cells. ON bipolar cells will depolarize in light, which will lead to an increased firing rate in ON-center ganglion cells. 'Retinal 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 stimulus 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. The fovea has smaller receptive fields than the peripheral retina. 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, also called the amount of convergence.

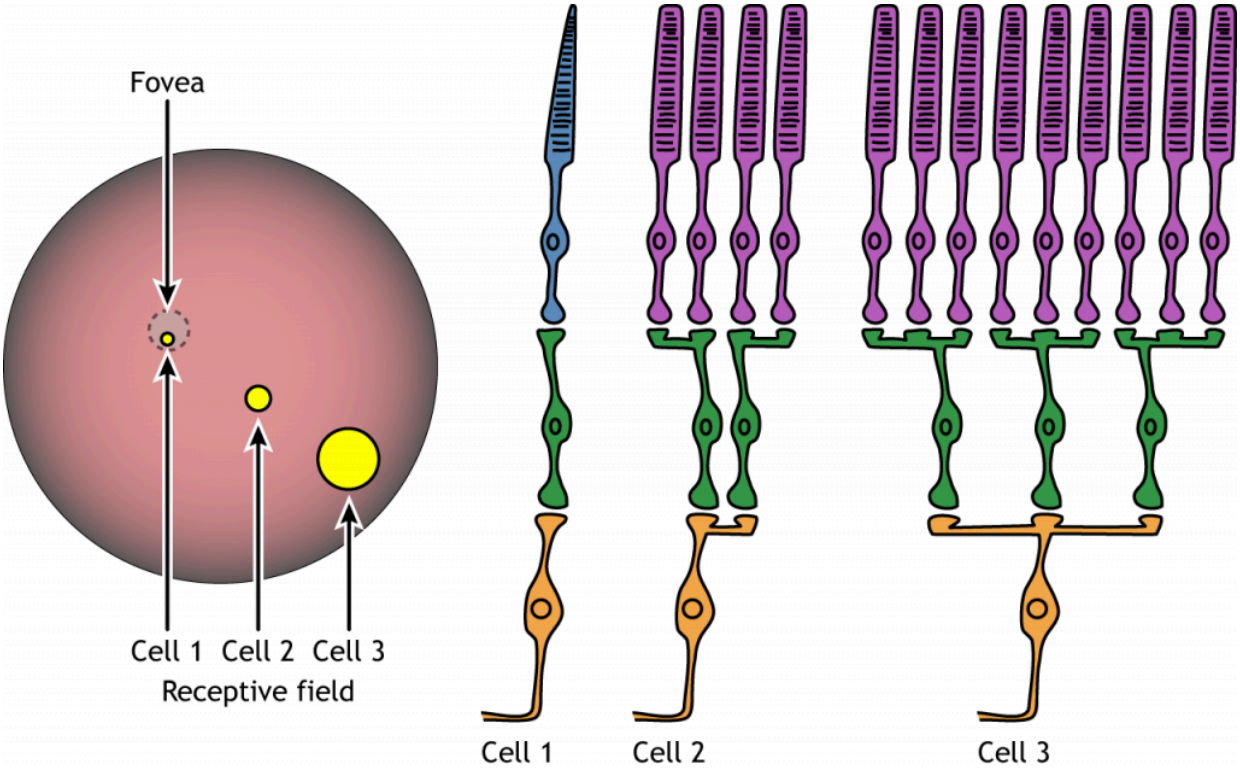

Figure 29.15. Ganglion receptive field sizes can vary depending on location of the bipolar and ganglion cells and the amount of convergence onto those cells. When the photoreceptors are in or near the fovea (Cell 1), the receptive fields are small. In the fovea, each bipolar cell receives input from only one photoreceptor and then synapses on only one ganglion cell. Toward the periphery (Cells 2 and 3), more photoreceptors synapse on each bipolar cell, and more bipolar cells synapse on each ganglion cell, making the surface area of the receptive field larger. 'Retinal Receptive Field' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive Field Example

Let's use an example of an ON-center bipolar cell to look at the structure of receptive fields in the retina. The bipolar and retinal ganglion cell receptive fields are divided into two regions: the center and the surround. The center of the receptive field is a result of direct innervation between the photoreceptors, bipolar cells, and ganglion cells. If a light spot covers the center of the receptive field, the ON-center bipolar cell would depolarize, as discussed above; the light hits the photoreceptor, it hyperpolarizes, decreasing glutamate release. Less glutamate leads to less inhibition of the ON bipolar cell, and it depolarizes.

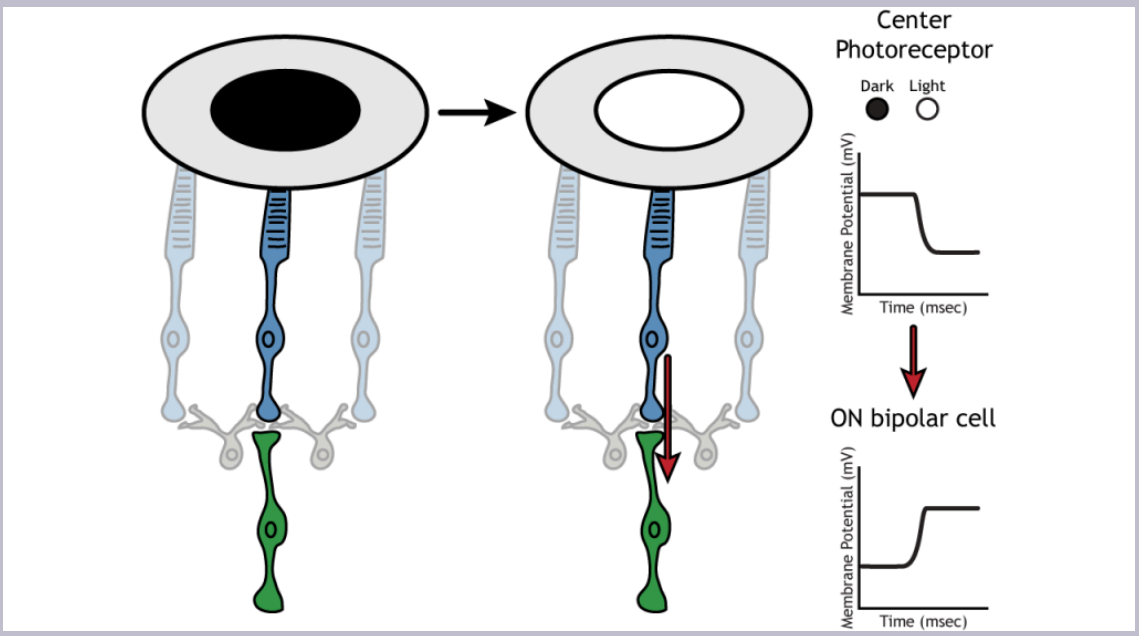

Figure 29.16. A photoreceptor in the center of an ON bipolar cell's receptive field moves from dark to light. The photoreceptor will hyperpolarize, and the ON bipolar cell will depolarize. The red arrows show the direct synaptic communication from photoreceptor to ON bipolar cell. 'Light in Center' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The surround portion of the receptive field is a result of indirect communication among the retinal neurons via horizontal and amacrine cells. The surround has an opposing effect on the bipolar or ganglion cell compared to the effect of the center region. That is to say, that the center and surround of the receptive field are opposite to each other. So, an ON-center

bipolar or ganglion cell, can also be referred to as an “ON-center OFF-surround cell”, and an OFF-center bipolar or ganglion cell can also be referred to as an “OFF-center ON-surround cell”.

Therefore, if light covers the surround portion, the ON-center bipolar cell would respond by hyperpolarizing. The light would cause the photoreceptor in the surround to hyperpolarize. This would cause the horizontal cell to also hyperpolarize. Horizontal cells have inhibitory synaptic effects, so a hyperpolarization in the horizontal cell would lead to a depolarization in the center photoreceptor. The center photoreceptor would then cause a hyperpolarization in the ON-center bipolar cell. These effects mimic those seen when the center is in dark. So, even though the center photoreceptor is not directly experiencing a change in lighting conditions, the neurons respond as if they were moving toward dark.

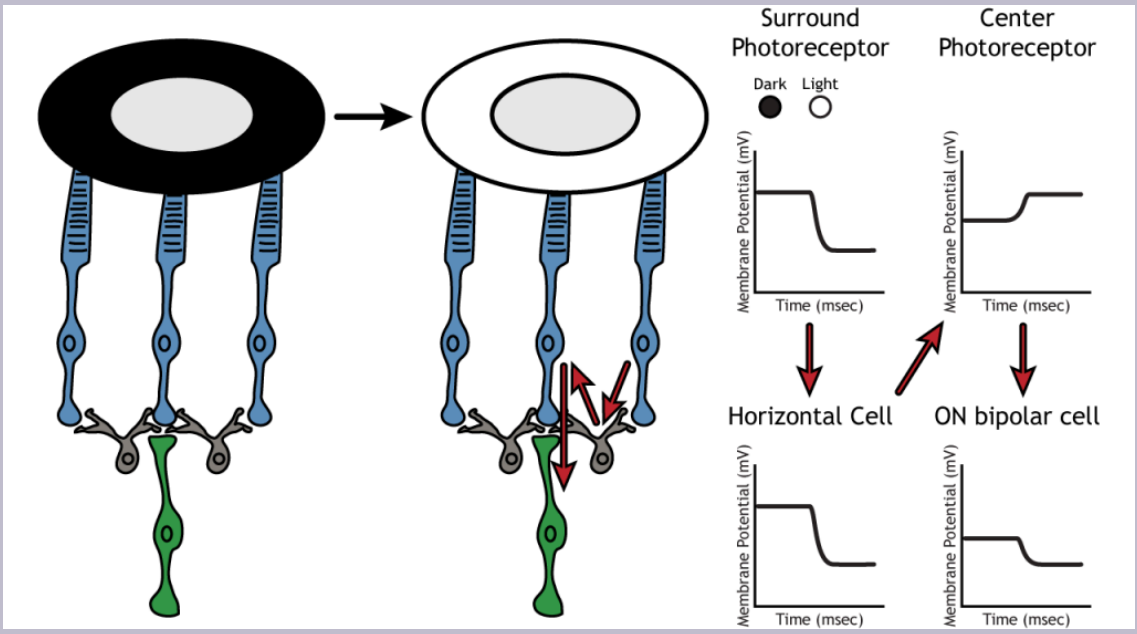

Figure 29.17. A photoreceptor in the surround of an ON bipolar cell’s receptive field moves from dark to light. The photoreceptor will hyperpolarize, and the postsynaptic horizontal cell will hyperpolarize. This will cause the center photoreceptor to depolarize, and the ON bipolar cell to hyperpolarize. The red arrows show the indirect synaptic communication between the surround photoreceptor and the ON bipolar cell. The surround photoreceptor synapses on the horizontal cell, which synapses on the center photoreceptor, which synapses on the bipolar cell. ‘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.

Lateral Inhibition

The center-surround structure of the receptive field is critical for **lateral inhibition** to occur. Lateral inhibition is the ability of the sensory systems to enhance the perception of edges of stimuli. It is important to note that the photoreceptors that are in the surround of one bipolar cell would also be in the center of a different bipolar cell. This leads to a direct synaptic effect on one bipolar cell while also having an indirect effect on another bipolar cell.

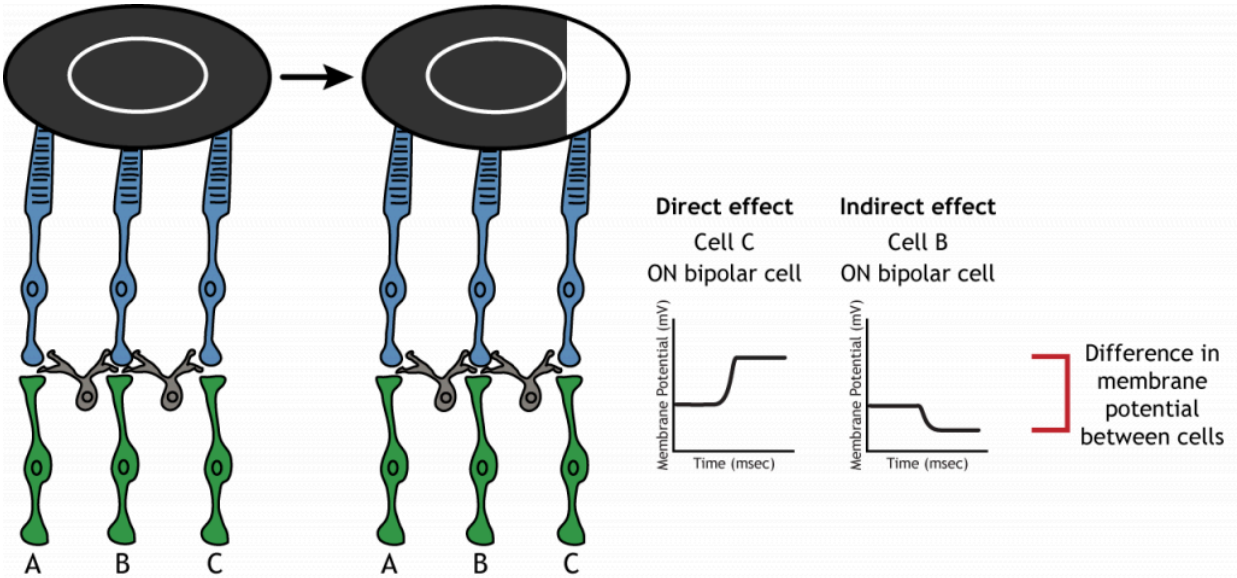

Figure 29.18. An edge of a light stimulus moves into the receptive field surround of ON bipolar cell B. This edge is also falling on the receptive field center of ON bipolar cell C. The light will cause bipolar cell C to depolarize because of the direct synapse with the photoreceptor. The light will also cause bipolar cell B to hyperpolarize because of the indirect synapses through the horizontal cell. This hyperpolarization causes a larger membrane potential difference between cells B and C that would occur if the horizontal cells were absent. The larger membrane potential difference between the cells will lead to an enhancement in the perception between the dark and light side of the edge. 'Lateral Inhibition' 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. Depending on the level of convergence on the bipolar and ganglion cells, receptive fields can contain many photoreceptors.

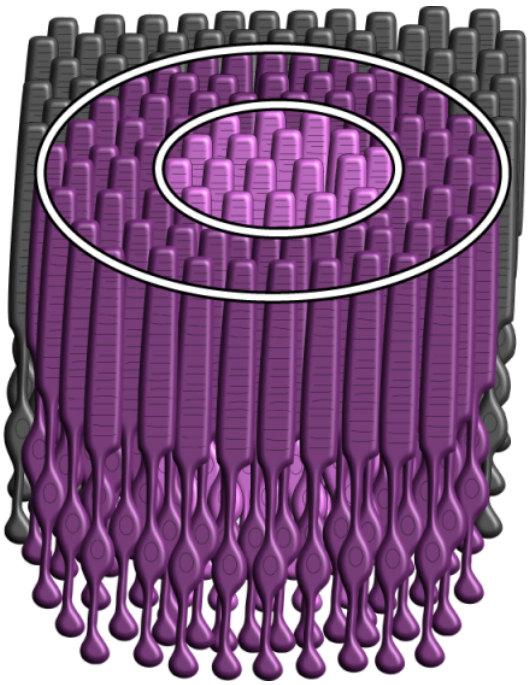

Figure 29.19. The receptive fields exist in two-dimensions along the surface of the retina. Depending on the location of the receptive field, and the amount of convergence that occurs at the bipolar or ganglion cell, the receptive field may contain many photoreceptors. 'Retinal surface' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Photoreceptors and bipolar cells do not fire action potentials
- Photoreceptors hyperpolarize in the light
- ON bipolar cells express inhibitory metabotropic glutamate receptors
- OFF bipolar cells express excitatory ionotropic glutamate receptors
- Receptive fields are circular, have a center and a surround, and vary in size
- Receptive field structure allows for lateral inhibition to occur

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/intro neuroscience1/?p=159#h5p-33

Additional Review

1. Compare and contrast rods and cones.
2. Compare and contrast the fovea and the optic disc.

Answers

Attributions

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- Fovea

30.

VISUAL SYSTEM: CENTRAL PROCESSING

In this chapter we will learn about how the information from the retina is processed centrally within the brain.

Visual Fields

Before learning the pathway that visual information takes from the retina to the cortex, it is necessary to understand how the retina views the world around us. The **full visual field** includes everything we can see without moving our head or eyes.

Resources

- Glossary Terms
- Scientist links to learn more
- Key Takeaways
- Test Yourself

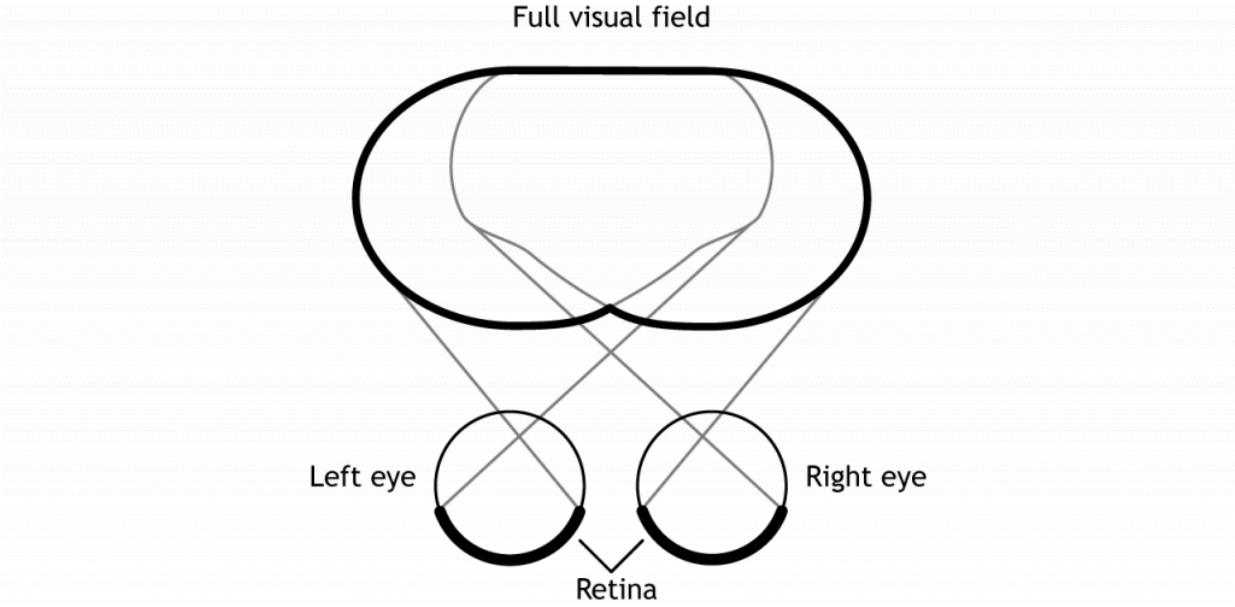

Figure 30.1. The two eyes together can view the entire visual field, which is all the visual space we can see without moving our head or eyes. 'Full Visual Field' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The full visual field can be divided in a few ways. Each individual eye is capable of seeing a portion of, but not the entire, visual field.

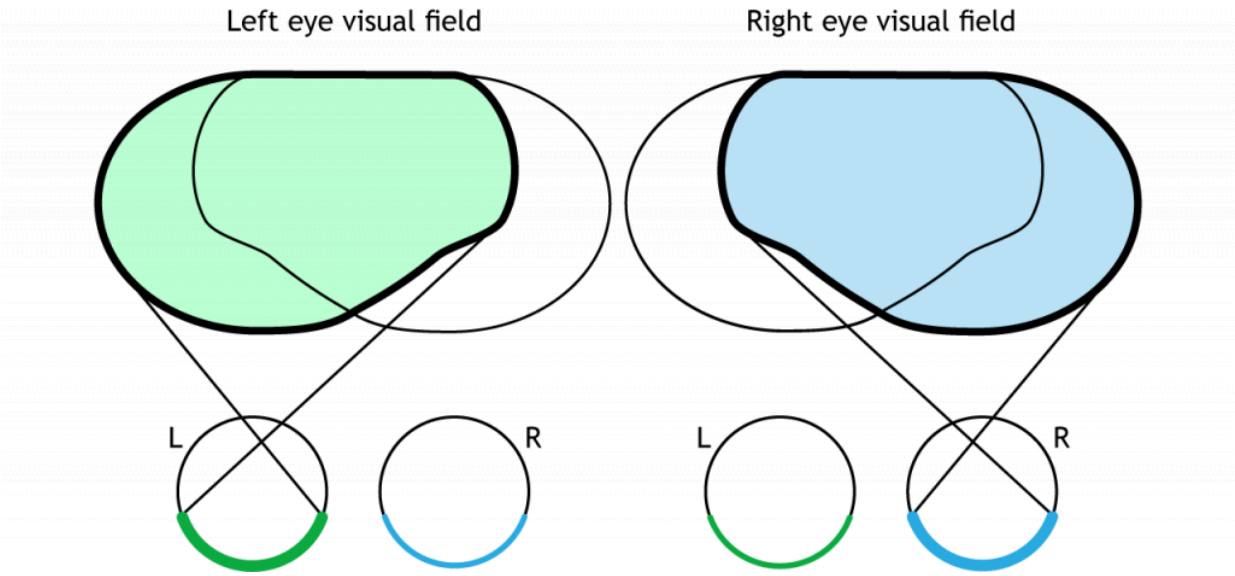

Figure 30.2. Each eye individually can view only a portion of the full visual field. 'Single Eye Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The full visual field can 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 **fovea** separates the retina into two sections: the **nasal retina** and the **temporal retina**. The nasal retina is the medial portion that is located toward the nose. The temporal retina is the lateral portion that is located toward the temples and temporal lobe. The nasal retina from one eye along with the temporal retina from the other eye are able to view an entire hemifield.

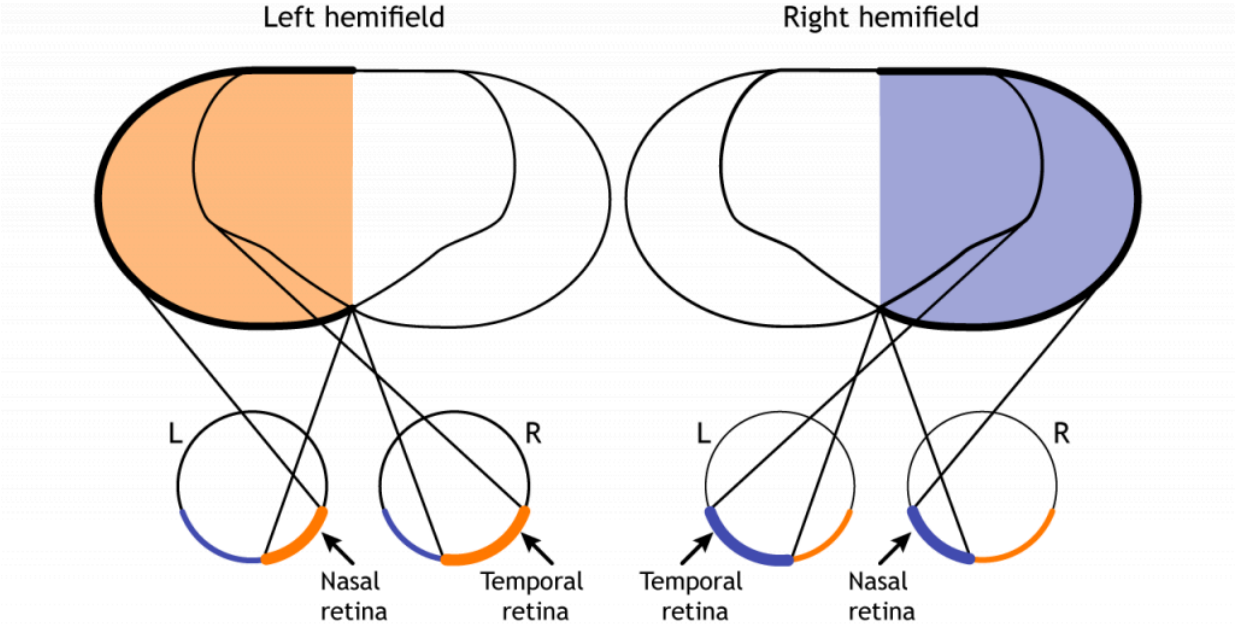

Figure 30.3. The full visual field can be divided into left and right hemifields. Both eyes contribute to viewing these regions. The nasal retina of the left eye and the temporal retina of the right eye view the left hemifield. The nasal retina of the right eye and the temporal retina of the left eye view the right hemifield. '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** and binocular regions. Each monocular field is visual space that can only be viewed by one eye. The **binocular** region is visual space that can be viewed by both eyes.

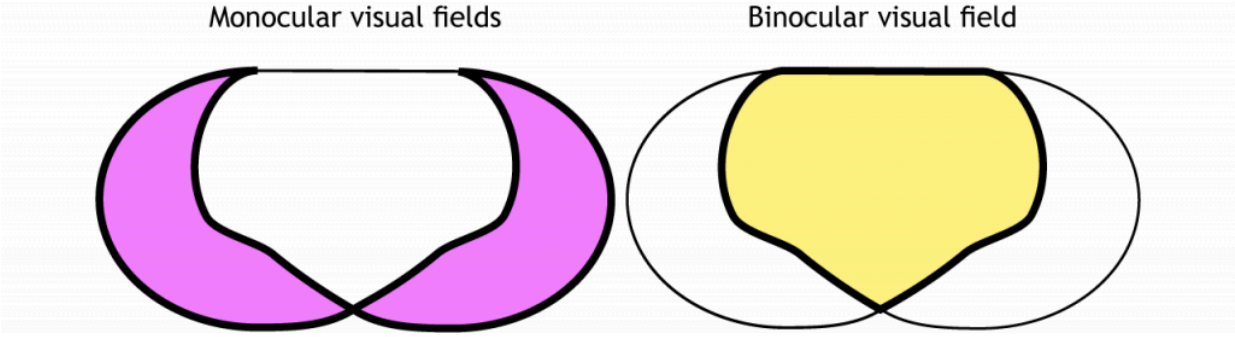

Figure 30.4. Monocular visual fields are viewed by only one eye and are located toward the periphery of the full visual field. The binocular visual field is viewed by both eyes and is located in the center of the full visual field. 'Monocular and Binocular Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway to Brain

Visual information from each eye leaves the retina via the ganglion cell axons at the optic disc, creating the **optic nerve**. The optic nerve, or cranial nerve II, exits the **posterior** end of the eyeball, and travels posteriorly along the **ventral** surface of the brain. Like all other cranial nerves, the optic nerve is paired, meaning there is one for each eye. Both optic nerves merge at a spot called the **optic chiasm**, then diverge yet again as they travel posteriorly towards the thalamus.

The axonal connections in the optic nerve are not quite as simple as its anatomical appearance. From each optic nerve, some of the nerve fibers cross the midline (decussate), headed towards the **contralateral** hemisphere. Other nerve fibers meet at the optic chiasm, but then project into the **ipsilateral** hemisphere.

Prior to entering the brain, axons from the nasal portion of each retina cross the midline at the optic chiasm but the temporal portion of each retina does not cross at the optic chiasm.

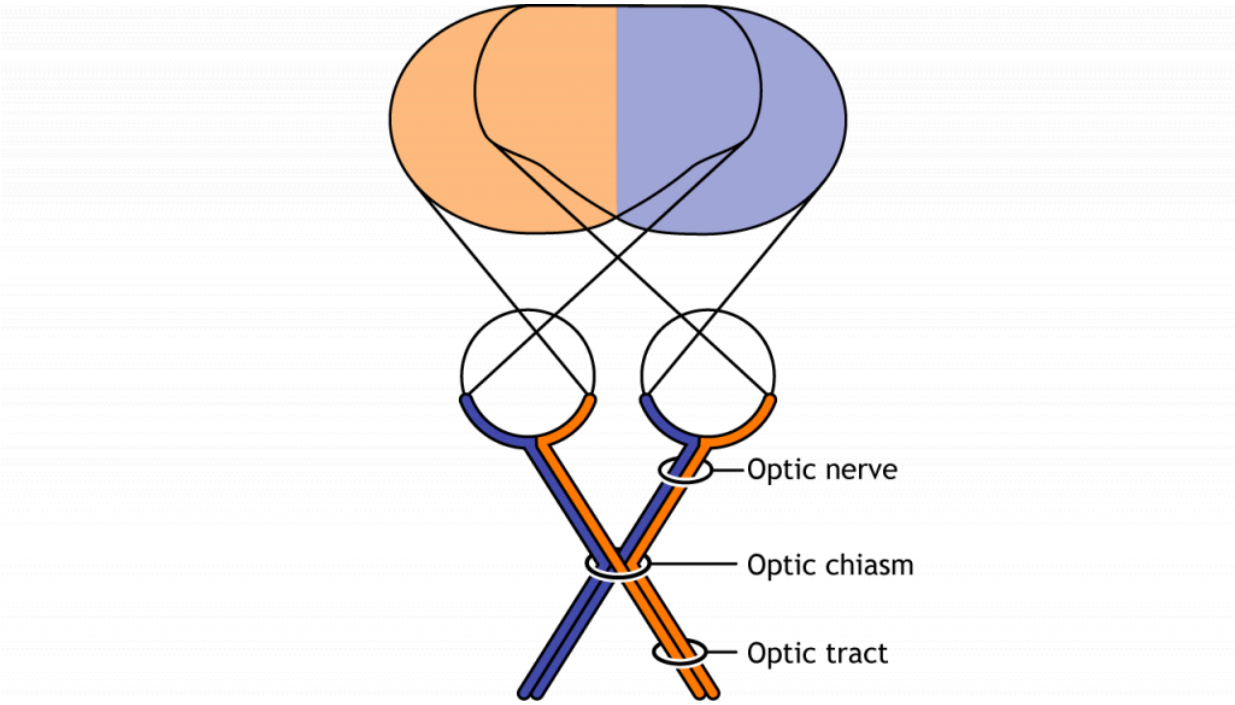

Figure 30.5. Information from each eye is carried away from the retina by the optic nerve. Information perceived by neurons in the nasal retina of each eye crosses the midline at the optic chiasm. Information from the contralateral visual hemifield then travels to the brain. 'Pathway from Retina' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the optic nerve (cranial nerve II) using the BrainFacts.org 3D Brain

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 (opposite side) visual hemifield. Therefore, the right side of the brain receives visual information from the left hemifield and vice versa. The easy way to keep track of this unusual system is to remember that all information from the left visual field enters the right hemisphere of the brain, while visual information from the right visual field enters the left hemisphere of the brain.

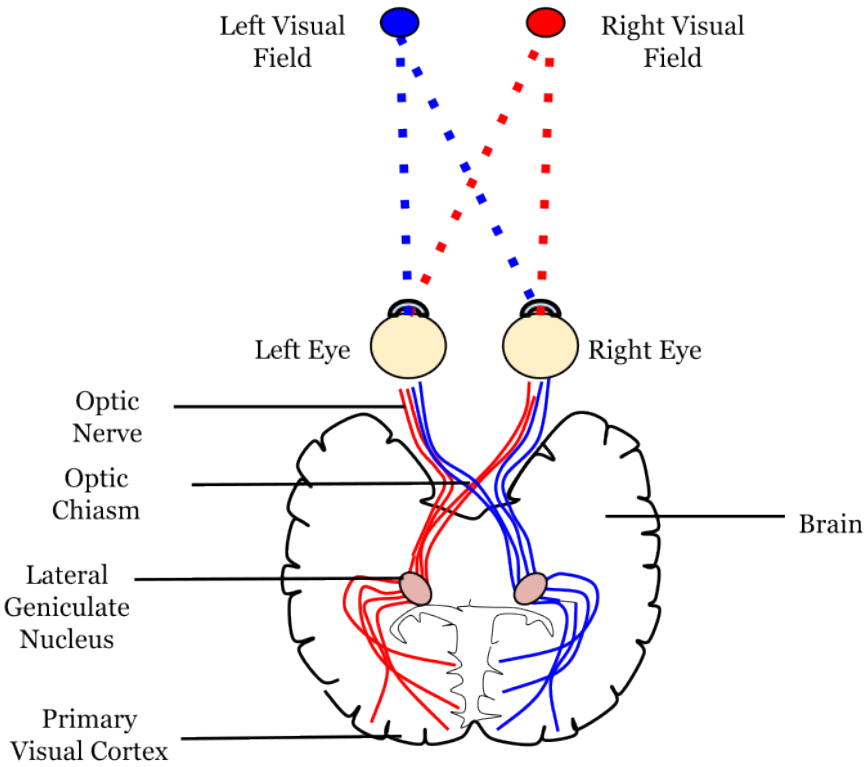

Figure 30.6 Pathway from the retina to the brain. Information collected from the left visual hemifield (shown in blue) comes by way of the left nasal retina and right temporal retina. This left visual hemifield information is processed within the right lateral geniculate nucleus and then the right primary visual cortex. Information collected from the right visual hemifield (shown in red) comes by way of the right nasal retina and the left temporal retina. The right visual hemifield information is processed within the left lateral geniculate nucleus and then the left primary visual cortex.

Pathways from the Retina

The retinal ganglion cells that exit the retina and project into the brain can take different paths. The

retinofugal projection (fugal means "to flee") is one of the major projection paths of the retinal ganglion cells. Most retinal output projects to the **lateral geniculate nucleus of the thalamus** and then to the **primary visual cortex**, however there are subsets of cells that are routed through other non-thalamic pathways.

Non-Thalamic Pathways

Not all of the axons convey direct visual information into the thalamus for visual perception. Some ganglion cells project to the **superior colliculus**, a midbrain region via the **retinotectal pathway** (recall that the superior colliculus is a structure of the tectum). This pathway communicates with motor nuclei and is responsible for pupillary control. Specifically, it is responsible for movements that will orient the head and eyes toward an object to focus the object in the center of the visual field, the region of highest visual acuity.

A subset of specialized retinal ganglion cells project to the **suprachiasmatic nucleus in the hypothalamus** through the **retinohypothalamic tract** (starts in the retina, ends in the hypothalamus). It does not carry any conscious visual information. The retinohypothalamic tract conducts light information from a small group of intrinsically-photosensitive retinal ganglion cells. This structure functions to help the body adapt its sleep-wake cycle in the face of changing day-night patterns This region is critical for circadian rhythms and the sleep/wake cycle.

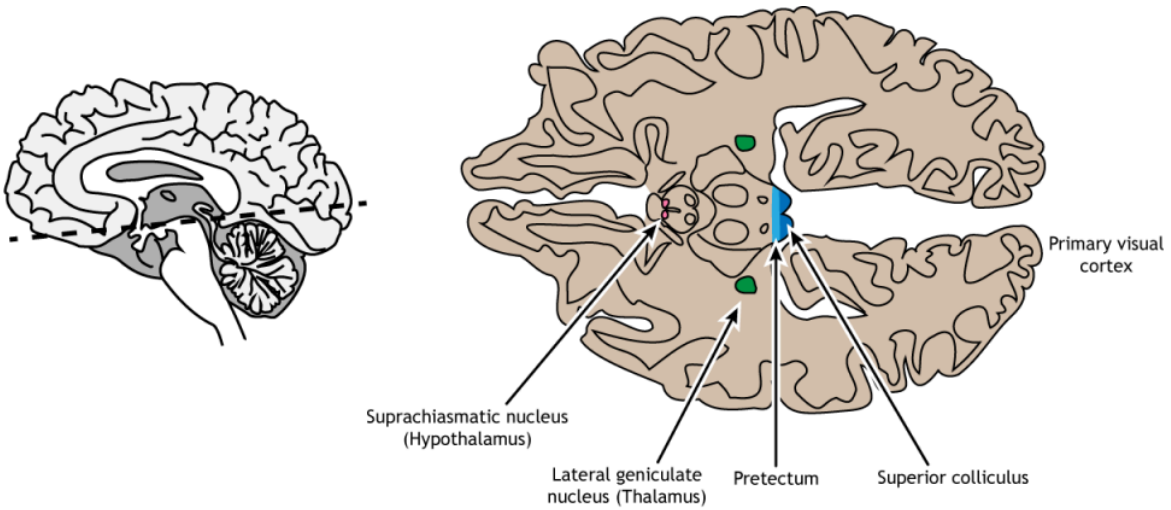

Figure 30.7. In addition to the thalamus, the retinal neurons send projections to other regions of the brain. The suprachiasmatic nucleus (pink) is located in the hypothalamus and is important for biological rhythms. The pretectum (light blue) is a midbrain structure that plays a role in muscle control of the pupil. Finally, the retina projects to the superior colliculus (blue), another midbrain region important in eye and head movements. The lateral geniculate nucleus of the thalamus (green) is also shown. 'Non-Thalamic Retinal Pathways' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

View the midbrain using the BrainFacts.org 3D Brain

Thalamic Pathway: Lateral Geniculate Nucleus

In conscious visual perception, the first synapse of the optic nerve is formed in the thalamus at a subregion called the **lateral geniculate nucleus, or LGN**. The optic tract enters the brain and ascends to synapse in the lateral geniculate nucleus of the thalamus. From there, axons project to the primary visual cortex, also called the striate cortex or V1, located in the occipital lobe.

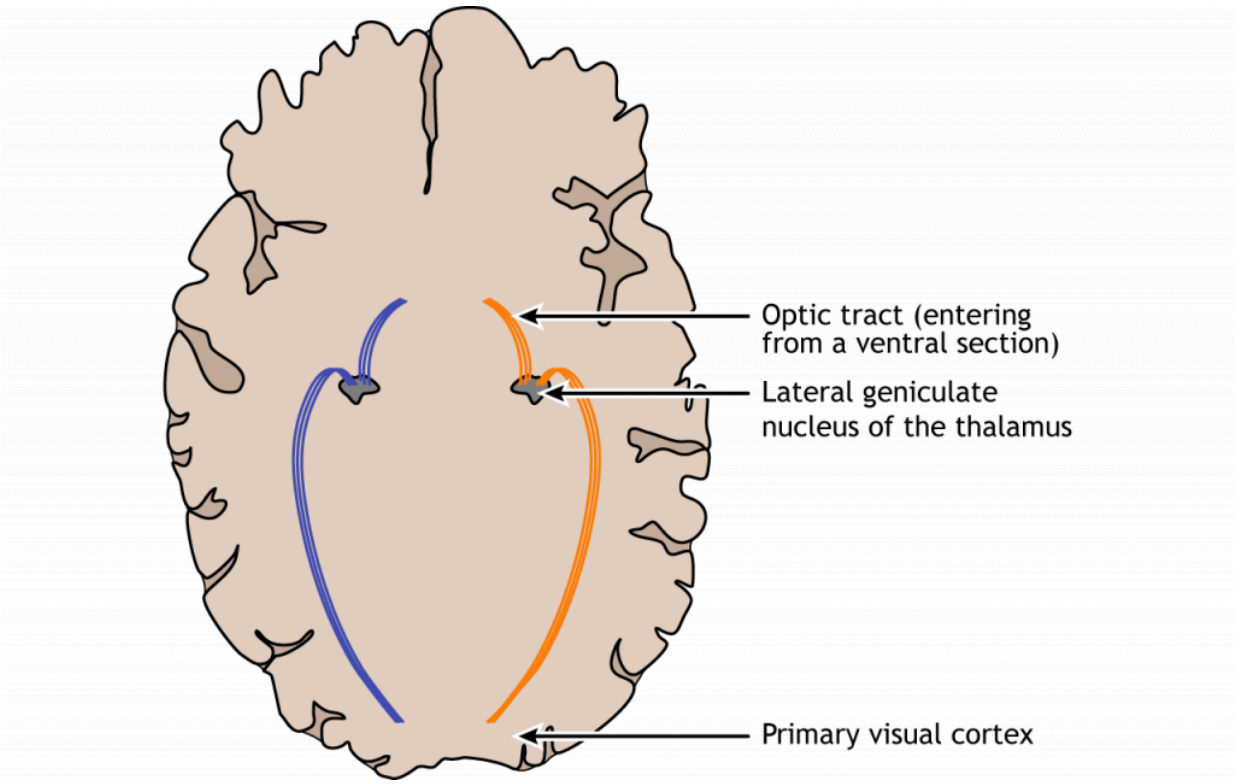

Figure 30.8. A horizontal section of the brain. The optic tract enters the brain and projects dorsally to the thalamus. Information is then sent to the primary visual cortex in the occipital lobe. 'CNS Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Lateral Geniculate Nucleus

The lateral geniculate nucleus of the thalamus (LGN) has six distinct layers when examined in cross section. The LGN serves as the first synaptic site of the retinal ganglion cells that exited the retina.

Importantly, visual information is separated at the level of the LGN such that visual information from each visual field is all processed in the contralateral LGN. This means that information from the left visual hemifield, collected via the right temporal retina and the left nasal retina will all be processed within the right LGN. Information from the right visual hemifield, collected via the left temporal retina and the right nasal retina will all be processed by the left LGN.

Within the LGN, input coming from each eye is kept separate by the layers of the LGN. For example, notice that half of the layers of the right LGN process information from the right eye and the other half of the layers process information from the left eye.

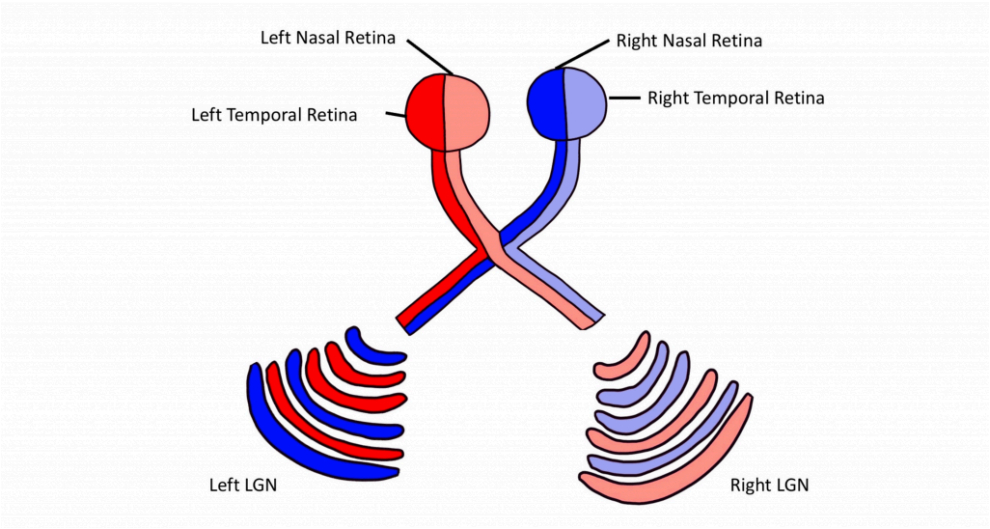

Figure 30.9. Lateral Geniculate Nucleus. The Lateral Geniculate Nucleus (LGN) has six layers in cross section. The visual information from the left visual hemifield, coming from the left nasal retina and the right temporal retina, is all processed by the right lateral geniculate nucleus. The visual information from the right visual hemifield, coming from the right nasal retina and the left temporal retina, is all processed by the left lateral geniculate nucleus. Within an individual lateral geniculate nucleus, the information from each eye is kept in separate layers. Information from the nasal retinas crosses and is processed by the contralateral

lateral geniculate nucleus, whereas information from the temporal retinas is processed by the ipsilateral lateral geniculate nucleus (does not cross). 'Lateral Geniculate Nucleus' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

The outputs of the LGN are a series of axonal bundles called the **optic radiations**. From the LGN of the thalamus, the optic radiations project to the **occipital lobe** at the **caudal** (posterior) end of the brain. Once visual information travels into the cortex, the process is less about sensation and mostly about perception.

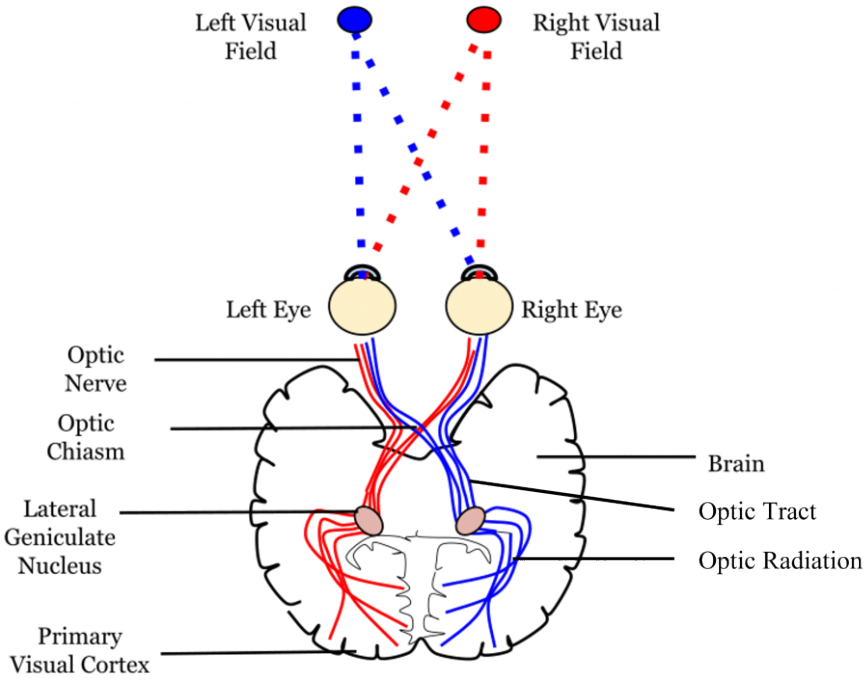

Figure 30.10. Pathway from the retina to the brain. Information collected from the left visual hemifield (shown in blue) comes by way of the left nasal retina and right temporal retina. This left visual hemifield information is processed within the right lateral geniculate nucleus and then the right primary visual cortex. Information collected from the right visual hemifield (shown in red) comes by way of the right nasal retina and the left temporal retina. The right visual hemifield information is processed within the left lateral geniculate nucleus and then the left primary visual cortex. Information from the LGN travels to the primary visual cortex via the optic radiations.

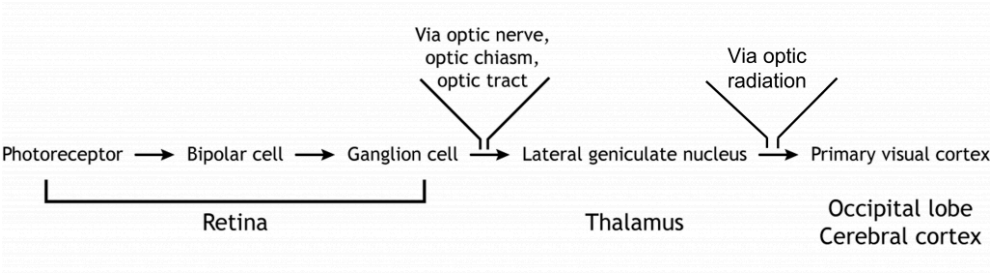

Figure 30.11. Visual information that is sent through the full visual pathway, therefore, moves from photoreceptor to bipolar cell to ganglion cell in the retina. It leaves the retina via the optic nerve, optic chiasm, and optic tract to the lateral geniculate nucleus of the thalamus and then travels to the primary visual cortex via the optic radiation. 'Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the thalamus using the BrainFacts.org 3D Brain

Striate Cortex (Primary Visual Cortex)

The outputs of the LGN are axons which form synapses in the **primary visual cortex**, which is also

called **V1** or the **striate cortex**. 'Striate' means 'stripe' and is named due to the presence of a large white stripe that can be seen in unstained tissue during surgical dissection. This white stripe is the bundle of incoming optic tract axons, which are heavily myelinated.

Each neuron in V1 receives visual information from a specific patch of retinal cells. This organizational pattern, where a section of retinal inputs map onto neurons of a specific section of V1, is called **retinotopic organization**. This retinotopic organization is conserved from the retina to the LGN, and finally to the primary visual cortex. Visual information from the fovea, despite being only 1% of the total visual field, takes up about half of all neurons in V1. After processing in V1, visual information is passed along to other cortical areas that contribute to various aspects of visual perception.

View the primary visual cortex using the BrainFacts.org 3D Brain

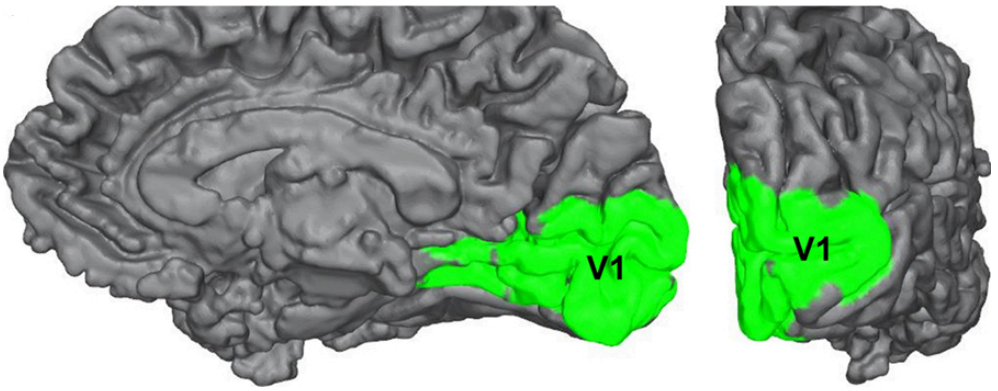

Figure 30.12. Primary Visual Cortex. The primary visual cortex (also called striate cortex or V1) is located in the posterior region of the human brain within the occipital lobes. In this image the primary visual cortex is marked with V1 and highlighted in green.

Cortical Layers

The cortex of the brain is arranged into six layers, named with the Roman numerals I-VI. The cells within these layers have different morphology. These cortical layers are especially visible within the striate cortex (V1). Within this region, the thickness of the cortex between the pia mater that is in contact with the top of the cortex and the white matter underlying the cortex is very thin (around 2 mm in thickness).

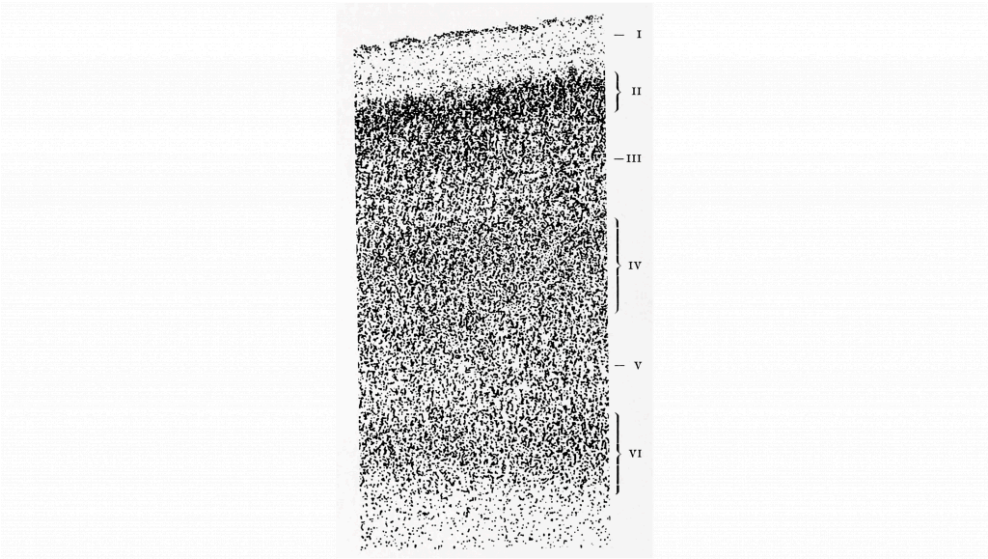

Figure 30.13. Laminar organization of the cortex. When looking at a cross section of the cortex, six distinct layers of cells can be observed. These layers are typically labeled by the Roman numerals I-VI. Cells within each of the layers have distinct morphology.

These cells within the six layers of the cortex are arranged in what are called 'cortical columns'. This arrangement was discovered by Dr. Vernon Mountcastle in the 1950s. You can imagine that due to the directionality of communication in neurons, that information travels up and down the cells within a single cortical column.

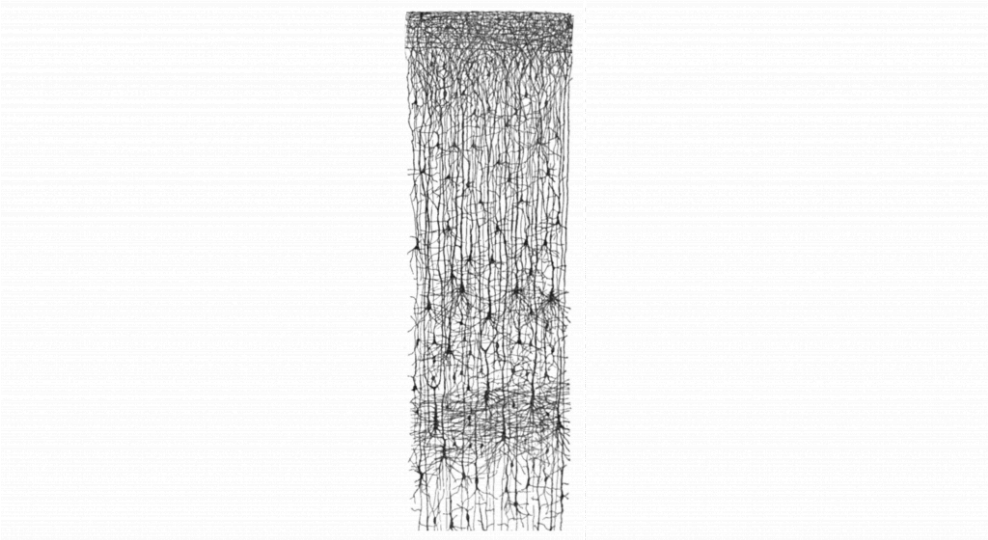

Figure 30.14. Columnar organization of the cerebral cortex. The cerebral cortex has cells that are organized into columns, where all the cells within a single cortical column communicate with each other.

Features of the Primary Visual Cortex:

Contributions of David Hubel and Torsten Wiesel

Dr. David Hubel and Dr. Torsten Wiesel followed up on this critical discovery by Mountcastle to describe neuronal processing within the visual cortex. Their discoveries in this field led to them being awarded the Nobel Prize in the field of Physiology or Medicine in 1981. Highlighted below are some of their major contributions.

Orientation Selectivity

Hubel and Wiesel used microelectrodes to map the functioning of the visual cortex. In one of their famous experiments, Hubel and Wiesel used anesthetized cats to determine how the visual cortex processes visual information. During their experiment, they were showing the anesthetized cat different visual stimuli through the projection of slides with different images onto a screen while recording from neurons within the visual cortex. Due to when this experiment was done, these slides were large and plastic and had to be physically inserted into a projector. In the process of inserting these slides into the projector, a bar of light was projected onto the screen by the edge of the slide. Quite by surprise, the act of changing the slides (and the bar of light that resulted) caused the neurons within the cat brain to fire action potentials. Hubel and Wiesel determined that the stimulus causing the neurons to fire was the angle of the bar of light projected on the screen.

In fact, the neurons within the visual cortex responded best to a line in a specific orientation and the firing rate of the neuron increased as the line rotated toward the "preferred" orientation. The firing rate is highest when the line is in the exact preferred orientation and different orientations are preferred by different neurons. This discovery was due to some great luck for Hubel and Wiesel as they were recording from neurons that had a preferred orientation that exactly matched the angle of changing the slides in their projector!

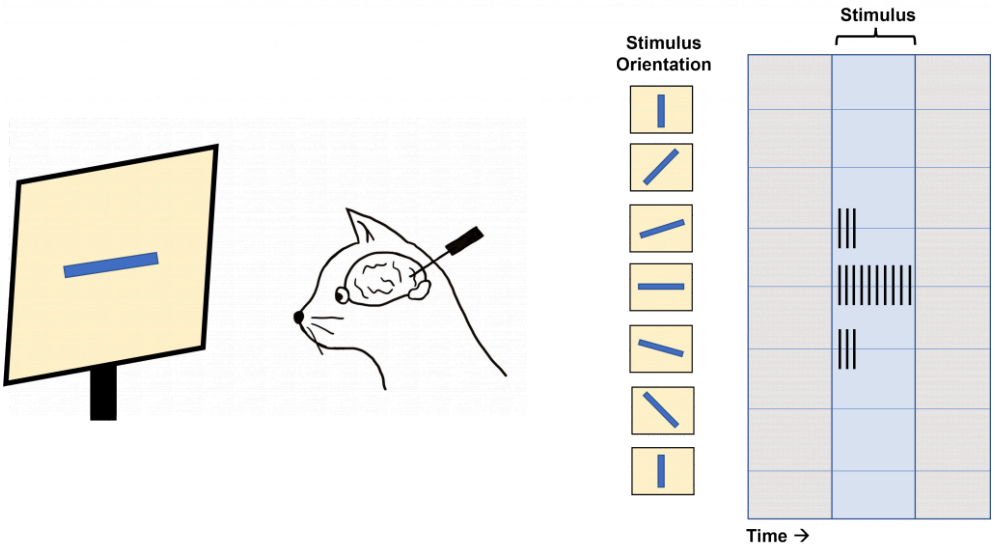

Figure 30.15. Orientation selectivity experiment. In Hubel and Wiesel's experiment they recorded from neurons within the primary visual cortex of anesthetized cats while showing them images on slides projected onto a screen (left). They found that neurons within the primary visual cortex fired action potentials in response to a bar of light in a specific orientation (horizontal in the image above). The most action potentials are fired when the bar of light is in this specific orientation. If the bar of light is in a similar orientation, but not the exact preferred orientation, less action potentials will fire. 'Orientation selectivity experiment' by

This orientation selectivity within the visual cortex is the same for all neurons located within a single cortical column. This means that the cells in each cortical column will respond optimally to a line at a preferred orientation. So, if a recording electrode is inserted vertically through the cortex to record from cells within a single cortical column, all cells will respond optimally to the same sensory stimulus. If the recording electrode is inserted horizontally, such that it records across multiple cortical columns, each cortical column will respond optimally to a different sensory stimulus.

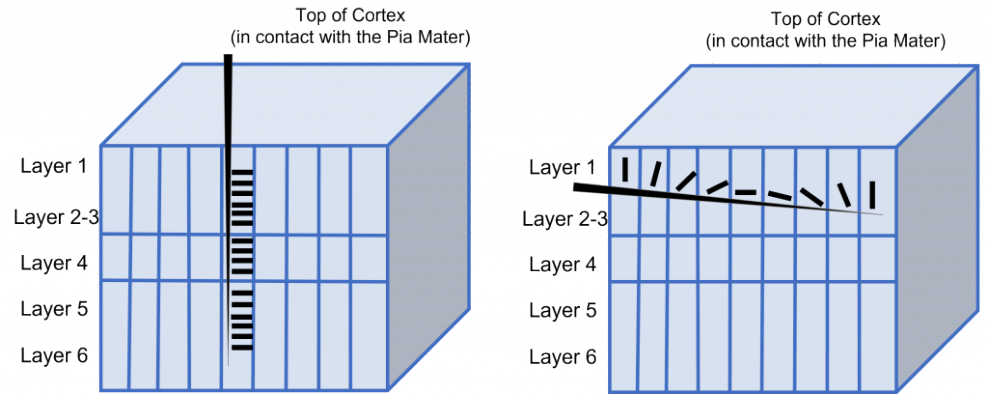

Figure 30.16. Orientation selectivity in cortical columns. Here a cross section of the cortex is show with layers I-VI labeled. In the left image, a recording electrode (black triangle) is inserted vertically into a single cortical column (columns divided by blue lines). All the cells in this cortical column respond to a bar of light in the horizontal orientation. Adjacent cortical columns respond to bars of light at different orientations. If a recording electrode is inserted horizontally, such that it records from multiple different cortical columns, each cortical column will respond to a bar of light at a specific orientation. 'Orientation selectivity in cortical columns'

Ocular Dominance Columns

Another experiment by Hubel and Wiesel determined the existence of **ocular dominance columns**, or columns of neurons within the visual cortex that respond preferentially to either the left or right eye.

For this experiment, Hubel and Wiesel injected a radioactive amino acid into one of the eyes of a monkey. This amino acid then travels by **anterograde** transport through the retinal ganglion cells of the eye through the first synapse at the lateral geniculate nucleus of the thalamus, and then through the next synapse with the striate cortex. Radioactivity within the striate cortex can then be visualized through the process of autoradiography.

In an autoradiograph image of the striate cortex, there are alternating areas that appear white in color with areas that appear black in color (similar to the stripes on a zebra). The areas of the cortex that appear white are the areas that took up the radioactive amino acid and are processing information from the injected eye. The areas of the cortex that appear black are areas that do not have the radioactive amino acid and are processing information from the eye that was not injected. Recall, that although information from the left visual hemifield is processed on the right side of the brain, the left visual hemifield information is collected from *both* eyes via the left nasal retina and right temporal retina. Therefore, *both* eyes are processed across both the left and right visual cortex.

Figure 30.17. Illustration of an autoradiograph showing ocular dominance columns within the primary visual cortex. When a radioactive amino acid is injected into one of the eyes of a monkey, the radioactive amino acid is taken up by the retinal ganglion cell and travels through anterograde transport to the primary visual cortex. Areas of the cortex that received synapses from the injected eye and have the radioactive amino acid will be visualized as white stripes within the primary visual cortex. Areas of the cortex that receive connections from the eye that was not injected with the radioactive amino acid will appear black in the

autoradiograph. 'Ocular Dominance Columns' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Interestingly, in newborn cats that had not had any visual experience, they did not observe the ocular dominance columns. Instead, they saw that the inputs of the left and right eye overlapped substantially within the visual cortex. Hubel and Wiesel were interested in understanding how these ocular dominance columns develop between infancy and adulthood and whether their development was dependent on visual experience.

For their experiment, they took a kitten immediately after birth, and sewed the right eye of the kitten closed, so that the eye could no longer have any visual experience, a condition called **monocular deprivation** ('mono' meaning 'one' and 'ocular' meaning 'eye'). After this six-week period of monocular deprivation, the eye of the cat was reopened so that it could take in the visual environment. A control group of cats had normal visual experience for this same six-week period.

In control cats that did not experience monocular deprivation, Hubel and Wiesel found that they developed normal ocular dominance columns at six weeks post birth. The cats that experienced monocular deprivation for the first six weeks of life, however, showed abnormal development of the ocular dominance columns. The columns that normally served the right eye (that was sewn shut) shrank in size, and the neighboring columns that served the left eye grew into the unoccupied cortical space. Hubel and Wiesel were able to conclude that visual experience was necessary for the ocular dominance columns to develop. In fact, they found that there was a **critical period** in cat visual development in the first six weeks of life where visual experience is required for normal visual development.

Importantly, these structural changes also translated into functional changes for the vision of the cat. Cats that experienced monocular deprivation had decreased visual function in the eye that was sewn shut for the rest of the cat's life. Even though the sewn shut eye was reopened after the critical

period, the development of the ocular dominance columns in the brain was already complete and thus the brain could never process visual information from the sewn shut eye.

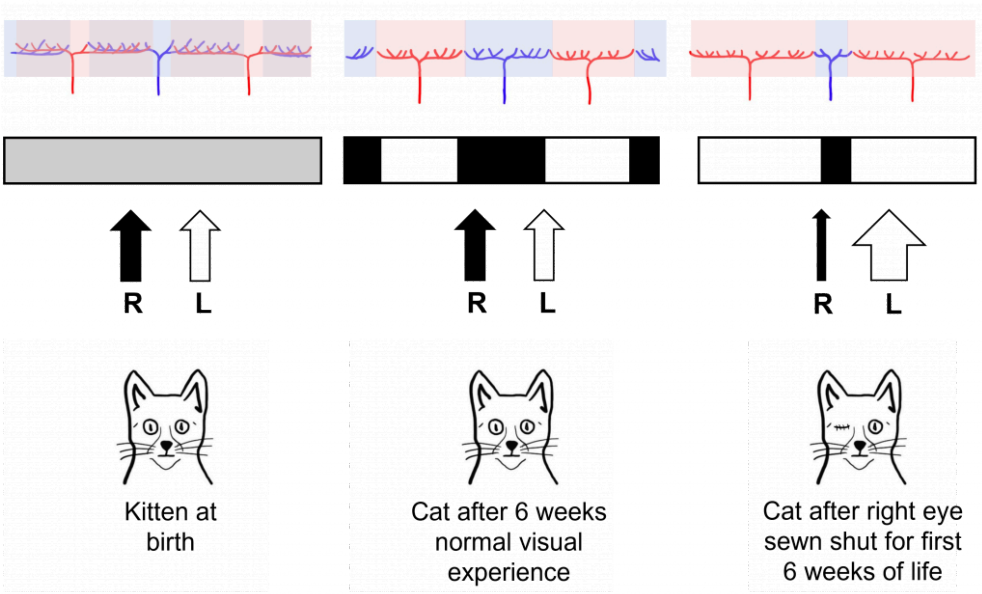

Figure 30.18. Development of ocular dominance columns. At birth, ocular dominance columns are not present in kittens (represented by gray bar). Both eyes (R and L) provide equal visual experience to the neurons of the primary visual cortex (represented by the arrows). The neurons that serve the cortex have overlapping inputs from the left and right eyes (shown by blue and red neurons). After six weeks of normal visual experience, ocular dominance columns are observed in cats-that is, there are areas of the cortex that process information from either the left or right eye (shown by black and white bars), and their neuronal inputs do not overlap (distinct areas of red and blue neurons).

When the right eye is sewn shut immediately following birth for six weeks, there is decreased input from the sewn shut eye (skinny black arrow) and thus increased input from the open left eye (large white arrows). This causes the ocular dominance columns to not develop normally. The ocular dominance columns that served the sewn shut eye shrink in response to the decrease in visual experience. The adjacent ocular dominance columns that serve the left eye, that remained opened, expand to fill in the cortical space that normally would have been take up by the right eye. As a result, the eye that was sewn shut has decreased brain area that

processes visual information from the eye and decreased visual function for the remainder of the cat's life. 'Ocular Dominance Column development' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Higher-Level Processing of Sensory Information

Sensory system processing of input does not end upon reaching the primary sensory cortex in any sensory system. Information typically gets sent from the primary sensory cortex to other sensory association regions throughout the brain. The characteristics of sensory information becomes more complex as this higher-level processing occurs.

Post-Striatal Processing

In the visual system, there are two broad streams of information that leave the striate cortex. Visual information passes through two streams of communication: the **dorsal stream** and the **ventral stream**. In the ventral stream, information 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. In the dorsal stream, information travels from the striate cortex up through the parietal lobe and is responsible for motion or spatial components of vision.

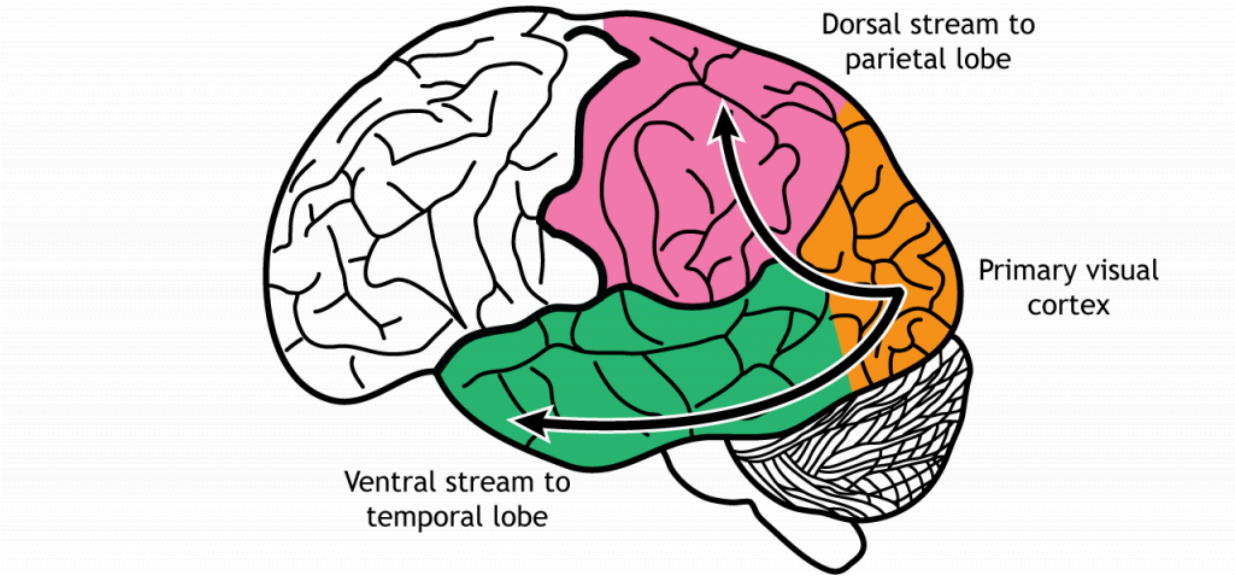

Figure 30.19. Information continues to be processed after reaching the primary visual cortex. The dorsal stream travels to the parietal cortex and is important for spatial components of vision. The ventral stream travels to the temporal lobe and is important for object recognition. 'Visual Streams' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Dorsal Stream

The dorsal stream is described as the "where" pathway because these structures help us identify where objects are located in the space around us. One of the most important regions in the dorsal pathway is **region MT, also called V5**, which contributes to perception of motion. In this region, neurons are preferentially activated by a specific direction of movement by an object – for example, left to right or up to down. As an example, remember the receptive fields in the primary visual cortex were activated by lines at a specific orientation. Like that, in V5, the neurons would be activated by lines moving in a specific direction.

As information continues to be processed through the dorsal stream, the neurons become selective for more complex motions. The dorsal stream is also important for processing our actions in response to visual stimulation, for example, reaching for an object in the visual field or navigating around objects while walking.

These structures also guide us when we move through our environments, contributing to our sense

of spatial awareness. For example, a task such as reaching out to grab an object in front of you uses a combination of these features, so this task is guided largely by dorsal stream structures.

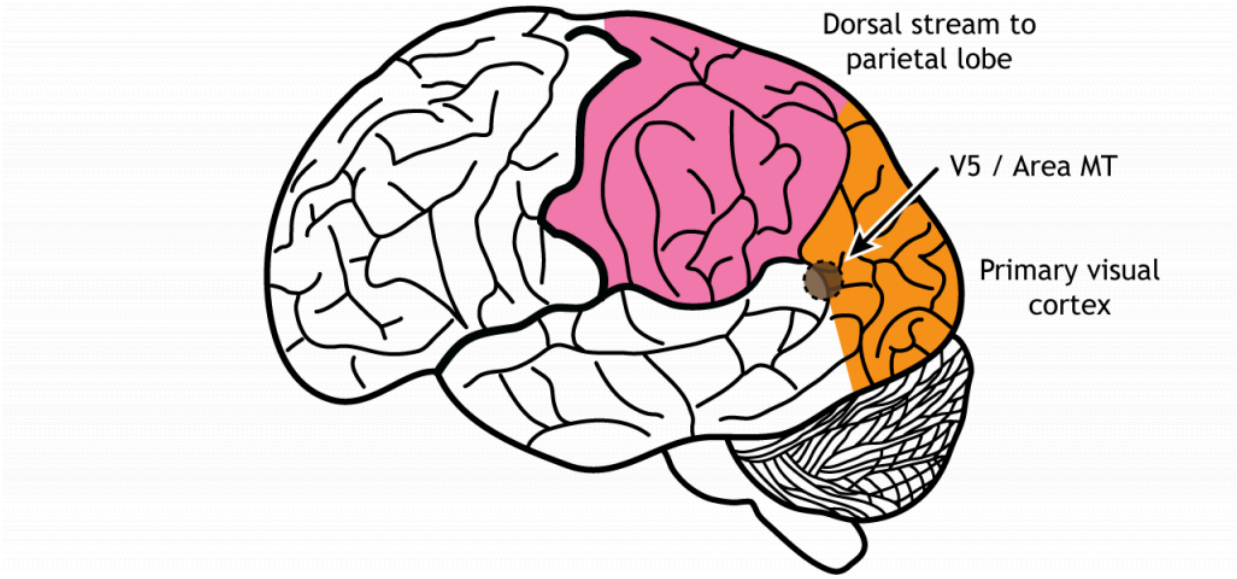

Figure 30.20. Area MT, also called V5, is an early processing region of the dorsal stream through the parietal lobe. Neurons in the region are activated by direction of an object in a specific direction. 'Area MT' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ventral Stream

The ventral stream is the "what" pathway, and helps in the identification of objects that we see. Object identification is a key function of our visual system. The ventral visual stream is responsible for this process. Further, ventral stream structures are important for visual memory. Like the more complex activation characteristics of **region MT** in the dorsal stream, neurons in Area V4 in the ventral stream show more complex receptive fields and show sensitivity to shape and color identification. In fact, there is a rare clinical condition in humans called **achromatopsia**, in which individuals have partial or complete loss of color vision. These individuals still have normal functioning cones within the retina, and normal LGN and primary visual cortex function. Instead, they typically have damage to occipital and temporal lobes, where the ventral stream is located.

A major output of area V4 is **area IT**, located within the inferior temporal lobe. As information travels to area IT it continues to be processed and differentiation of objects occurs. Neurons located in

area IT are important in learning and memory in visual perception (have I seen that before?), and have been found to respond to colors and shapes.

Another region within the ventral stream called the **fusiform face area**, located in the fusiform gyrus, which lies on the ventral aspect of the temporal lobe, contains neurons that are activated by faces and can be specialized to one specific face. When the visual system senses these complex stimuli, those signals get processed through these ventral stream pathways. These incoming stimuli are compared with the memories stored in the ventral stream, and this comparison contributes to our capacity for perception and identification.

The two streams are not independent of each other. Rather, successful organisms require the melding of both components of visual perception. For example, imagine you are a prehistoric organism living in a food-scarce environment. Approaching a small berry tree, you would use ventral stream structures to correlate the berries with memories: Did these berries taste good and give me the calories I need to survive? Or did these berries make me violently ill, and are therefore probably poisonous? If they are the delicious berries that I want, I will use the dorsal stream structures to take note of their precise location so I can reach out for them and pick the berries . In this example, proper interaction of the dual streams contributes to goal-driven actions.

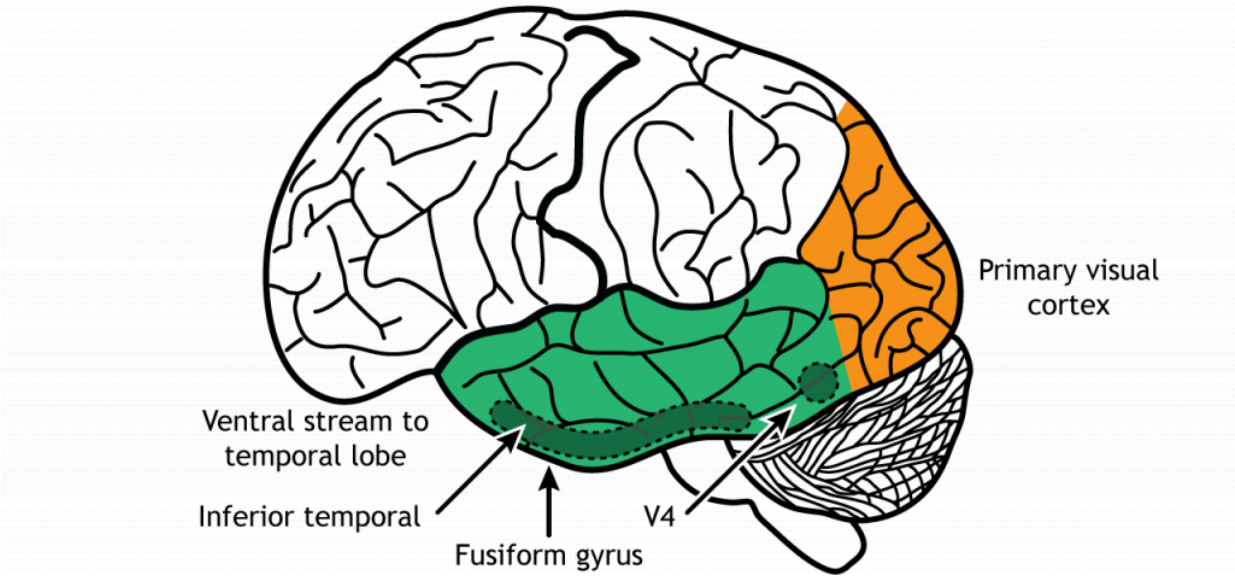

Figure 30.21. The ventral stream is first processed by area V4, which recognizes shapes and color. Information the continues through the inferior temporal lobe and sends information to regions like the fusiform gyrus, which is an area responsible for the recognition of faces. 'Ventral Stream' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The inferior temporal lobe also makes reciprocal connections with the structures in the **limbic system**. The limbic system plays an important role in processing emotions and memory, both of which are significant components to visual perception. The **amygdala** ties visual stimuli with emotions and provides value to objects. A family member will have emotional ties that a stranger will not. The **hippocampus** is responsible for learning and memory and helps establish memories of visual stimuli.

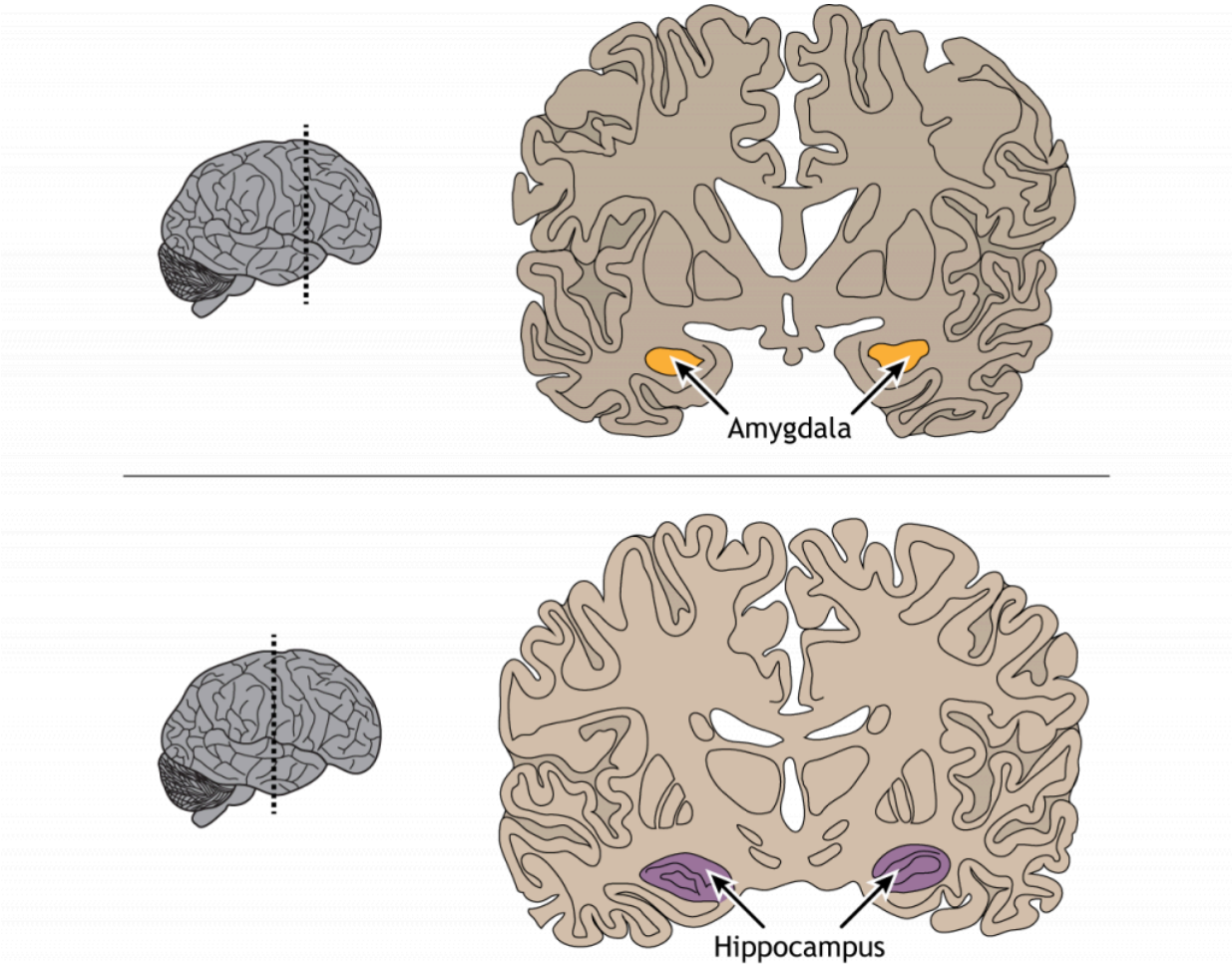

Figure 30.22. The limbic system structures, the amygdala and the hippocampus, also play important roles in visual processing. Both regions are located deep in the temporal lobe and have reciprocal connections with the ventral stream as is it moves through the temporal lobe. 'Deep Temporal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the amygdala using the BrainFacts.org 3D Brain

View the hippocampus using the BrainFacts.org 3D Brain

Key Takeaways

- The nasal and temporal retinal regions are responsible for viewing specific regions of the visual field
- Some retinal projections cross the midline at the optic chiasm, causing the left side of the brain to process the right visual hemifield and vice versa
- The retinal axons synapse in the lateral geniculate nucleus of the thalamus. Information then travels to the primary visual cortex
- Receptive fields and the preferred visual stimuli for neuron activation become more complex as information moves through the visual pathway
    - Primary visual cortex neurons have linear receptive fields are are activated by a line in a specific orientation
    - Area MT / V5 is activated by motion in a specific direction
    - Area V4 is activated by specific shapes and colors
    - The fusiform gyrus is activated by faces
- The retina also projects to midbrain regions
- Ocular dominance columns that process information from either the left or right eye develop during a critical period of development

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/introneuroscience1/?p=175#h5p-49

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31.

AUDITORY SYSTEM: THE EAR

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Our nervous system is equipped with a variety of specialized biological "tools" that can detect much more than just photons of light. We can detect the shape of air waves, and interpreting those signals give us sound information and the perception of music. In this chapter we will trace how sounds travel through the structures of the ear, ultimately causing the auditory receptors to alter their activity and send their signals to the brain.

Properties of Sound

Unlike photons of light, sound waves are compressions and rarefactions of a medium. For us land animals, that medium is usually air, but sound waves can propagate very well in water or through solids. Before we get to the anatomical structures involved in sound perception, it is important to first understand the physical nature of sound waves. All sounds, from the clattering of a dropped metal pan to the melodies of a Mozart violin concerto, are contained in their corresponding sound waves. Two components of sound waves are **frequency** and **amplitude**.

1. **Frequency**, or "How often do the sound waves compress?" The greater the frequency, the higher the pitch. The highest notes humans are able to hear is around 20,000 Hz, a painfully-shrill sound for those who can hear it. People often tend to lose their high frequency hearing as they age. On the opposite end of the spectrum, low frequency sounds are the deep rumbles of bass, and the human ear can hear sounds down in the 20 Hz range.
2. **Amplitude**, or "How much do the waves displace the medium from baseline?" The larger the amplitude of the wave, or the greater distance between the peak and the trough of the signal, the

louder the sound is. Loudness is measured in decibels (dB). To give you an idea of approximate sound intensities, the background noise of a quiet library is about 40 dB, and a typical conversation is close to 60 dB. A rock concert or lawnmower is between 100 and 110 dB, which is right around the pain threshold. Prolonged exposure to these high amplitude sound waves can lead to permanent damage to the auditory system resulting in hearing loss or tinnitus (a ringing in the ear, even in the absence of a sound stimulus).

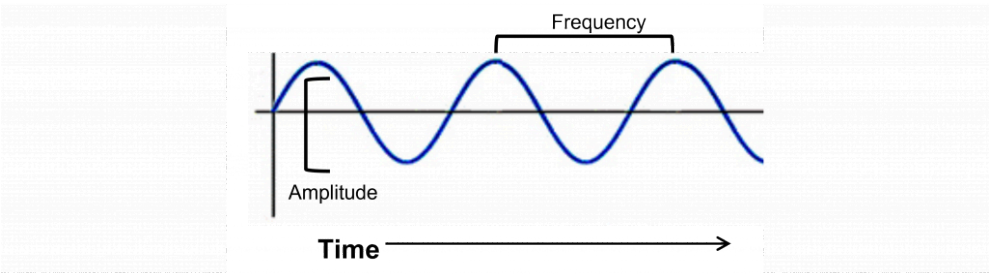

Figure 31.1. Sound Waves. The frequency of sound waves is measured as the number of peaks that occur over time and corresponds to the pitch of sound. Higher frequency sound waves have a higher pitch whereas lower frequency sounds waves have a lower pitch. The amplitude of sound waves is measure from the peak of the wave to the trough and corresponds to how loud a sound is. Larger amplitude waves are louder, whereas smaller amplitude waves are quieter.

Physical Structures of the Auditory System: Outer Ear

Our auditory system is a series of physical structures and nervous system components that are responsible for conveying sound waves into meaning and context.

The external component of the auditory system begins with the **pinna**. Its shape functions as a funnel, capturing and channeling sound waves into the auditory canal. The pinna and the **auditory canal** are parts of the outer ear. Also, because the pinna is asymmetrical, its shape helps us determine where a sound is coming from. In some nonhumans, the pinna serves these functions and more. For instance, some animals are able to disperse excess heat through their ears (elephants), and some even use them to display emotion (dogs, horses).

At the end of the auditory canal is the **tympanic membrane**, or ear drum. This membrane is a very delicate piece of tissue at only 0.1 mm thin and is subject to damage by physical injury such as head trauma, nearby explosions, or even changes in air pressure during scuba diving. When incoming sound waves reach the tympanic membrane, it vibrates at a matching frequency, and amplitude. The tympanic membrane also represents the boundary between the outer ear and the middle ear.

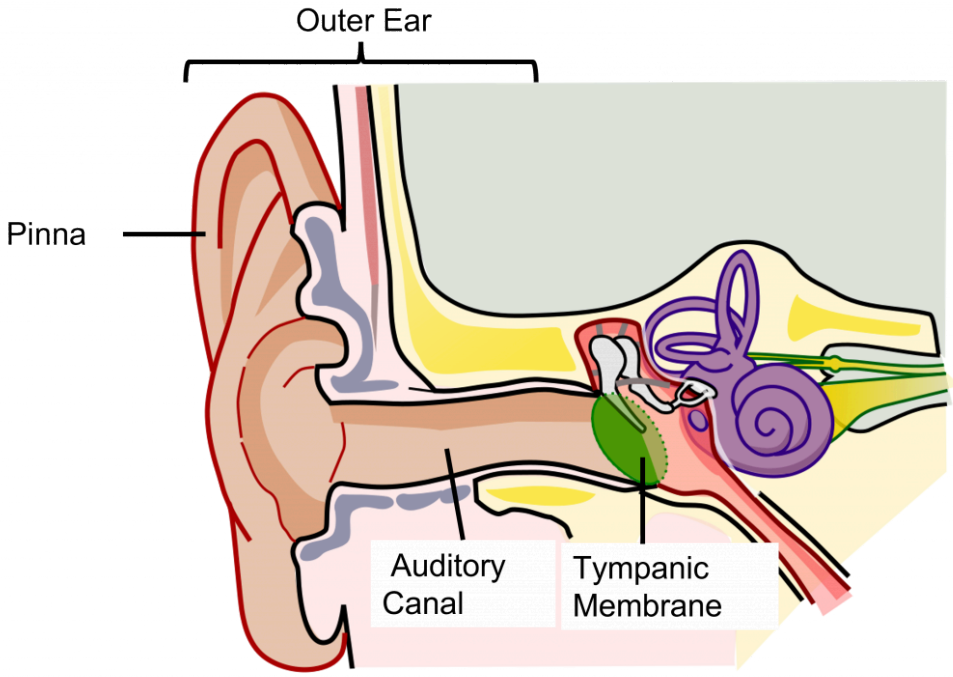

Figure 31.2. Human outer ear anatomy. The outer ear (highlighted in brown) consists of the pinna, which acts as a funnel to direct sound waves into the auditory canal. The tympanic membrane separates the auditory canal from the middle ear.

Physical Structures of the Auditory System: Middle Ear

The middle ear is an air-filled chamber. Physically attached to the tympanic membrane are the ossicles, a series of three bones that convey that vibrational sound information. These bones in order, called the **malleus**, **incus**, and **stapes**, conduct vibrations of the tympanic membrane through the air-filled middle ear. The stapes has a footplate that attaches to a structure called the **oval window**, which serves as the junction between the middle ear and the inner ear. The middle ear serves important functions in both sound amplification and sound attenuation.

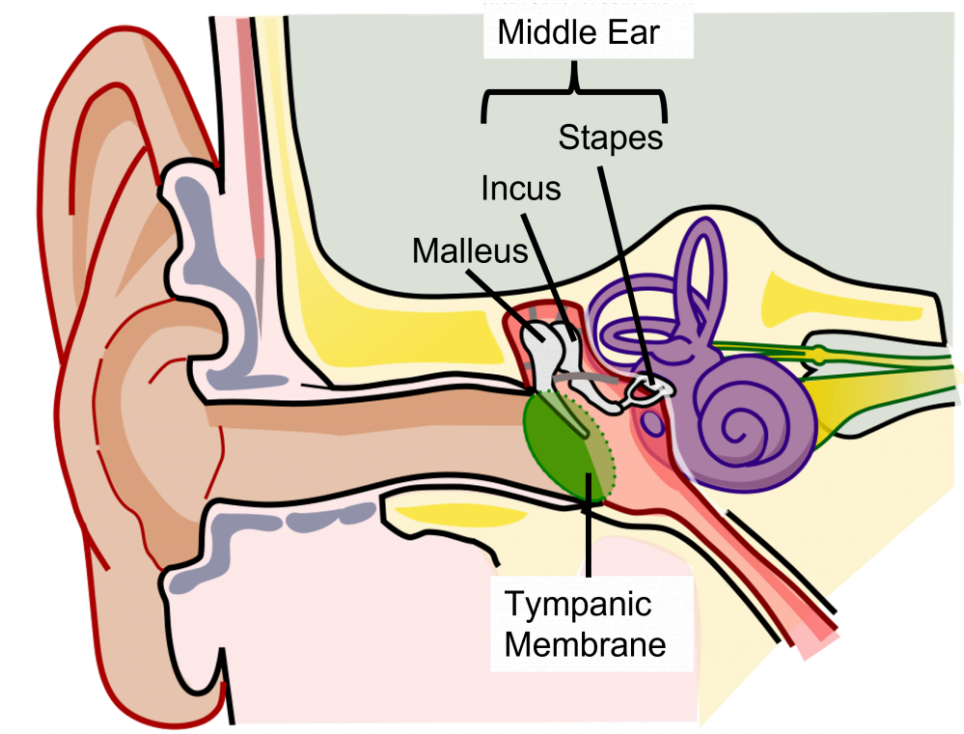

Figure 31.3. Human middle ear anatomy. The tympanic membrane separates the outer ear from the middle ear (highlighted red in this image). The middle ear is an air filled chamber that contains three small interconnected ossicles (bones): the malleus, incus, and stapes. The malleus is physically attached to the tympanic membrane. The malleus then connects to the incus, and the incus connects to the stapes. The stapes is shaped like a stirrup and is connected to the oval window that separates the middle ear from the inner ear.

Sound Amplification

The tympanic membrane and the ossicles function to amplify incoming sounds, generally by a tenfold difference. This amplification is accomplished through 2 mechanisms:

1. Due to the ossicles being connected, the ossicles act in a lever-like fashion to amplify the movements of the tympanic membrane to the oval window
2. The stapes has a smaller area on the oval window than the tympanic membrane, thus movements of the larger tympanic membrane must be transformed into smaller and stronger vibrations at the oval window.

This amplification is important because the inner ear is filled with liquid rather than air, and sound waves do not travel very well when moving from air into a denser medium – think about how muffled sounds are when you submerge your head underwater.

Sound Attenuation

The movement of the ossicles are partially regulated by two different muscles, the **tensor tympani muscle** which connects with the malleus, and the **stapedius muscle** which connects to the stapes. When these muscles contract, it causes the ossicles to be more rigid and for the ossicles to move less, which decreases the intensity of loud sounds. This response, called the **acoustic reflex**, dampens incoming sound by about 15 dB. (This is why we talk much louder than normal when we first leave a concert: we have lessened auditory feedback from our ears, so we tend to talk louder to compensate.) The muscles contract at the onset of loud noises with a slight delay of 50-100ms.

Physical Structures of the Auditory System: Inner Ear

The inner ear is a fluid-filled structure made up of two structures: the **cochlea** that functions in hearing, and the **semicircular canals** that function in balance.

The auditory part of this structure is a small spiral-shaped structure about the size of a pea, called the cochlea (cochlea is named for the Ancient Greek word “snail shell”.) The cochlea has two small holes at its base: the **oval window** and the **round window**.

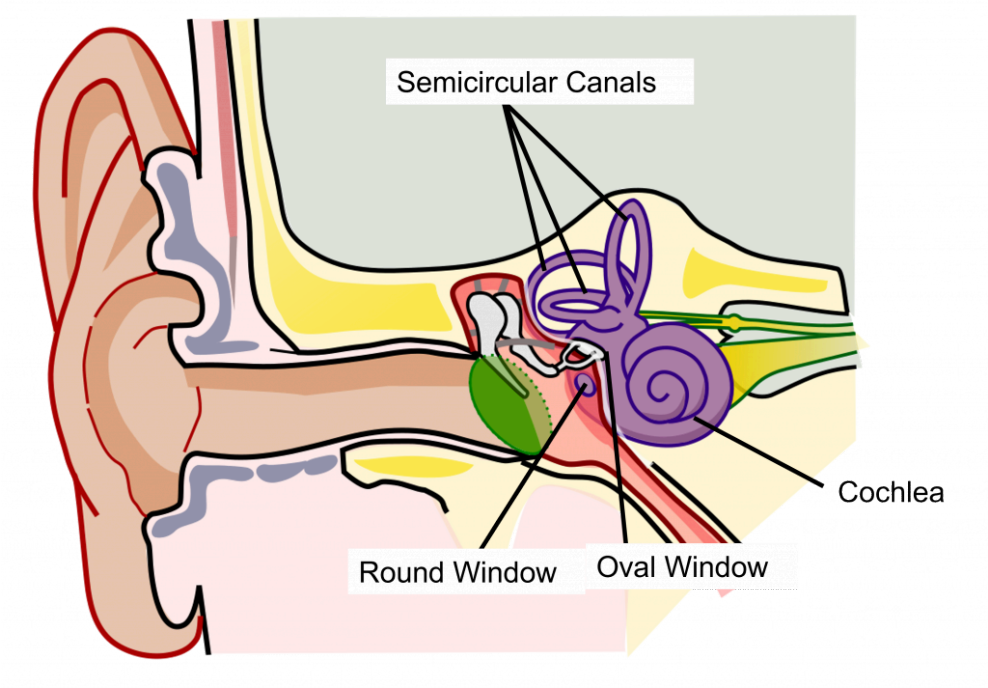

Figure 31.4. Human inner ear anatomy. The inner ear has two structures: the semicircular canals and the spiral-shaped cochlea. The structures of the inner ear are filled with fluid. They are separated from the air-filled middle ear by two membranes called the oval window and the round window.

Cross Section of the Cochlea

When we examine a cross-section of the cochlea, we can see that there are 3 distinct fluid-filled chambers called the **scala vestibuli**, the **scala media**, and the **scala tympani**. These chambers are separated from each other by membranes.

The fluid found within the scala vestibuli and scala tympani is called **perilymph** and it has a low concentration of potassium and a high concentration of sodium. The scala media is filled with a fluid called **endolymph** that has a high concentration of potassium and a low concentration of sodium.

Reissner's membrane separates the scala vestibuli from the scala media. The **basilar membrane** separates the scala tympani from the scala media.

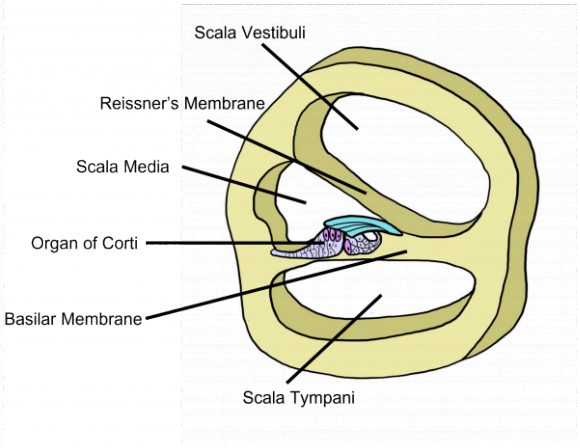

Figure 31.5. Cochlea cross section. In cross section, the three chambers of the cochlea can be observed. Reissner's membrane separates the scala vestibuli from the scala media. The basilar membrane separates the scala media from the scala tympani. The Organ of Corti is embedded within the basilar membrane and extends into the scala media. 'Cochlea Cross Section' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Basilar Membrane

Think of the cochlea as a rolled-up cone. If this cone was theoretically unrolled, the widest diameter portion, called the **base**, would be closest to the oval window, while the narrowest portion, called the **apex**, would be at the center of the spiral.

The basilar membrane runs down the middle of the cochlea. The width of the basilar membrane changes as it runs down the length of the cochlea from the base to the apex. This change in shape from the base to the apex is important: objects with different stiffness vibrate at different frequencies. The base of the cochlea is stiff and rigid and will vibrate at high frequencies. Whereas the apex is wider and less stiff, so it vibrates at lower frequencies.

Because different frequencies of sound affect different areas of the basilar membrane, the basilar membrane is what is referred to as **tonotopically organized**. In fact, you can think about the way that frequencies are mapped to the basilar membrane similar to a backwards piano.

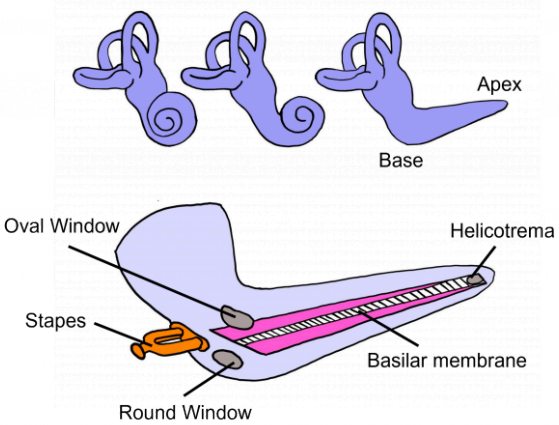

Figure 31.6. Basilar membrane. When the cochlea is uncoiled, it is easier to see the different structures. The basilar membrane runs down the middle of the cochlea. The oval window and round window are located at the base of the cochlea and the stapes foot plate connects to the oval window. The helicotrema is a hole in the basilar membrane at the apex of the cochlea, allowing the perilymph of the scala vestibuli to connect to the perilymph of the scala tympani. by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Let's consider how sounds will affect the cochlea. For simplicity's sake, the figure here shows only the scala vestibuli and the scala tympani (not the scala media) with the basilar membrane running down the middle. Keep in mind that due to the flexibility of Reissner's membrane that separates the scala vestibuli from the scala media, we can assume that pressure changes in the scala vestibuli are transferred through the scala media, ultimately affecting the basilar membrane.

1. When sounds move through the outer and middle ear, it causes vibration of the stapes footplate at the oval window. The movement of the stapes at the oval window is similar to a piston pushing at the oval window at the same frequency and amplitude as the incoming sound.
2. When the stapes pushes into the oval window, it causes movement of the perilymph within the scala vestibuli.
3. This causes the sounds to move through the cochlea as a wave from the base to the apex, displacing the flexible basilar membrane at different locations dependent on the frequency of sound.
4. At the apex of the basilar membrane is a hole called the helicotrema that connects the perilymph of the scala vestibuli to the perilymph of the scala tympani and allows for the pressure to be transferred from the scala vestibuli to the scala tympani.
5. The pressure then moves through the scala tympani back towards the base of the cochlea until it pushes out at the round window.

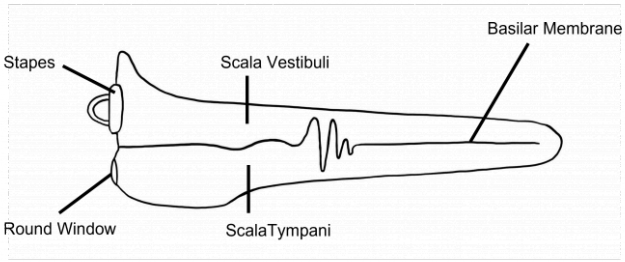

Figure 31.7. Basilar membrane displacement. The basilar membrane runs down the middle of the cochlea. The stapes pushes in at the oval window to displace the perilymph of the scala vestibuli. The movement of the fluid causes the flexible basilar membrane to be displaced like a wave. The pressure moves through the fluid of the scala vestibuli and then around the helicotrema and back through the fluid of the scala tympani, displacing the round window. 'Basilar Membrane Displacement' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

The Organ of Corti

Embedded within the basilar membrane is a structure called the **Organ of Corti**. The Organ of Corti is the first nervous system structure that is responsible for processing physical vibrations and converting them into signals that the nervous system can interpret. The Organ of Corti contains the components necessary for converting sound waves into action potentials. Recall that the scala media that surrounds the Organ of Corti contains endolymph, a fluid that has a high concentration of potassium and a low concentration of sodium.

A separate membrane hangs over the Organ of Corti called the **tectorial membrane**. Recall that "tectum" means roof. The tectorial membrane acts as a roof over the Organ of Corti.

Embedded along the interior surface of the Organ of Corti are the somata of **hair cells**, the primary sensory neurons that interpret physical movement. They are named "hair cells" because of their cellular structure; each hair cell has somewhere between 30 and a few hundred hair-shaped stereocilia that protrude away from the Organ of Corti, reaching into the endolymph.

Importantly, hair cells are ***not*** neurons. They do not produce action potentials and do not have axons. In fact, hair cells are a specialized type of epithelial cell. We have two different populations of hair cells, the **inner hair cells** and outer **hair cells**.

- The outer hair cells are arranged in three rows. Their stereocilia extend into the endolymph and are physically embedded within the tectorial membrane.
- The inner hair cells are arranged in a single row. Their stereocilia extend into the endolymph but are not embedded within the tectorial membrane. Instead, the stereocilia of the inner hair cells freely float within the endolymph.

Although the hair cells themselves are not neurons, the mechanical bending of the hair cell stereocilia will be converted into a neural signal. Hair cells synapse on **spiral ganglion cells** (neurons). The axons of the spiral ganglion cells make up the auditory nerve, which will project into the cochlear nuclei of the medulla.

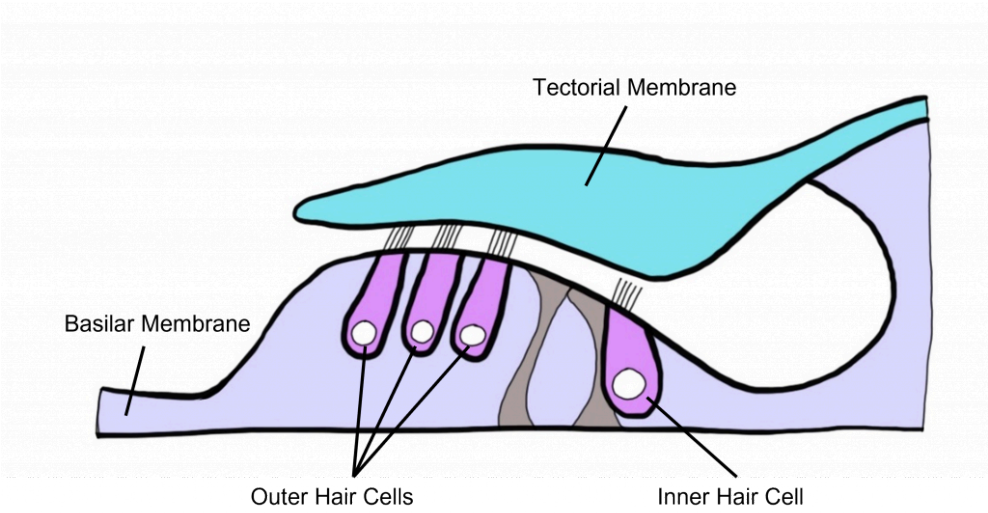

Figure 31.8. Organ of Corti. The Organ of Corti is embedded in the basilar membrane. There are three rows of outer hair cells and one row of inner hair cells. The tectorial membrane extends over the hair cells. The hair-like projections of the outer hair cells are embedded within the tectorial membrane, whereas the hair-like projections of the inner hair cells are not embedded within the tectorial membrane. 'Organ of Corti' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Neural Components of the Auditory System

As we have learned, when a vibration reaches the oval window, this causes the basilar membrane to move in response to the change in pressure. The basilar membrane is located at the base of the hair cells, and as the basilar membrane moves up and down, it pushes the hair cell stereocilia into the tectorial membrane above, causing the stereocilia to bend.

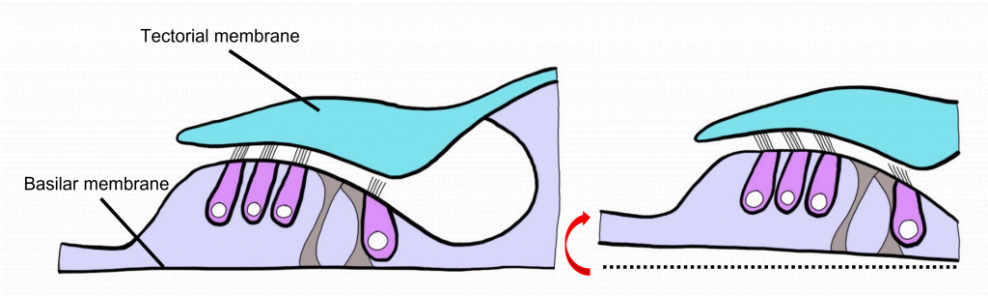

Figure 31.9. Basilar membrane movement causes hair cell stereocilia to bend. The movement of the basilar membrane in response to sound causes the hair cell stereocilia to be pushed into the stationary tectorial membrane, causing them to bend. 'Basilar movement bends stereocilia' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Hair Cells

Let's take a closer look at the structure of the hair cell.

The stereocilia of the hair cell have different lengths and are arranged from shortest to tallest. At the tip of each stereocilium are mechanically-gated ion channels. These are mechanically-gated because they open and close in response to physical movement. The stereocilia are linked together with spring-like proteins called **linker proteins**. These linker proteins are specifically attached to small covers that block movement through mechanically-gated ion channels when closed.

The stereocilia can bend in two different directions, toward the shortest stereocilium or towards the tallest stereocilium. At rest (no sound), the stereocilia are not bent. Some of the mechanically-gated ion channels are open, and some are closed.

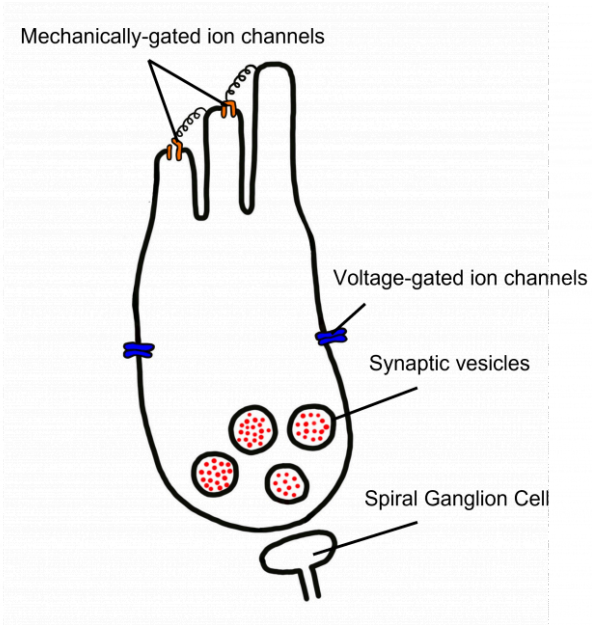

Figure 31.10. Hair cell at rest. When the stereocilia are not being bent some of the mechanically-gated ion channels at the tips of the stereocilia are open and others are closed, and the cell is neither depolarized or hyperpolarized. When the hair cell is at rest, synaptic vesicles do not release neurotransmitters at the spiral ganglion cell synapse. 'Hair cell at rest' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

When the stereocilia bend towards the tallest stereocilium, the distance between the stereocilia increases and the spring-like linker proteins are stretched, causing the opening of the covers on the mechanically-gated ion channels.

Recall that the stereocilia are surrounded by endolymph, which is high in potassium and low in sodium. When the mechanically-gated ion channels are opened, potassium ions will flow into the hair cells, moving down its concentration gradient. As the positively charged potassium ions move into the hair cell, it causes the hair cell to depolarize.

If the stereocilia instead bend towards the shortest stereocilium, the distance between the stereocilia

gets smaller. The mechanically-gated ion channels cannot open and the channels that were previously opened when the cell was at rest, will now be shut. As a result, there is less potassium influx into the hair cell and thus less positive charge in the hair cell than there was at rest, leading to hair cell hyperpolarization.

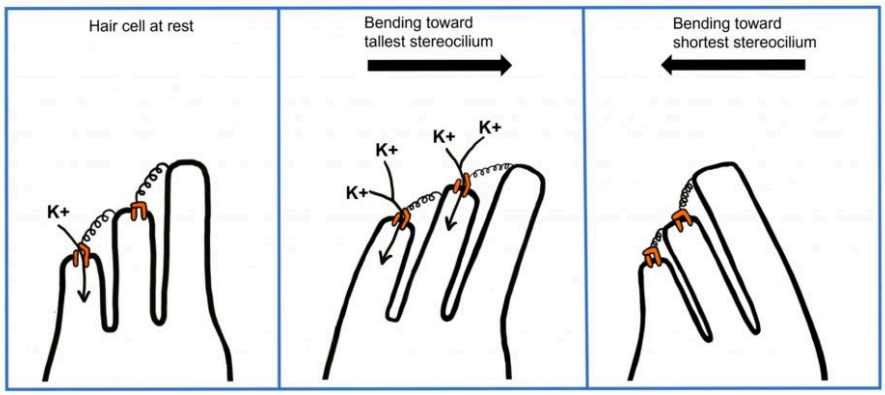

Figure 31.11 Hair cell at rest, in a depolarized state, and a hyperpolarized state. When the hair cell is at rest, some of the mechanically-gated ion channels at the tips of the stereocilia are open and some are closed (left). When the stereocilia are bent in the direction of the tallest stereocilium the linker proteins open the mechanically-gated ion channels. When mechanically-gated ion channels are open, potassium flows into the cell down its concentration gradient, allowing for a large influx of potassium ions leading to depolarization of the hair cell (middle). When the stereocilia are bent in the direction of shortest stereocilium the

linker proteins close the mechanically-gated ion channels, no longer allowing for potassium influx. This leads to the hair cell being hyperpolarized (right). 'Hair cell at rest, in a depolarized state, and a hyperpolarized state' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Hair Cell Signaling

Located within the hair cell are vesicles that are filled with glutamate (an excitatory neurotransmitter). When hair cells are depolarized, this causes the opening of **voltage-gated calcium channels** in the hair cell membrane. The influx of calcium will ultimately cause the vesicles full of glutamate to fuse with the hair cell membrane and release the glutamate into the synapse with the spiral ganglion cell.

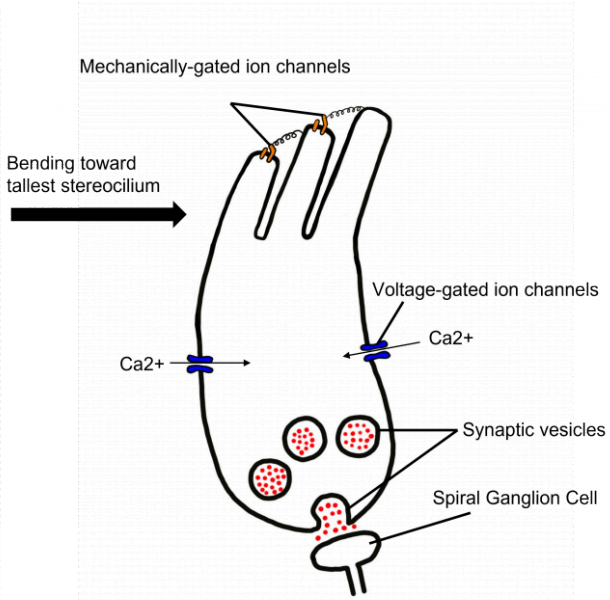

Figure 31.12. Depolarized hair cell. When the stereocilia bend in the direction toward the longest stereocilium, this stretches the linker proteins and opens the mechanically-gated ion channels at the tips of the stereocilia. Potassium flows into the cell, down its concentration gradient, depolarizing the hair cell. This change in membrane potential opens voltage-gated calcium channels. The influx of calcium into the hair cell causes synaptic vesicles to fuse with the membrane and release glutamate (red circles) into the synapse with the spiral ganglion cell. 'Depolarized hair cell' by Valerie Hedges is licensed under a Creative Commons Attribution-NonC

Spiral Ganglion Cell Innervation

Most of the spiral ganglion cells (>95%) collect information from the inner hair cells. In fact, one inner hair cell will synapse onto many different spiral ganglion cells. Whereas a small number of spiral ganglion cell (<5%) collect information from the outer hair cells. Thus, the inner hair cells are responsible for sending the majority of auditory signals from the cochlea into the brain for processing.

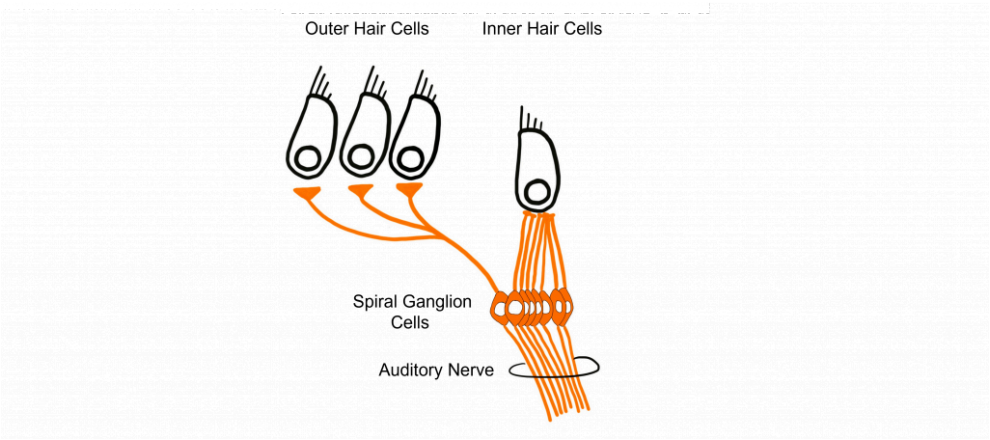

Figure 31.13. Hair cell innervation. Many spiral ganglion cells collect information from the inner hair cells, whereas only a small number of spiral ganglion cells collect information from the more numerous outer hair cells. The axons of spiral ganglion cell make up the Auditory nerve. 'Hair cell innervation' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Cochlear Amplifier

Although the outer hair cells are not responsible for the majority of the signal to the spiral ganglion cells, they serve another function. The outer hair cells function as the **cochlear amplifier** to increase the intensity of vibrations within the cochlea. It is estimated that the outer hair cells increase sound by anywhere between 20 and 80 dB.

There is a motor protein called **prestin** within the outer hair cell membrane. As a motor protein, prestin can mechanically contract and elongate within the outer hair cells, changing the length of the outer hair cell. The membrane of the outer hair cell shortens and lengthens with the movement of the

basilar membrane. When the basilar membrane is displaced upwards, this causes the prestin protein to contract, further shortening the length of the outer hair cell. When the basilar membrane is displaced downward, the prestin protein elongates the length of the outer hair cell. Essentially, the prestin within the outer hair cells amplifies the movement of the basilar membrane in both directions.

When the cochlear amplifier is functional, it doesn't only change the displacement of the basilar membrane, but it also has effects on the inner hair cells. The cochlear amplifier will cause the inner hair cells to bend more than they would without the amplifier present. In this way, although the outer hair cells have fewer direct signals to the spiral ganglion cells, they still contribute to the firing of the auditory nerve through their influence on the inner hair cells.

Hearing Loss

Many people experience permanent hearing loss, a decrease in volume by 25 dB or more. Hearing loss is divided into two categories.

Conductive hearing loss is a result of changes to the auditory system up to the oval window, such as a tumor in the ear canal, a perforation of the tympanic membrane, or changes in middle ear pressure (such as how everything sounds muffled while changing altitudes when an airplane takes off, for example).

Sensorineural hearing loss results from changes at the level of the inner ear or further up in the neural pathway, such as hair cell damage, a brain tumor, bacterial or viral infections, or exposure to various toxins or drugs.

The most common cause of hearing loss is excessive noise exposure. Although the acoustic reflex is capable of dampening the intensity of the incoming vibrations, prolonged exposure to high amplitude sound waves can still cause damage. Motorcycles, the maximum volume on headphones, or loud venues like concerts and clubs can produce sounds in the 95-110 dB range, which can cause some permanent hearing loss. Additionally, the acoustic reflex is not fast enough to minimize damage from sudden, loud sounds in excess of 120 dB, such as a

gunshot. All of these sources of acoustic trauma are preventable by wearing appropriate hearing protection, which can decrease the intensity of sounds by up to 30 dB. Old age is another common cause of hearing loss, likely because older people have had more accumulated exposure to noise.

An estimated 1 in 3 people older than 65 have hearing deficits. We are born with about 15,000 hair cells, but throughout the course of our life, many get damaged irreparably. Hair cells at the base of the cochlear are more sensitive to injury, so it is common for people to lose sensitivity to high-frequency sounds. The loss of these hair cells can begin as early as a person's 20s. Partial hearing loss can be reversed with the help of medical devices. A hearing aid is a processor that helps to filter out background noise, decrease pitch, and amplify incoming sounds.

A cochlear implant is a surgically-implanted device that receives incoming sound information and directly stimulates the auditory nerve via electrodes, bypassing the external components of the auditory system.

Key Takeaways

- The ear anatomy can be divided into the air-filled outer and middle ear, and the fluid-filled inner ear
- The cochlea within the inner ear is a chambered structure that contains the tonotopically-arranged basilar membrane and the Organ of Corti.
- Sounds displace the basilar membrane and bend hair cells in different directions, causing either depolarization or hyperpolarization depending on the direction of movement

- Outer hair cells and inner hair cells are differentially innervated, with many more spiral ganglion cells collecting information from the inner hair cells than the outer hair cells
- The outer hair cells are called the 'cochlear amplifier' due to their ability to contract and 'amplify' the movement of the basilar membrane, thus allowing more signals to the inner hair cells

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://openbooks.lib.msu.edu/introneuroscience1/?p=625#h5p-39

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32.

AUDITORY SYSTEM: CENTRAL PROCESSING

All sensory systems follow the same general path of communication into our nervous systems and awareness. First, the incoming signal must reach a that can change its electrical properties in response to the stimulus. Then, that information initiates a series of signals into the CNS, reaching structures such as the thalamus, primary sensory cortical areas, and finally, higher order perception. Although there are several sensory components throughout our body that detect these signals, there are no sensory receptors in our central nervous system. We previously saw this pattern for the visual system, and now we'll see it mirrored in many ways by the auditory system. For the auditory system, following the activation of hair cells within the cochlea, sound information is transmitted to brain structures including the thalamus and cortex for processing to be perceived as sounds.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Central Auditory Pathway

Hair cells within the cochlea form glutamatergic synapses onto spiral ganglion cells. The axons of these neurons make up the **vestibulocochlear nerve (Cranial nerve VIII)**. Neurons project to and synapse on neurons within the **ipsilateral cochlear nuclei of the medulla**. Because the medulla neurons only process sound from one ear, these cells are referred to as **monaural**. (one ear).

The cochlear nuclei neurons within the medulla have axons that split and synapse on both the **ipsilateral** and **contralateral superior olive within the pons**. The superior olive is the first structure

that processes sound information from both ears, so it is referred to as binaural. All remaining structures in the central auditory pathway process sounds from both ears, and thus are also **binaural**.

From the pons, neurons travel via the **lateral lemniscus** (a lemniscus is a collection of axons) and then synapse on the **inferior colliculus of the midbrain tectum**. Signaling within the inferior colliculus is important for interactions between multiple sensory inputs and a motor response. These inferior colliculus neurons are particularly responsive to biologically-relevant sounds, such as unexpected noises, which may signal an approaching predator. Processing in the inferior colliculus helps the animal focus their attention on these stimuli.

The inferior colliculus then conveys that auditory information into the **medial geniculate nucleus**, one of the nuclei of the thalamus. These thalamic neurons then send projections into the **primary auditory cortex** located dorsally in the temporal lobe.

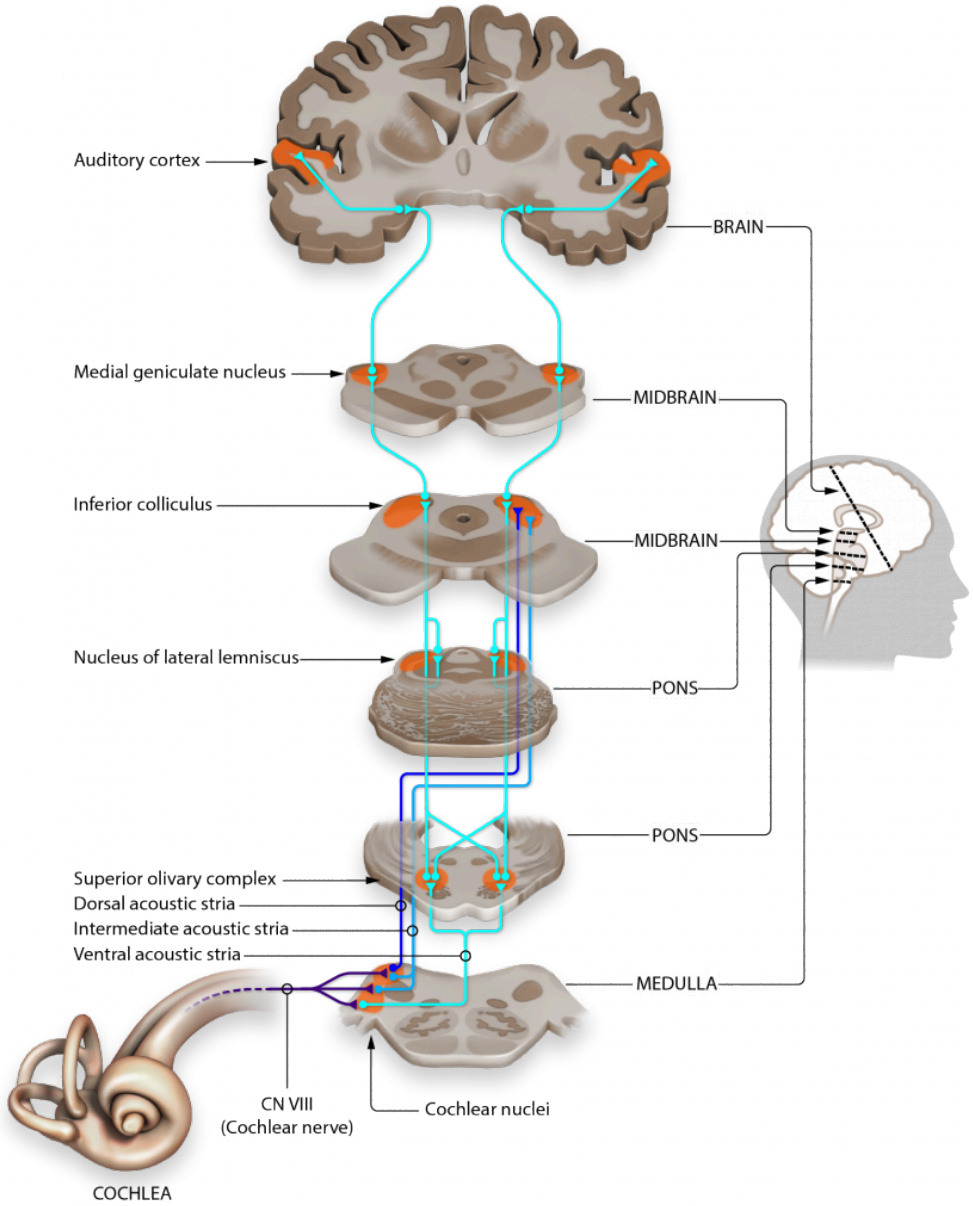

Figure 32.1. Central auditory pathway. Cranial nerve VIII carrying auditory information synapses onto cells of the ipsilateral cochlear nuclei of the medulla. The cochlear nuclei neurons within the medulla have axons that split (shown in light blue) and synapse on both the ipsilateral and contralateral superior olivary complex within the pons. Neurons then travel via the lateral lemniscus to the inferior colliculus. The inferior colliculus then conveys auditory information into the medial geniculate nucleus of the thalamus. The thalamic neurons then send projections into the primary auditory cortex in the temporal lobe.

Tonotopy

The structures responsible for the central processing of sound, including the basilar membrane, the spiral ganglion, the cochlear nucleus, the inferior colliculus, and the auditory cortex are **tonotopically** organized, meaning that adjacent physical areas are responsible for conveying information from adjacent frequencies. For example, the hair cells that respond most to 440 Hz vibrations are right next to cells that respond maximally to 441 Hz, but far away from cells that respond most to 14,000 Hz. Likewise, in the auditory cortex, the cells that best process 440 Hz are adjacent to those that best process 441 Hz, but far away from those that maximally respond to 14,000 Hz.

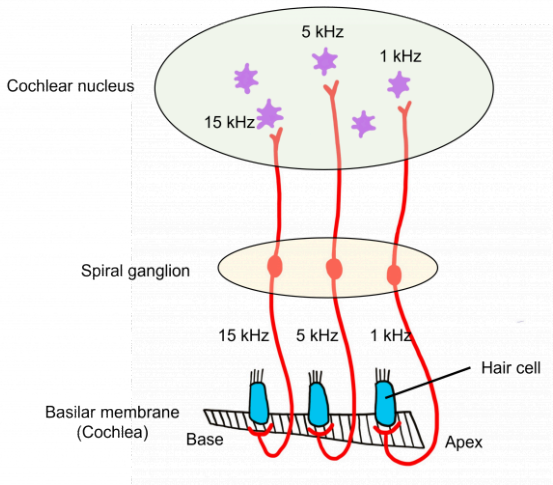

Figure 32.2. Tonotopy within the auditory system. Structures throughout the central auditory pathway are tonotopically organized. Hair cells within the basilar membrane respond to different frequencies, with hair cells located nearer the base responding to high frequency sounds and hair cells located nearer to the apex responding to low frequency sounds. This organization is conserved through the spiral ganglion cells and within the cochlear nucleus, with adjacent physical areas responsible for conveying information from adjacent frequencies. 'Tonotopic Organization' by Valerie Hedges is licensed under a Creative Commons

Auditory Cortex

The auditory cortex (also called A1) is located within the temporal lobes in both hemispheres of the brain. Similar to the visual cortex, the auditory cortex is also made up of 6 layers of cells that have columnar organization. Each cortical column responds to a specific frequency. The auditory cortex is **tonotopically** organized like the other structures in the central auditory pathway. It is organized as isofrequency bands, like strips, that respond to relatively the same frequency.

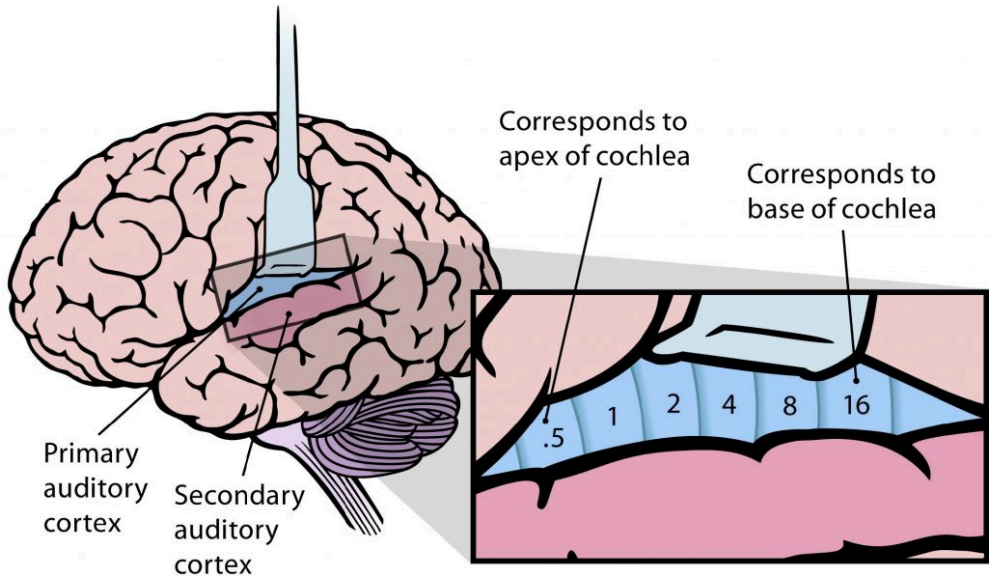

Figure 32.3. Primary auditory cortex. The primary auditory cortex is located within the temporal lobes of the brain. It is tonotopically organized, maintaining the tonotopic organization of the cochlea, into isofrequency bands of cortex that each respond to relatively the same frequency of sound (frequencies shown in kHz).

Sound Localization

Sound localization is an important function for animals. We can localize sounds in the horizontal plane and the vertical plane via different mechanisms.

Localizing Sounds in the Horizontal Plane

When considering how we localize sounds in the horizontal plane, we assume that the sound does not change in elevation. As humans, our ears are located on the sides of our heads, which means that sounds will arrive at our ears at different times depending on the origin of the sound. The time between when sound reaches the first ear until the time it reaches the second ear is referred to as the **interaural time difference** (ITD).

If we assume that there are 20 cm between the two ears of a human, then we can determine the ITD for the left ear. If a sound is coming directly from the right, then there will be a 0.6 msec ITD for the left ear. If sounds are coming from directly in front of a person, then the time that it takes to reach the right ear will be exactly the same as the time that it takes to reach the left ear, thus there is no ITD (0 msec). If we consider an intermediary angle of sound origin coming from 45° we can determine that the ITD will be 0.3 msec, exactly between the values from when sounds originate directly in front and directly to the right.

In order for us to locate sounds in the horizontal plane, we need a brain structure that can process information from both ears. Recall from the central auditory pathway that the first structure that processes information from both ears (**binaural**) is the superior olive.

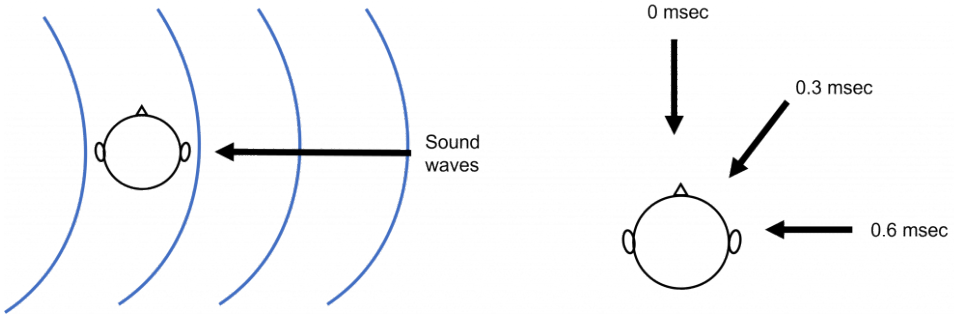

Figure 32.4. Sound localization in the horizontal plane. Sounds in the horizontal plane reach the ears at different times creating an interaural time delay between the ears. When sound waves are coming from the right, the sound waves reach the right ear before they reach the left ear. If we assume that there is a 20 cm distance between the ears, then the interaural time delay for the left ear when sounds are coming directly from the right, will be 0.6 msec. Sounds that come from directly in front of the head will reach both ears simultaneously, and thus there will be a 0 msec interaural time delay. A sound originating at an intermediate angle, directly between in front and to the right,

will have a 0.3 msec interaural time delay for reaching the left ear. 'Sound localization in the horizontal plane' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

One of the primary functions of the superior olive is to help us figure out if a sound originates from the left or the right side of our head by determining this **interaural time difference**. Let's imagine a sound wave originating from the left. The sound will interact with the left ear before it interacts with the right ear. When the sound interacts with the left ear, it will activate the hair cells in the left cochlea, the left spiral ganglion, and then the left cochlear nucleus (all monaural structures). The left cochlear nucleus cells will generate action potential that will travel along their axons toward the superior olive.

After a short delay, the sound wave will interact with the right ear, thus activating the hair cells of the right cochlea, the right spiral ganglion, and the right cochlear nucleus. The right cochlear nucleus will then generate its own action potential that will travel toward the superior olive. While this is occurring, the action potential generated by the left cochlear nucleus has traveled further along the left cochlear nucleus cell axon.

The action potentials generated from both the left and right cochlear nucleus will converge within the superior olive (a binaural structure). The axons of the cochlear nucleus cells have different length paths before they reach the neurons of the superior olive, allowing them to act as '**delay lines**'. The neurons of the superior olive act as **coincidence detectors**. When the action potentials arrive at one superior olive neuron at the same time, the postsynaptic potentials will **summate**, leading to maximal activation of this superior olive neuron and the generation of an action potential. If the action potentials do not arrive at the same time, then summation will not occur. The specific superior

olive neuron that experiences the summation translates to where in the horizontal plane the sound originated, allowing us to localize sounds.

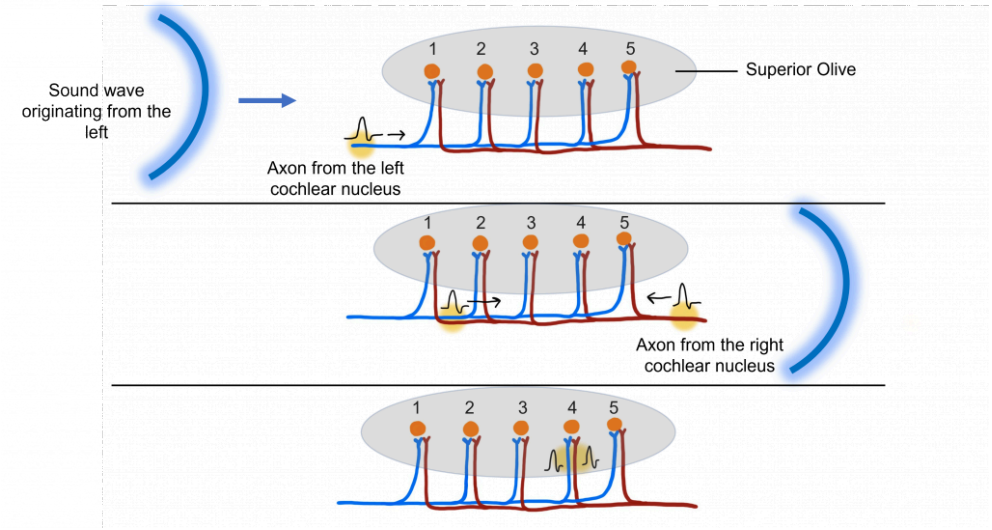

Figure 32.5. Interaural time differences are determined by the superior olive. When a sound is coming from the left, the sound will activate the structures of the left ear. An action potential will be fired by the left cochlear nucleus neurons (shown in blue) that will be carried down to the superior olive (top panel). The left cochlear nucleus neuron axon branches to synapse on the cells of the superior olive, labeled 1-5 for this example. The path that the action potential will travel to reach each of these cells is a different length, thus it will take different amounts of time for the action potential to travel to each superior olive cell. After a brief time, the sound wave will reach the right ear and

activate the structures of the right ear (middle panel). The action potential generated by the neurons of the right cochlear nucleus will travel down their axons (shown in red). While this is occurring, the action potential that is coming from the left is still traveling down the blue axons. When the action potentials arrive at the same cell simultaneously from both the left and right cochlear nucleus, the postsynaptic potentials will summate and maximally excite cell number 4 in this example (bottom panel). 'Superior Olive' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Humans are better at localizing sounds in the horizontal plane when we can detect the onset of the sound. However, when there are continuous tones, we need to utilize different ways to localize sounds in the horizontal plane. We can use interaural intensity (loudness) differences to localize sounds when they are continuous. Sounds are louder the closer you are to them. A difference in volume between what one ear and the other ear perceives can also be evaluated by neurons in the superior olive.

Interaural intensity differences are also useful in localizing high frequency sounds in the horizontal plane. At high frequencies (that have a wavelength shorter than the distance between our ears), the head creates a '**sound shadow**' for the ear opposite the sound. When a high frequency sound is coming directly from the right side, the head creates a sound shadow for the left ear, making the sound louder for the right ear than it is for the left ear. Again, if a high frequency sound originates from directly in front of a person, then the sound will reach the ears with the same intensity, as the sound shadow will be behind the head. When a high frequency sound originates from an intermediate angle, then there will be intermediate intensity differences between the two ears.

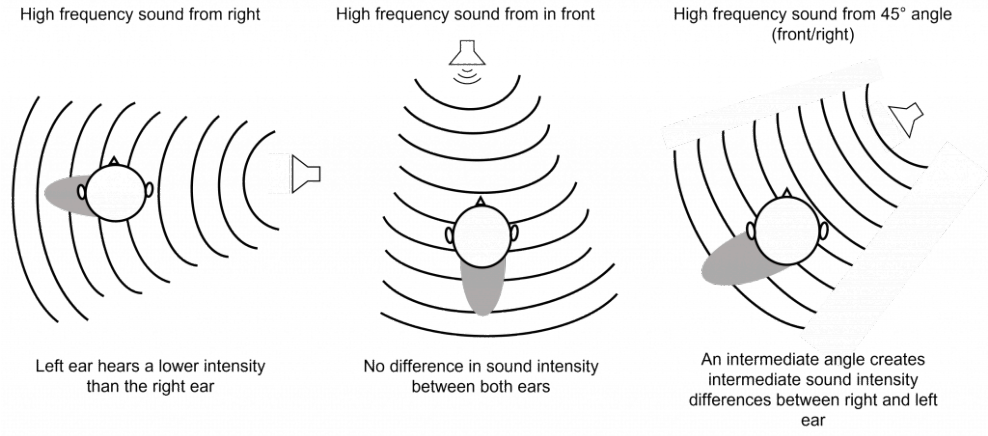

Figure 32.6. Interaural intensity differences. High frequency sounds that have a wavelength shorter than the distance between the ears will cause the head to create a sound shadow. A sound shadow will decrease the intensity (volume) of the sound in the ear opposite to the sound origin. When a high frequency sound is coming from the right, the head will create a sound shadow for the left ear, causing the left ear to hear a lower intensity sound. When a sound comes from directly in front of a person, the sound shadow will be behind the head and the intensity of the sound will be the same between the left and right ear. Sounds that come from an intermediate

angle will cause an intermediate intensity difference between the ears. 'Interaural intensity differences' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Low frequency sounds do not create a sound shadow like high frequency sounds. This is because the wavelength of low frequency waves (e.g. 200 Hz) have a wavelength longer than the width of the distance between the ears, so the intensity will be the same at both ears but the sound will arrive at the two ears at different times (**interaural time difference**).

High frequency sounds (e.g. 7000 Hz) have a wavelength that is shorter than the width of the distance between the ears, which is why the head creates a sound shadow that will alter the intensity of the sound between the two ears.

Interaural time difference is used for low frequency sounds in the 20-2000 Hz range, whereas **interaural intensity difference** is used for high frequency sounds in the 2000-20,000 Hz range. Together these two processes are called the **duplex theory of sound localization**.

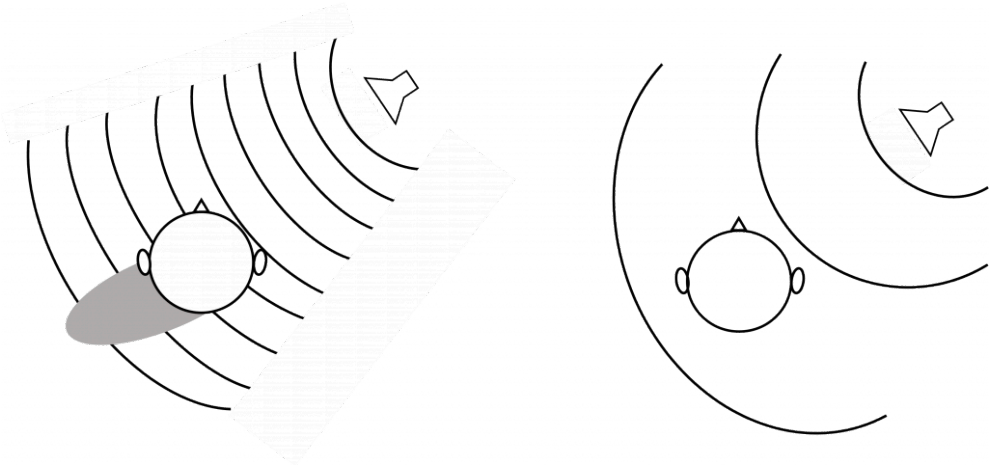

Figure 32.7. High frequency versus low frequency sound localization in the horizontal plane. High frequency sounds have a shorter wavelength and cause the head to create a sound shadow that will make the sounds different intensities between the two ears (left image). Low frequency sounds have a longer wavelength that the head does not interfere with, thus the head does not create a sound shadow. Instead, the sound waves reach the ears at different times, creating an interaural time difference (right image). 'High frequency versus low frequency sound localization' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-Share

Localizing Sound in the Vertical Plane

Because both ears (in humans and most non-humans) are at the same height, sounds in the vertical plane that change in elevation alone can be difficult to localize. This is because the interaural time difference and interaural intensity between the two ears remains constant as elevation changes. This is why sometimes people and animals tilt their heads to try to hear better.

The structure of our pinna is important in vertical localization. Recall that our **pinna** is the external portion of our ear that funnels sounds into the auditory canal. For sound localization, the pinna has many ridges and folds, which cause sound waves to be reflected off these bumps and take different paths on their way to the auditory canal. The pinna of humans is relatively fixed in location, but other animals (like dogs) have the ability to move their pinna to better localize sounds.

Interestingly, not all animals have ears that are located at the same height on their head. Some species of owls have ear openings at different heights on their heads, increasing their ability to localize the source of a sound on the vertical axis. By having ears at different heights, the owls are able to use interaural time differences in the vertical plane because the sound will reach their ears at different times.

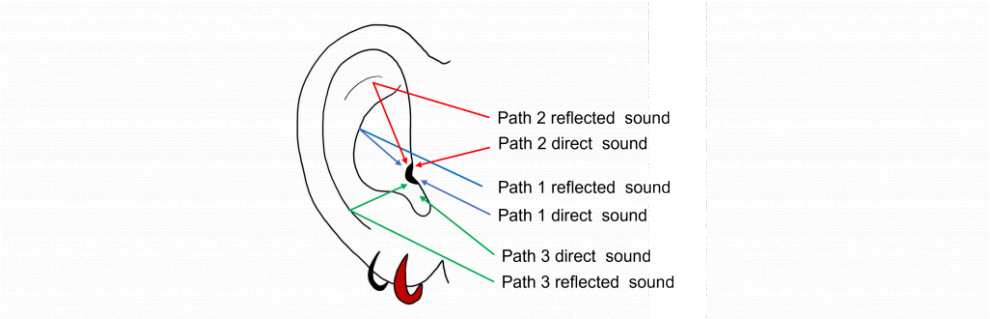

Figure 32.8. Vertical plane sound localization. The pinna is critical for sound localization in the vertical plane. Sounds take different paths and are reflected around the folds and bumps of the pinna that help us localize sounds in the vertical plane. The human pinna has a fixed location which decreases our ability to locate sounds in the vertical plane compared to species that have the ability to move their pinna. 'Vertical plan sound localization' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Key Takeaways

- Cranial nerve VIII carries auditory information into the cochlear nucleus, superior olive, inferior colliculus, medial geniculate nucleus of the thalamus, and finally to the primary auditory cortex.
- Structures of the central auditory pathway are tonotopically organized.
- In the horizontal plane, low frequency sounds are localized through interaural time differences and high frequency sounds are localized through interaural intensity differences.
- The superior olive is responsible for calculating interaural time differences.
- Sound localization in the vertical plane is more difficult for humans, but is aided by the structure of the pinna.

Test Yourself!

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33.

VESTIBULAR SYSTEM

When we tilt our head to the side, or look up and down, that movement information is conveyed to our brain using the vestibular system. The vestibular system is a sort of three-dimensional compass that can detect head movement, and that information helps us figure out how our head is oriented and how to balance ourselves in changing conditions. The vestibular system is made up of two structures that are intimately tied in with the anatomical features of the inner ear.

Adjacent to the cochlea within the inner ear is a structure called the vestibular labyrinth made up of the **otolith organs** (**saccule and utricle**) and the **semicircular canals**.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Otolith Organs

Next to the cochlea and within the vestibular labyrinth are two membranous sacs, the **saccule** and the **utricle**. Collectively, these structures are called the **otolith organs** and are responsible for determining gravity through the tilt of the head and **linear acceleration**. These structures are centrally located within the vestibular labyrinth.

Due to their differences in structure, the two otolith organs have slightly different functions. The saccule is more sensitive to vertical movements, like when you are standing in a moving elevator. The utricle is more responsive to horizontal movements, such as when driving.

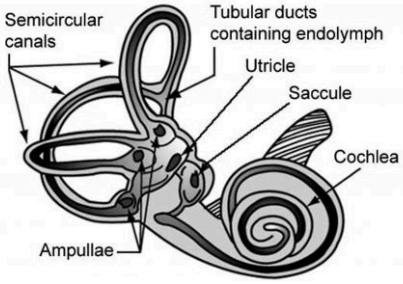

Figure 33.1 Structures of the inner ear. The semicircular canals and otolith organs (utricle and saccule) are part of the vestibular labyrinth that functions in balance. The cochlea is also located within the inner ear and has auditory system function.

Similar to the other inner ear structure, the cochlea, the structures of the vestibular labyrinth also contain hair cells. The hair cells located within the otolith organs are biologically similar to the hair cells in the cochlea. These hair cells have stereocilia that extend into a gelatinous cap that contains **otoconia**, which are small crystals of calcium carbonate. The otolith organs are important in sensing gravity. Tilting the head causes the otoconia to move (due to gravity), which will push the hair cell stereocilia and cause them to bend.

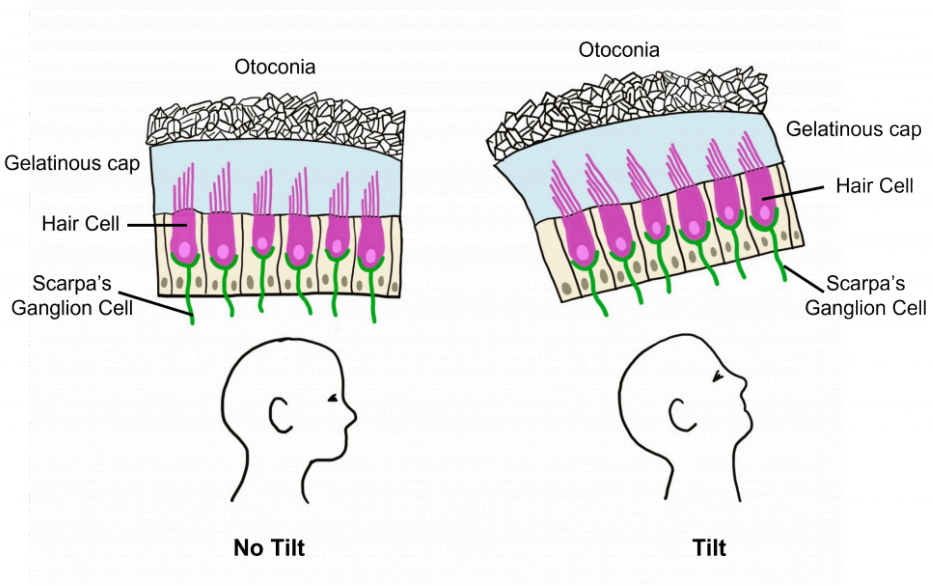

Figure 33.2. Otolith organ hair cells. Within the otolith organs (the saccule and the utricle) there are hair cells that have stereocilia that extend into a gelatinous cap. Over the gelatinous cap are otoconia (calcium carbonate crystals). When the head is tilted, the movement of the otoconia mechanically bends to stereocilia. The hair cells of the otolith organs send their signals to Scarpa's ganglion axons that transmit vestibular information into the central nervous system. 'Otolith organ hair cells' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

The tallest stereocilium (singular of stereocilia) is called the kinocilium. Similar to the function of hair cells within the cochlea, movement that bends the stereocilia toward the kinocilium results in depolarization due to potassium influx through open mechanically-gated ion channels within the tips of the stereocilia. Movement that bends the stereocilia away from the kinocilium causes the mechanically-gated ion channels to close, decreasing potassium influx and causing hyperpolarization.

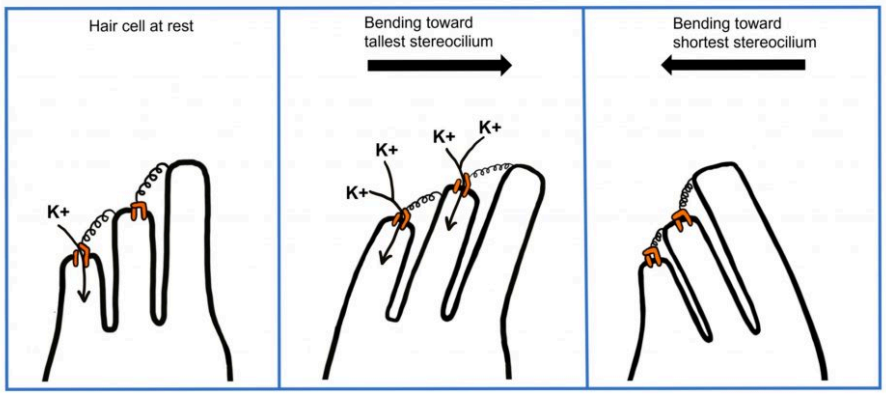

Figure 33.3. Hair cell at rest, in a depolarized state, and a hyperpolarized state. When the hair cell is at rest, some of the mechanically-gated ion channels at the tips of the stereocilia are open and some are closed (left). When the stereocilia are bent in the direction of the tallest stereocilium the linker proteins open the mechanically-gated ion channels. When mechanically-gated ion channels are open, potassium flows into the cell down its concentration gradient, allowing for a large influx of potassium ions leading to depolarization of the hair cell (middle). When the stereocilia are bent in the direction of shortest stereocilium the

linker proteins close the mechanically-gated ion channels, no longer allowing for potassium influx. This leads to the hair cell being hyperpolarized (right). 'Hair cell at rest, in a depolarized state, and a hyperpolarized state' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Semicircular Canals

The other major structure of the vestibular labyrinth are the **semicircular canals**. The semicircular canals are the structures that are responsible for detecting head rotation and **angular acceleration**.

Anatomically, the semicircular canals are a series of three arch-shaped membranous tubes within the vestibular labyrinth, each one oriented at a right angle to each other. Because of this shape, the semicircular canals sense and convey information about any direction of head movement.

These semicircular canals are filled with **endolymph**, the same potassium-rich solution that is in the cochlea that is important for auditory sensation. At the end of each of the three canals is a small swelling called the **ampulla**. Contained in the ampulla is a gelatinous membrane called the **cupula**. Here, hair cells extend stereocilia into the cupula. The tallest stereocilium is again referred to as the kinocilium.

When we rotate our head, the endolymph within the semicircular canals has a delay in movement

due to inertia, and as a result the endolymph will move the cupula in the opposite direction of head movement. The physical movement of the cupula also pushes the cilia of the hair cells within the cupula. As previously discussed in the cochlea and the otolith organs, these hair cells also have mechanically-gated ion channels located in the tips of the stereocilia and function in the same way, with deflection towards the kinocilium resulting in depolarization and deflection away from the kinocilium resulting in hyperpolarization.

When we stop rotating, the endolymph within the semicircular canals continues to move for a brief period of time due to inertia (which contributes to our feeling of dizziness when we stop rotating).

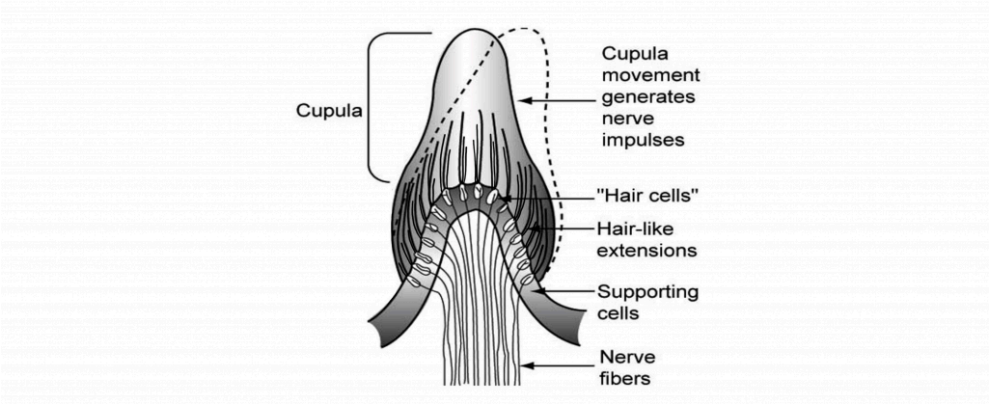

IMAGE 33.4. Semicircular canal cupula and hair cells. The hair cells of the semicircular canals are located with the ampulla of the semicircular canals. A gelatinous cupula covers the hair cell stereocilia. When the head rotates, the endolymph within the semicircular canals pushes the gelatinous cupula causing it to deflect in the opposite direction of head movement. When the cupula moves, the hair cell stereocilia within the cupula are bent, which causes either depolarization or hyperpolarization depending on the direction of movement.

Central Vestibular Pathways

The vestibular system is responsible for coordinating our balance through our head and body

movements. As such, the neurons of the vestibular system signal to motor neurons that adjust head, eye, and body position.

The vestibular hair cell information is passed to the brain via excitatory synapses onto a branch of the vestibulocochlear nerve (CN VIII). The cell bodies of these neurons are in **Scarpa's ganglion**. These axons send projections to several brain areas, notably the cerebellum, which is a structure critically important for balance. CN VIII also projects into the vestibular nuclei of the medulla. From there, neurons signal to areas of the thalamus that ultimately control motor areas of the face, extraocular motor neurons that ultimately control eye movement, and the spinal cord that is responsible for limb and neck motor movements to help maintain body and head position.

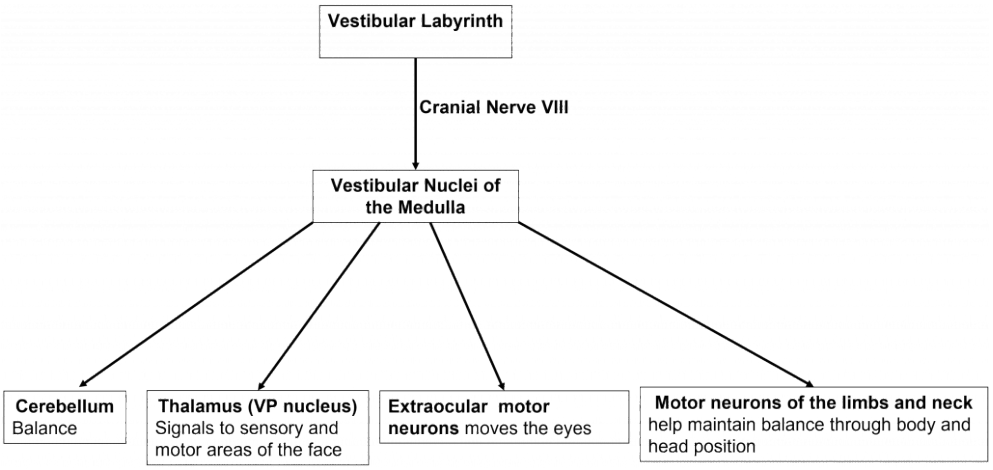

IMAGE 33.5. Central vestibular pathways. Vestibular information is carried by Cranial Nerve VIII (the vestibulocochlear nerve) to the vestibular nuclei within the medulla. From the medulla, vestibular information is conveyed to multiple structure to control vestibular sensation. Connections to the cerebellum are important in maintaining balance. Other connections that are routed through the ventral posterior (VP) nucleus of the thalamus is important in sensation and motor activity of the face. Connections to the extraocular motor neurons are important in orienting the eyes to maintain balance. Lastly, connections to motor neurons that control the

limb and neck muscles help maintain body balance and our head position. 'Central vestibular pathways' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Key Takeaways

- The vestibular labyrinth is located within the inner ear and functions in our sense of balance.
- The structures of the vestibular labyrinth are the otolith organs (the saccule and utricle) and the three semicircular canals.
- The vestibular labyrinth structures also contain hair cells similar to the hair cells within the auditory system. Bending the stereocilia in the direction of the tallest stereocilium results in depolarization of the hair cell and bending in the direction of the shortest stereocilium results in hyperpolarization.
- The vestibular labyrinth structures signal to multiple brain areas to control head movement, eye movements, and balance.

Test Yourself

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34.

GUSTATORY SYSTEM

Your gustatory system, which mediates your sense of taste, helps you walk the line between health and illness. It acts as a short-range detection system, as you must actually put something in your mouth to taste it.

The gustatory system guides you towards foods that are energy rich and keeps you away from food that could make you sick. Humans can perceive five basic tastes: salty, sour, bitter, sweet, and umami. These specific taste modalities all support this balance. Sweet foods taste good because foods rich in sugar, such as fruit and wheat, contain large amounts of usable energy, and humans have evolved to find these foods appetizing. In contrast, toxic compounds are often bitter, causing you to respond with feelings of disgust. Salty taste indicates a substance with high salt content and sour taste indicates an acidic food, and umami taste indicates a high protein food.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Some of our taste is innate, like sweetness, whereas other tastes are learned like bitterness. This explains why many individuals do not initially like the taste of coffee, and why many individuals prefer to have their coffee with sugar when they first start drinking it. Our tastes can also be modified by our dietary needs, like craving a salty food.

Organs of Taste

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 are sensitive to food and play a role in taste perception.

Other sensory information is also tightly linked to our sense of taste. Smell is important in our sense

of taste as odorant compounds from food can reach odor receptors in the nasal cavity. How a food looks (sense of vision) is also important to how it tastes. The texture and temperature of the food is also important (somatosensory information). Even a sense of pain, related to the spicy level of the food relates to our sense of taste.

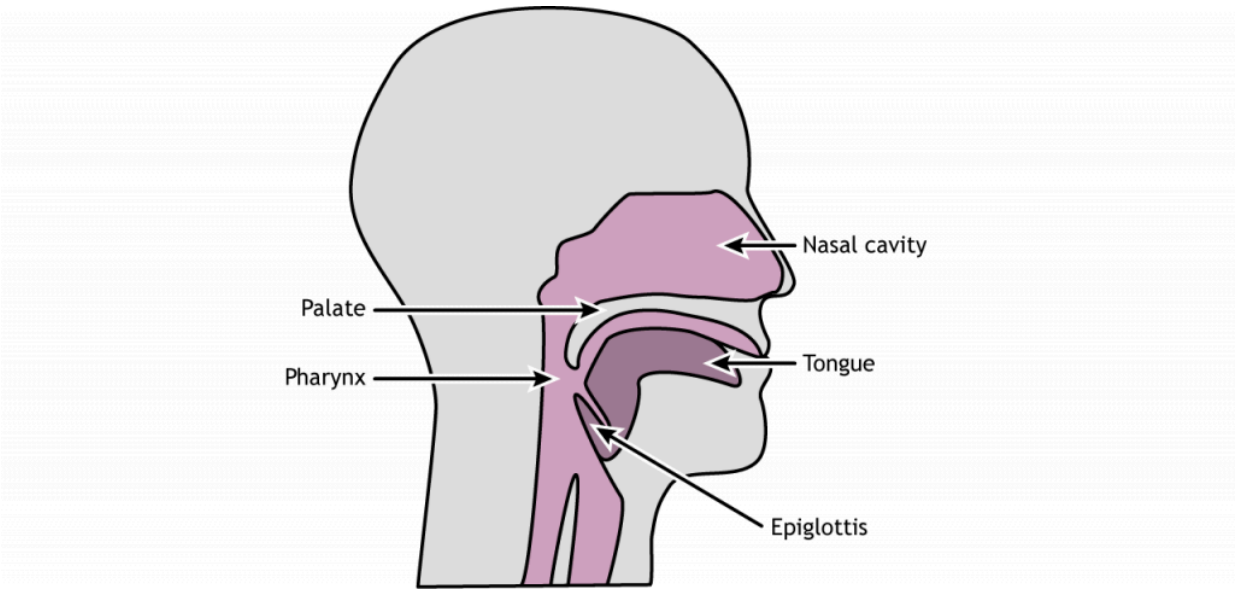

Figure 34.1. The tongue is the primary location for taste receptors cells, but receptors are also located along the palate, pharynx, and epiglottis. Additionally, airborne compounds from food can reach odor receptors in the nasal cavity. The sense of smell plays an important role in the perception of flavor. 'Throat Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

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 and release neurotransmitters on afferent axons that send taste perception information to the brain.

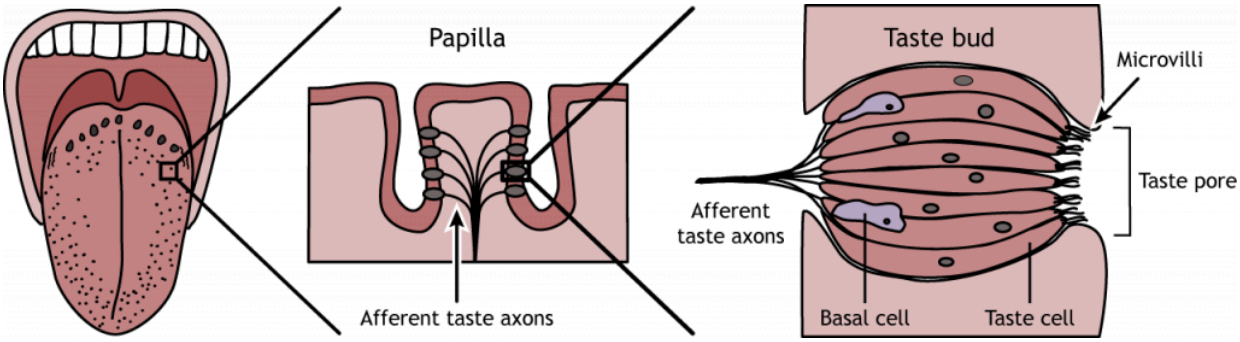

Figure 34.2. The visible bumps on the surface of the tongues are papillae that house taste buds. Taste buds are made up of taste cells and basal cells. The taste cells synapse on afferent axons that send information to the central nervous system. Tastants in food access the taste cells via the taste pore, where the food particles interact with the microvilli of the taste 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 entire surface. However, some regions of the tongue have a slightly lower threshold to respond to some tastes over others. The tip of the tongue is the region most sensitive to sweet, salt, and umami tastes. The sides are most sensitive to sour, and the back of the tongue to bitter tastes.

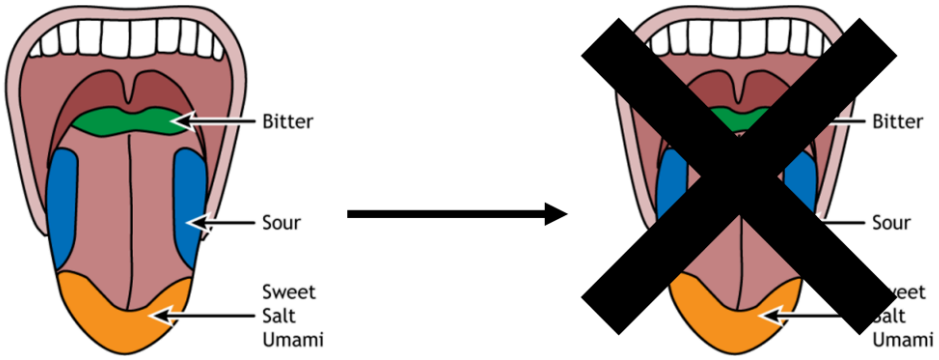

Figure 34.3. Although all tastes can be perceived across the entire tongue, sensitivity levels vary for each taste. The front of the tongue has the lowest threshold for sweet, salt, and umami tastes; the side of the tongue has the lowest threshold for sour tastes, and the back of the tongue has the lowest threshold for bitter tastes. It is inaccurate to map each of the tastes to a single region of the tongue because each area of the tongue is capable of sensing each type of taste.

Taste transduction

Currently, it is believed that humans sense five basic tastes: Salty, sour, sweet, bitter, and umami. Salty and sour taste are both mediated by ionotropic taste receptors, while sweet, bitter, and umami taste are mediated by metabotropic taste receptors.

Salt

Salt taste is mediated by the presence of epithelial 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.

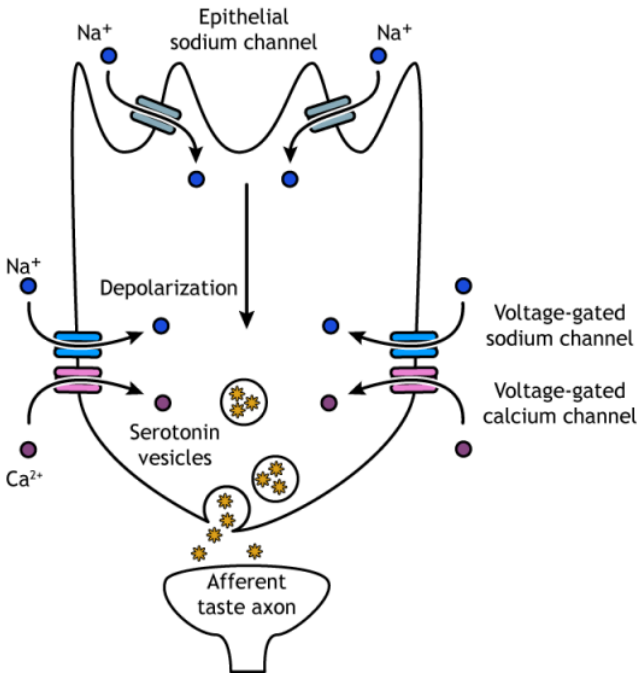

Figure 34.4. When salty foods are ingested, the sodium from the food enters the taste cell via open epithelial sodium channels. The resulting depolarization opens voltage-gated sodium and calcium channels, leading to release of serotonin onto the afferent taste axon. 'Salt Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Salty foods elicit a biphasic response depending on concentration. Foods cooked with a low concentration of salt taste bland and are not very appetizing; however, high salt concentrations elicit a strong aversive reaction – imagine how disgusted you were when you first tried to cook and were overly generous with the salt!

Additionally, the appeal of salt at a given moment depends on our body's need for salt at the

time. Several hormones such as the appetite-stimulating hormone ghrelin contribute to regulating the concentration of salt in the body by mediating Na+ absorption. Current salt levels can also impact appetite for salt. For example, in chronically-sodium deprived animals, high salt solutions are highly rewarding.

Why are we so sensitive to the taste of salt? As it turns out, both sodium and chloride are essential nutrients. They are critical for maintaining blood volume and pressure, for regulating body water, for maintaining muscle contractions, and mediating action potentials.

Sour

Foods taste sour because of their acidity, and when acids are present in water, they produce hydrogen ions (protons). Therefore, a sour food has high acidity and a high concentration of hydrogen ions, thus a low pH. The exact mechanism for sour taste transduction has 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 increase in intracellular calcium causes release of serotonin into the synapse.

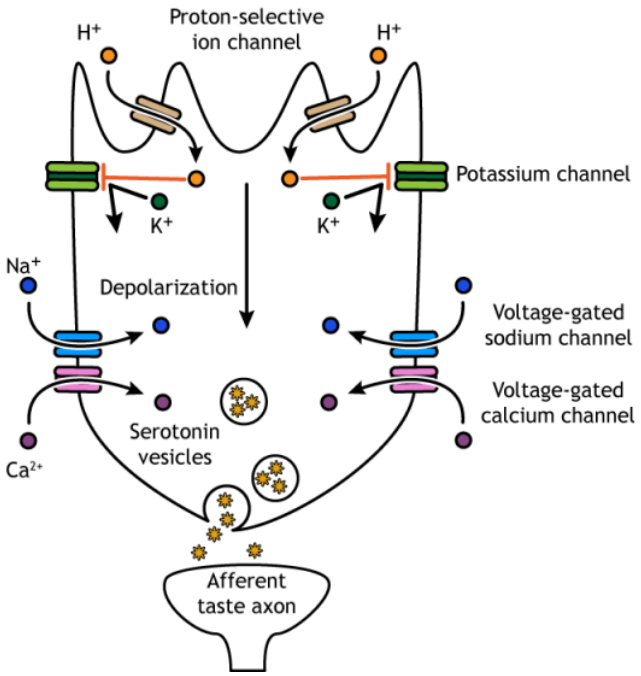

Figure 34.5. When sour foods are ingested, the protons from the acid enter the cell via open ion channels. The protons then block potassium channels. The resulting depolarization opens voltage-gated sodium and calcium channels, leading to release of serotonin onto the afferent taste axon. 'Sour Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The purpose for our ability to sense acids in our food is under debate. Sour tastants do not inherently provide any nutritional value, except in the case of Vitamin C. Humans and other higher primates cannot synthesize Vitamin C on their own, so it's possible that we evolved to find a combination of sourness and sweetness attractive enough to consistently consume Vitamin C-rich fruits. However, sour can be aversive, motivating us to avoid spoiled or unripe foods that might contain pathogens.

Bitter

Bitter, sweet, and umami compounds all activate taste receptor cells via G-protein coupled receptors. The bitter receptors are from the T2R family of receptor proteins; humans have over 25. Each taste cell can express most or all of the different receptor types, allowing for the detection of numerous molecules, which is important when wanting to avoid dangerous substances like poisons and toxins.

Activation of the G-protein receptor activates phospholipase C, which in turn increases production of the second messenger inositol triphosphate. Inositol triphosphate causes the release of calcium from intracellular stores. Calcium causes the opening of ion channels, allowing the influx of sodium. These ion changes depolarize the cell and cause ATP-specific channels to open, allowing ATP to flow out of the cell and enter the synapse to act on the afferent taste axon by binding to purinergic receptors on the postsynaptic cell.

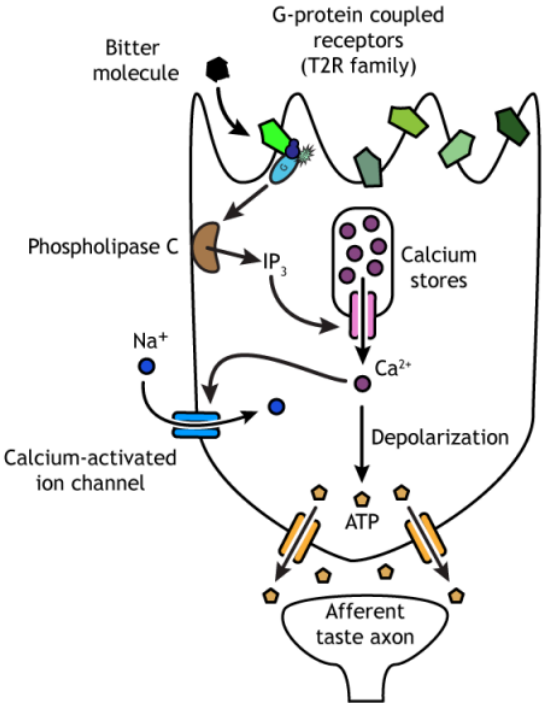

Figure 34.6. Bitter foods activate G-protein receptors, which initiate the phospholipase C second messenger system. IP3 releases calcium from intracellular stores, and the calcium opens ion channels that allow sodium influx. The resulting depolarization causes ATP release onto the afferent taste axon. 'Bitter Taste Transduction' 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 G-protein coupled dimers, meaning two separate proteins function together as one. The receptors are encoded by 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 release calcium from intracellular stores and increase the influx of sodium. 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.

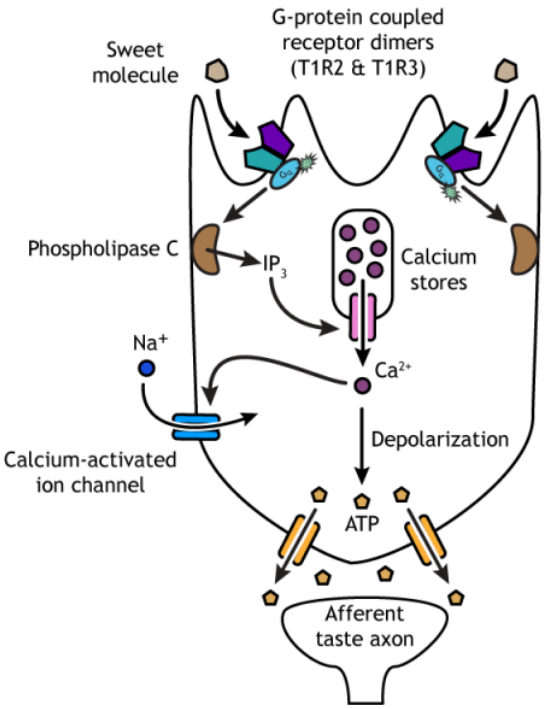

Figure 34.7. Sweet foods activate G-protein receptor dimers, which initiate the phospholipase C second messenger system. IP3 releases calcium from intracellular stores, and the calcium opens ion channels that allow sodium influx. The resulting depolarization causes ATP release onto the afferent taste axon. 'Sweet Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sugars like glucose and sucrose are essential for the survival of a species, since they are the main source of cellular energy. Therefore, our ability to detect sweetness plays a central role in regulating how much energy we take into our bodies. Of all the taste modalities, sweet is the strongest driver of food selection.

Umami

Umami is the taste of savory deliciousness, such as the taste of rich chicken broth, a perfect medium-rare steak, or aged cheese. The word is derived from the Japanese word umai, which means "delicious."

Umami is signaled when a molecule of glutamate (chemically the same as the neurotransmitter) binds to T1R1/T1R3 receptors.

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.

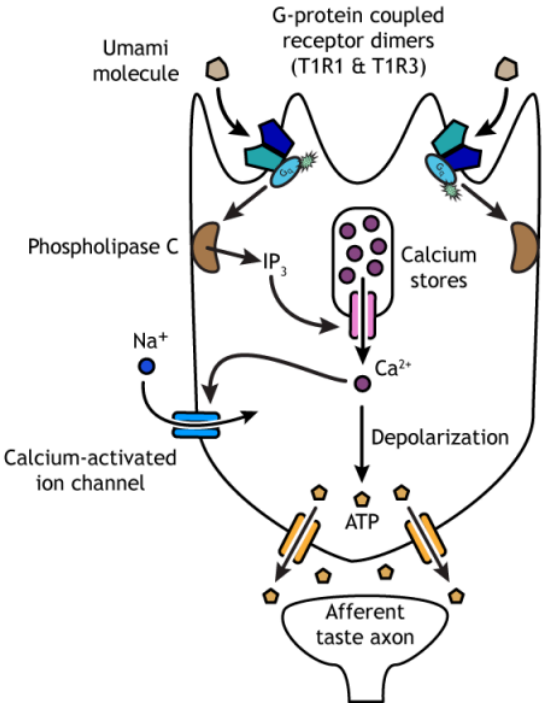

Figure 34.8. Umami compounds activate G-protein receptor dimers, which initiate the phospholipase C second messenger system. IP3 releases calcium from intracellular stores, and the calcium opens ion channels that allow sodium influx. The resulting depolarization causes ATP release onto the afferent taste axon. 'Umami Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Through evolution, we have come to prefer the taste of umami because glutamate is a byproduct of cooking food. Cooking foods changes their chemical properties, thereby improving digestion, reducing toxicity, and increasing absorption of nutrients. Glutamate is one of the byproducts in the process of heating a food, and so it benefits us to appreciate these flavors.

Coding Properties of Taste

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. Most 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.

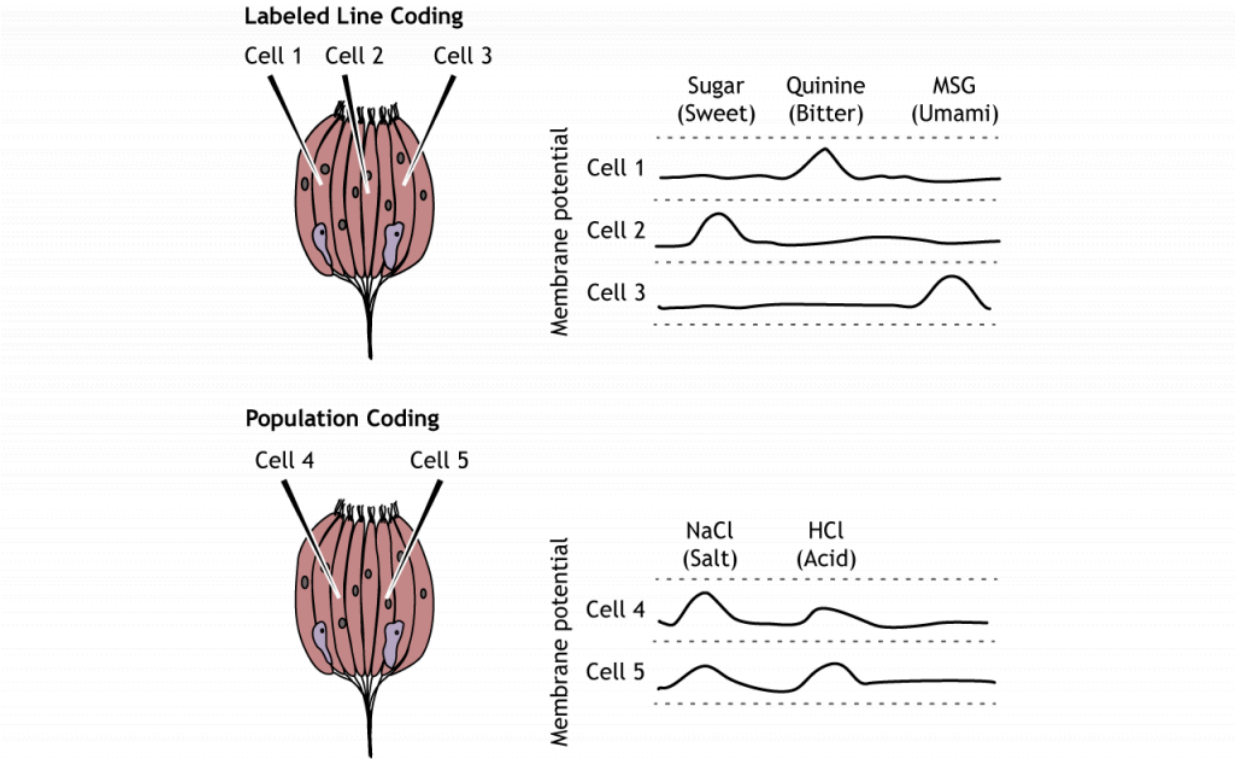

Figure 34.9. Labeled lined coding occurs when one sensation (in this case, a specific taste) leads to activation of the sensory cell. In this example, Cell 1 is activated only by quinine, a bitter compound, Cell 2 is activated only by sugar, a sweet compound, and Cell 3 is activated only by MSG, an umami compound. Most taste cells in the tongue use labeled line coding. Population coding results from broader activation, where multiple sensations can activate a sensory cell and perception is a result of information from a population of cells. In the example, Cells 4 and 5 are activated by both salt and acid compounds. 'Taste Coding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway

The tongue is innervated by three cranial nerves. The front two-thirds of the tongue is innervated by cranial nerve VII (Facial nerve). The back third is innervated by cranial nerve IX (Glossopharyngeal nerve). Finally, the epiglottis and pharynx are innervated by cranial nerve X (Vagus nerve). 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 that is to say, taste information from the left half of the tongue gets represented in the left hemisphere of the brain, and visa versa.. Projections within the brain also exist between the taste regions and the hypothalamus and amygdala.

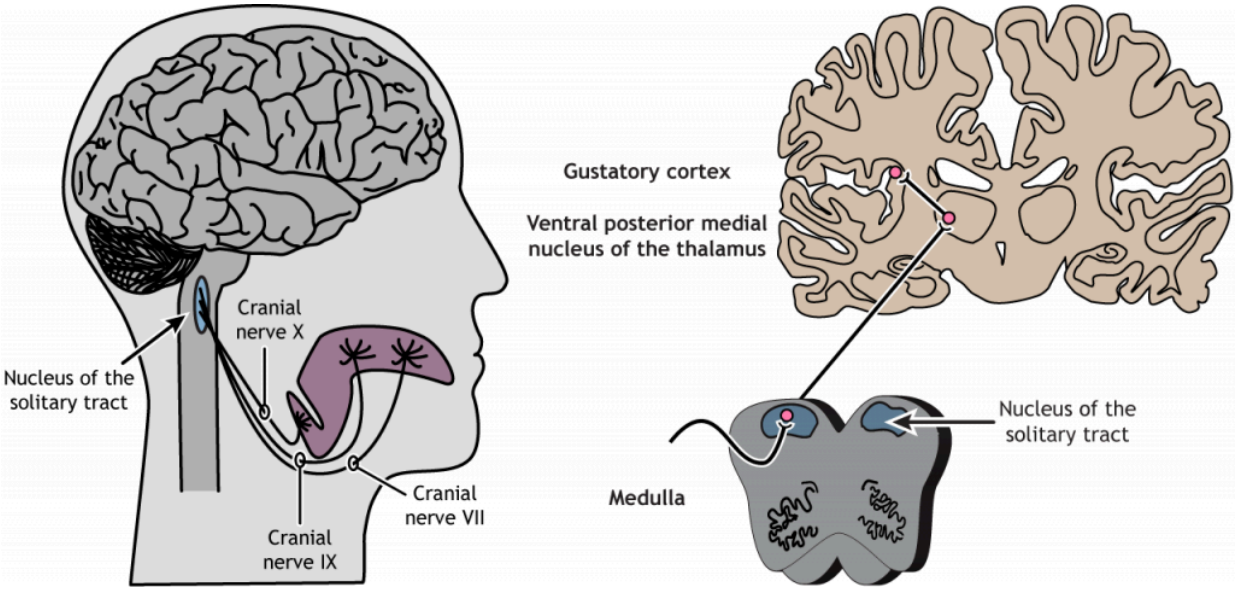

Figure 34.10. Taste information from the tongue travels through cranial nerves VII, IX, and X to the nucleus of the solitary tract in the medulla. Neurons in the brainstem project to the ventral posterior medial nucleus of the thalamus and then on to the gustatory cortex. 'Taste Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

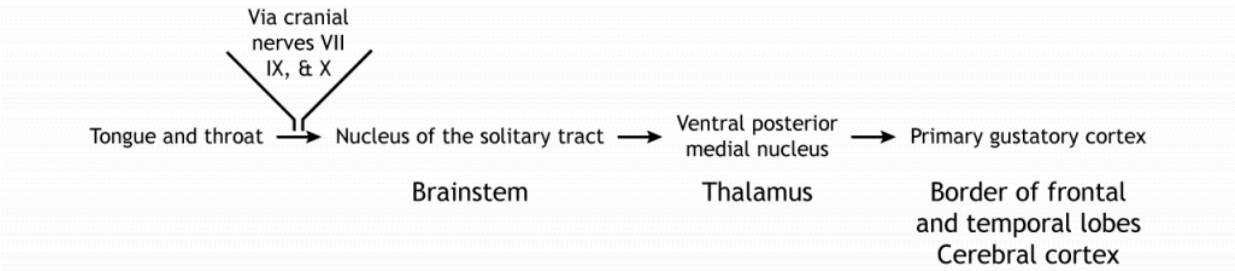

Figure 34.11 Axons from sensory afferents from the tongue and throat travel to the nucleus of the solitary tract in the brainstem via cranial nerves VII, IX, and X. The second-order brainstem neurons project to the ventral posterior medial nucleus of the thalamus. The thalamic third-order neuron projects to the primary gustatory cortex, which is located at the border of the frontal and temporal lobes. 'Taste Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the facial nerve (cranial nerve VII) using the BrainFacts.org 3D Brain
View the glossopharyngeal nerve (cranial nerve IX) using the BrainFacts.org 3D Brain
View the vagus nerve (cranial nerve X) using the BrainFacts.org 3D Brain
View the thalamus using the BrainFacts.org 3D Brain

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. Test how your senses combine to create flavor at home!

View the orbitofrontal cortex using the BrainFacts.org 3D Brain

Key Takeaways

- 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
- 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

Test Yourself!

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35.

OLFACTORY SYSTEM

Resources

- Glossary Terms
- Scientist links to learn more
- Key Takeaways
- Test Yourself

Olfaction is the ability to sense and perceive volatile chemicals that are suspended in the air. The typical human can distinguish up to 10,000 distinct odors, ranging from the sweet aroma of esters produced by apples and oranges, to the putrid smells of sulfurous compounds produced by skunks and rotten eggs. Because odors can drift along in the air, some chemicals can be detected long before the source is within eyesight: think about smelling a burning bonfire from miles away.

Smells affect our conscious behavior. They can motivate us to approach freshly-baked bread or avoid a rotting animal carcass. These chemicals serve as survival cues: bread gives us energy-rich carbohydrates while a decaying carcass can expose us to disease.

Smell is often used in communication between animals, especially in reproductive behaviors, territory marking and identification of individuals. Olfaction is one of the oldest functions we possess as animals. While our sense of smell has seemed to take a backseat to other senses relative to other animals (about 2% of the total mouse brain mediates smell, while only a scant 0.01% of the volume of the human brain is dedicated to this function), scientists now appreciate that our olfactory system is simply more specialized. For example, humans use the smells of sweat to clue us into the emotional state of others, and we can even subconsciously detect sickness through body odor.

Anatomy of the Olfactory System

Your sensation of smell begins when odorant molecules travel through your nostrils and pass through the nasal cavity, an empty, air-filled space just behind the front of the skull.

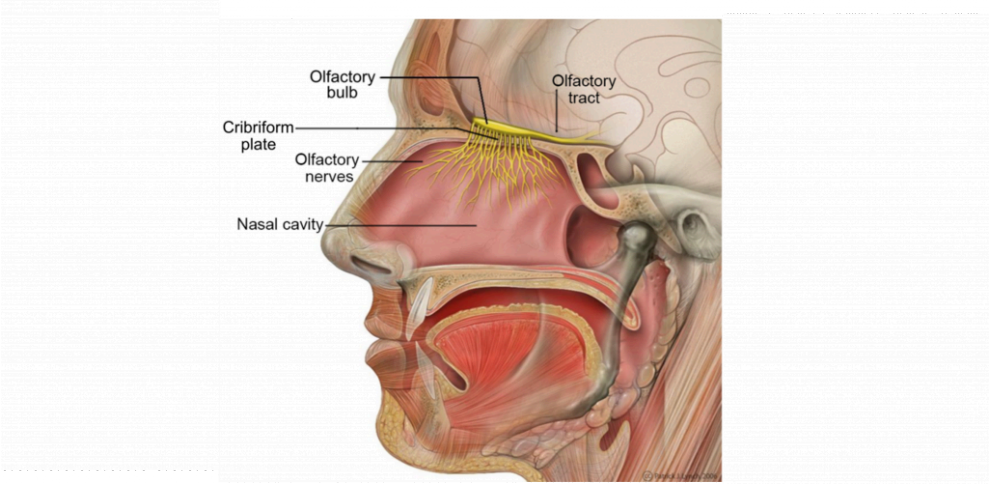

Figure 35.1. Olfactory system structures. Odorants enter through the nostrils into the nasal cavity, which is a large air-filled chamber. The olfactory epithelium is located at the dorsal most portion of the nasal cavity. This is where the odorants interact with olfactory receptor neurons (labeled as olfactory nerves in this image).

The odorants dissolve in the mucus covered dorsal-most portion of the nasal cavity, an area called the **olfactory epithelium**. Embedded within the olfactory epithelium are olfactory receptor neurons, supporting cells, and basal cells.

The axons of the olfactory receptor neurons travel through a sheet of bone called the **cribiform plate** before going to the **olfactory bulb**. Collectively, the axons of the olfactory receptor neurons make up **Cranial Nerve 1 (Olfactory Nerve)**.

Also found within the olfactory epithelium and surrounding the olfactory receptor neurons are **supporting cells** and **basal cells**. The supporting cells help dispose of dead and dying cells, metabolize pollutants, and may also help to physically maintain the epithelium by producing mucus. The basal cells function to replace the olfactory receptor neurons.

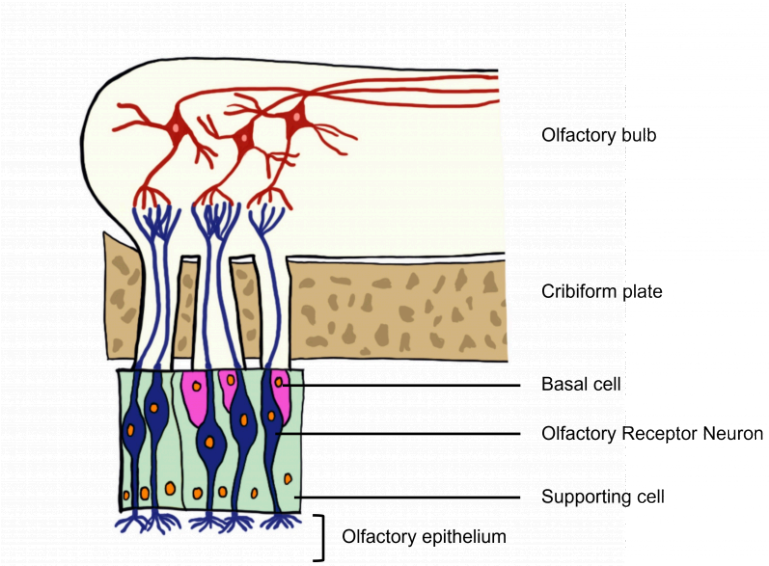

Figure 35.2. Olfactory receptor neurons in the olfactory epithelium. Olfactory receptor neurons are embedded within the olfactory epithelium. In addition to the olfactory receptor neurons, there are also basal cells and supporting cells. The axons of the olfactory receptor neurons exit through holes within the cribiform plate and then synapse within the olfactory bulb where they synapse onto the secondary cells (mitral cells). 'Olfactory receptor neurons and olfactory epithelium' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Olfactory Receptor Neurons

The **olfactory receptor neurons** begin processing smell. They serve as the sensory neurons for the olfactory system. Olfactory receptor neurons are **bipolar** neurons, that have a single dendrite with many **cilia** that are exposed to the epithelial surface. The cilia stretch into the mucus of the olfactory epithelium and act to increase the surface area of the neurons, providing increased space for odorants to interact with the olfactory receptor neurons. When the odorants dissolve in the mucus they interact with **odorant receptor proteins** on the cilia of the olfactory receptor neuron.

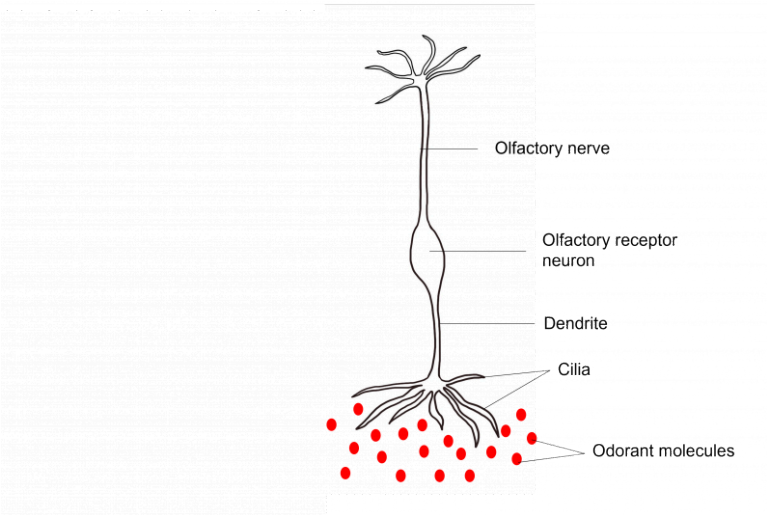

Figure 35.3. Structure of olfactory receptor neuron. Olfactory receptor neurons are bipolar and have a single dendrite that extends into the olfactory epithelium. Projecting from the dendrite are cilia that spread out into the olfactory epithelium to increase the surface area of the cell that can interact with odorants. The odorants bind to odorant receptor proteins on the cilia of the cells. 'Structure of olfactory receptor neuron' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Their proximity to the air make them the only neurons that are directly exposed to the outside world. Unfortunately, this causes them to encounter all sorts of dangers such as toxins, particulates, and

microbes. They are one of the few known populations of neurons where adult **neurogenesis** regularly occurs, each having a lifespan in the range of 30 days to a year. The average human olfactory system has somewhere between 6-20 million olfactory receptor neurons.

Olfactory Transduction

Though taste uses different signaling systems for transduction of each of the different tastes, olfaction uses a single system for transduction. First, odorants bind to **odorant receptor proteins** (a G-protein-coupled receptor) on the cilia of the olfactory receptor neurons.

Odorant Receptor Proteins

It is estimated there are about 1,000 different genes (about 3% of the total human genome) that code for roughly 400 different odorant receptor proteins. Each olfactory receptor neuron expresses only one type of odorant receptor protein. The initial research into the genetics underlying these neurons earned Drs. Linda Buck and Richard Axel a Nobel prize in 2004.

Odorant receptor proteins are transmembrane G protein-coupled receptors that have extracellular binding sites on their surface that bind to odorants. Each receptor differs in their specific binding pockets. Importantly, the receptor does not bind to one specific odorant, but rather binds to a specific molecular feature of the odorant. This means that many odorants can activate more than one odorant receptor protein, ultimately allowing each odorant to generate a unique pattern of activity across the olfactory receptor neurons.

Thus, analyzing the activity of a single olfactory receptor neuron is not sufficient to understand how that odorant alters neural signaling. Rather, the olfactory system uses **population coding**.

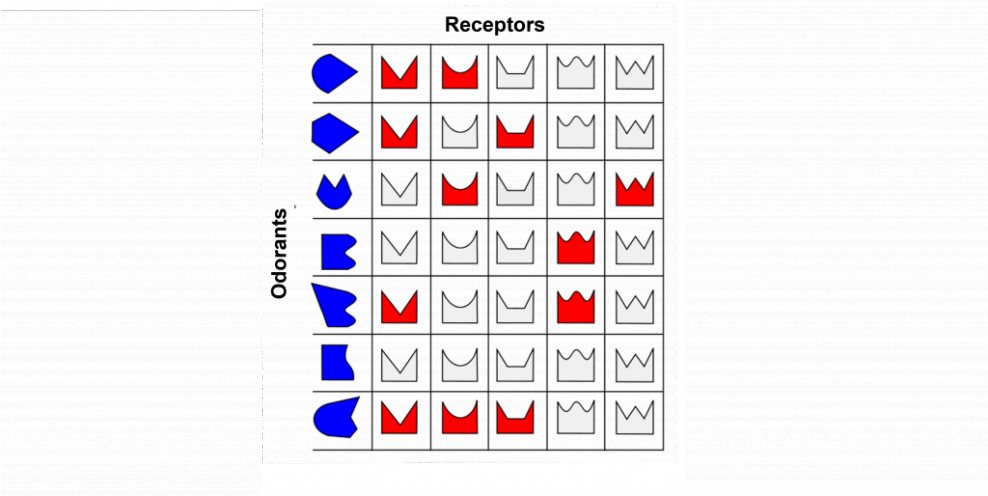

Figure 35.4. Odorant receptor proteins. Odorants are shown as the blue shapes on the left of the image. Each odorant has different features that allows for it to act with different odorant receptor proteins. The odorant receptor proteins are shown in red if the odorant can bind to that odorant receptor protein. The binding pocket within the odorant receptor protein does not need to match the entire shape of the odorant molecule, but rather just one structural feature of the odorant. In the top row of image, the odorant can bind to the two left-most odorant receptor proteins.

Odorant Receptor Protein Example

In this example we are looking at three different olfactory receptor neurons that express different types of odorant receptor proteins labeled Cell 1 ('blue' odorant receptor), Cell 2 ('orange' odorant receptor), and Cell 3 ('purple' odorant receptor). These neurons are exposed to four different odorants (vanilla, lavender, mint, and rose), and their neural activity is measured via an electrode.

When looking at the response to the 'Vanilla" odor, cell 1 shows an increase in the rate of action potentials, cell 2 shows very little activity, and cell 3 shows an increase in action potentials. Whereas the 'Lavender' odor only causes a response in cell 2. The 'Mint' odor causes very little activity in cell 1, and increased activity in both cell 2 and cell 3. Lastly, the 'Rose' odor causes an increase in activity in cell 1 and cell 2, but very little activity in cell 3. These recordings demonstrate that a single odorant can cause changes in activity in more than one type of olfactory receptor neuron, due to the receptor proteins recognizing more than one type of molecular feature of the odorant molecules.

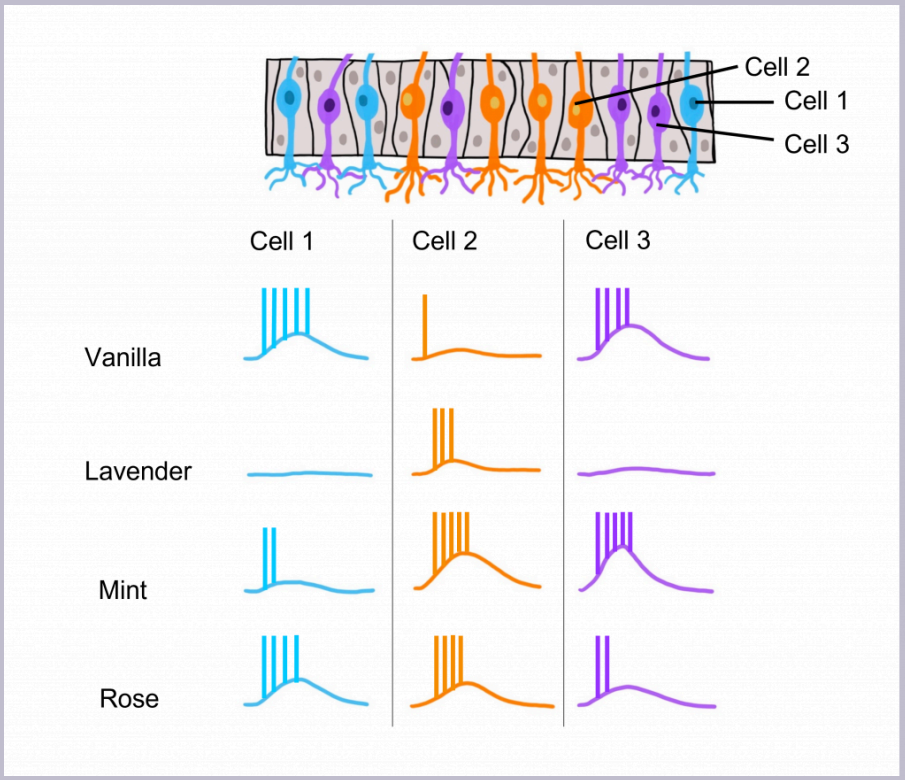

Figure 35.5. Example of population coding for olfactory receptor neurons. Three different cells are labeled within the olfactory epithelium (cell 1- blue, cell 2,- orange, and cell 3- purple). Recordings of action potentials for each of the three cells are shown when presented with different odorants (vanilla, lavender, mint, and rose). Each of the cells responds to more than one different odorant. Some cells respond preferentially to a single odorant. For example cell 2 preferentially responds to lavender odors. Odorant receptor proteins use population coding to code for different odorants. This means that the activity of a population of cells must be measured to

determined how an odorant ultimately alters neuronal signaling. 'Population coding for olfactory receptor neurons' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Transduction Pathway

After the odorant binds to the odorant receptor protein, the receptor activates an associated G protein called G_{olf}. This protein complex is 90% similar to the stimulatory G protein G_s , and likewise triggers activation of adenylyl cyclase, elevating the intracellular concentration of cyclic AMP. cAMP binds to cyclic nucleotide-gated cation channels that when opened, allow for the influx of calcium and sodium. The influx of calcium opens calcium-activated chloride channels. Olfactory receptor neurons have high intracellular chloride concentration, so the opening of the chloride channel results in chloride flowing out of the cell. Together, this causes the olfactory receptor neuron to **depolarize**, leading to membrane depolarization within the dendrite. This change in membrane potential is called a "**receptor potential**". If depolarization crosses threshold potential within the olfactory receptor neuron cell body, then the olfactory receptor neuron will fire action potentials down its axons that make up the olfactory nerve toward the olfactory bulb.

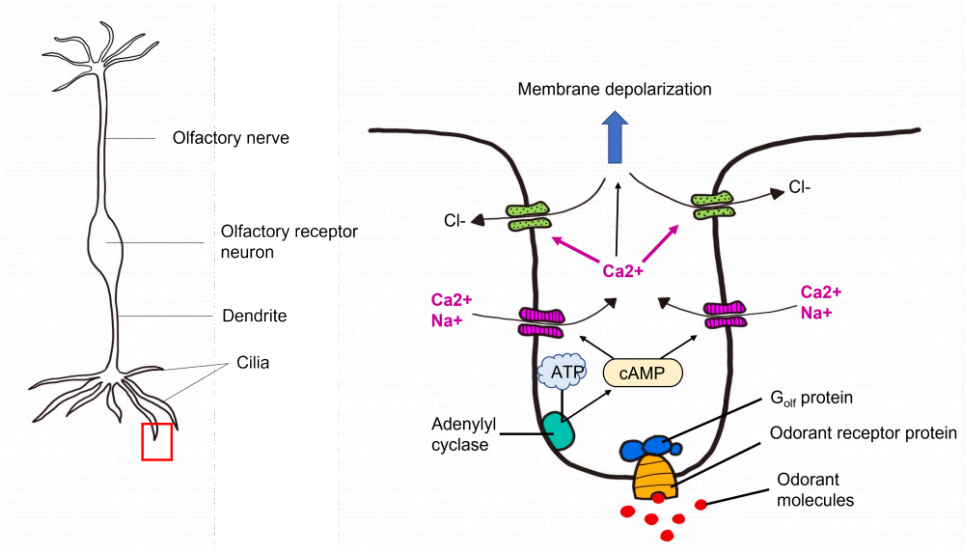

Figure 35.6. Olfactory receptor neuron transduction. Odorant molecules binds to odorant receptor proteins located on the cilia of olfactory receptor neurons. Odorant receptor proteins are G-protein coupled receptors that are coupled to Golf. Similar to activation of Gαs, activation of Golf increases activity of adenylyl cyclase, which in turn increases cAMP production within the cell. cAMP causes the opening of cation channels in the cell membrane that allow for the influx of both calcium (Ca2+) and sodium (Na+). The calcium influx opens chloride channels. Chloride concentration is high within the olfactory receptor neurons, so chloride flows out of the cell.

The increase in positively charged ions combined with the loss of negatively charged ions from inside the cell leads to membrane depolarization. 'Olfactory receptor neuron transduction' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Olfactory receptor neurons encode the intensity of smells through the frequency of action potential firing, which changes in accordance with the concentration of odorant molecules. Imagine standing over a fresh-baked pizza and inhaling deeply. Due to the high concentration of odorant molecules in the air, several receptors will be activated, leading to frequent neuronal firing. Now, imagine you are down the block from a pizza restaurant, getting only a slight whiff of those same scents. Here, the concentration of odorants is low, meaning that the Olfactory receptor neurons fire less frequently.

Termination of Olfactory Signaling

Because odorants are found in the air, they are highly mobile and can easily diffuse away, no longer having the ability to activate odorant receptor proteins. Olfactory signaling can also be terminated through the activity of enzymes located within the mucus of the olfactory epithelium.

Our perception of smells can also fade, even if the odorant is still present in the air. The odorant receptor neurons can adapt to the presence of an odorant, and thus no longer signal its presence.

Central Olfactory Pathway

The axons of the olfactory receptor neurons pass through the skull through a tiny series of holes at the cribriform plate. These primary neurons form synaptic connections onto neurons in the olfactory bulb called **mitral cells**, forming the beginning of the olfactory nerve (CN I). Like the optic nerve, the olfactory nerve runs along the **ventral** surface of the brain.

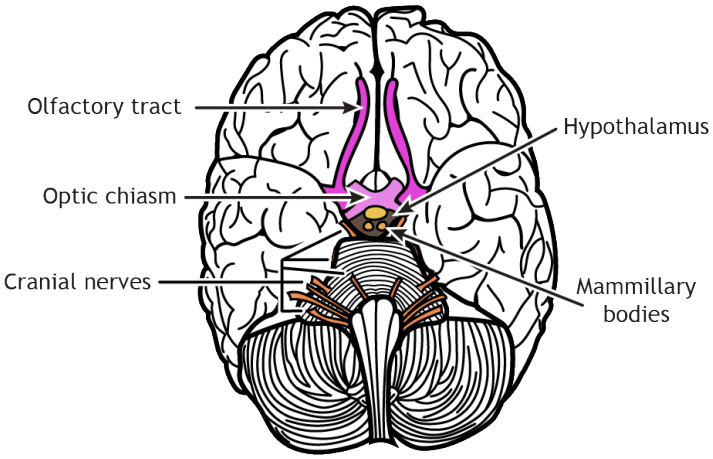

Figure 35.7. Human olfactory bulbs and tracts. In this ventral view of the brain, the optic bulbs and tracts (colored pink) run along the ventral surface of the brain.

Glomeruli within the Olfactory Bulb

The site of synaptic connectivity between the olfactory receptor neurons and the secondary neurons in the olfactory bulb (mitral cells) is a highly specialized clump of tissue called a **glomerulus**. The typical human has a little under 2,000 glomeruli, and each glomerulus only receives inputs from olfactory receptor neurons that express the same type of odorant receptor proteins. This means that even through the olfactory receptor neurons that express the same type of odorant receptor protein are spread out throughout the olfactory epithelium, the axons of those neurons all converge within the same glomerulus.

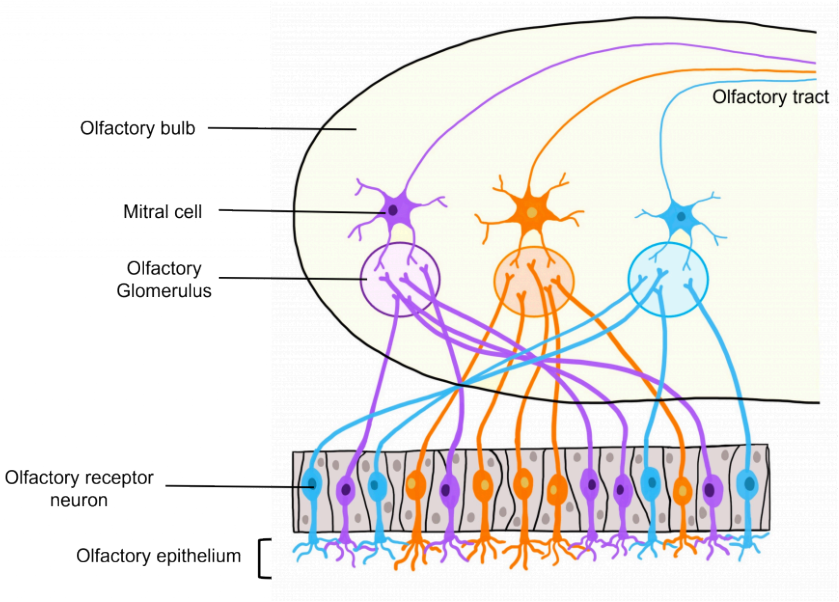

Figure 35.8. Olfactory glomeruli. Olfactory receptor neurons that contain the same type of odorant receptor protein are spread throughout the olfactory epithelium. All neurons that contain the same odorant receptor protein all synapse onto a common olfactory glomerulus within the olfactory bulb. Within the olfactory glomerulus is a synapse onto the secondary mitral cells. The axons of the mitral cells make up the olfactory tract that will carry the olfactory signal into the brain. 'Olfactory glomeruli' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International

License.

Brain Targets of Olfactory Neurons

Axons leave the olfactory bulb via the olfactory tracts and project to two different targets.

First, some cells project to the **olfactory tubercle**, are routed through the **medial dorsal nucleus of the thalamus** and then to the **orbitofrontal cortex**. This pathway is responsible for our conscious perception of smell.

Other cells project directly to the **olfactory cortex** and other related structures found within the **temporal lobes, like the hippocampus**. This makes the olfactory system the only sensory system that does not have to first pass signals through the thalamus before cortical processing. This pathway may play roles in discriminating odors, and the emotional, motivational, and memory-related aspects of smell.

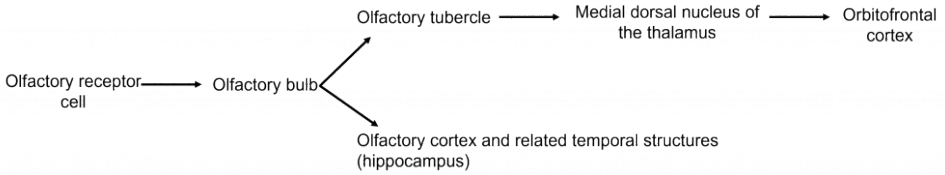

Figure 35.9. Projection of olfactory information. Olfactory receptor neurons send information to the olfactory bulb. From the olfactory bulb information can be routed through the olfactory tubercle, then to the medial dorsal nucleus of the thalamus, and finally the orbitofrontal cortex for processing of olfactory information. Alternatively, olfactory information can leave the olfactory bulb and be routed directly to the olfactory cortex and other related temporal structures like the hippocampus. This makes the olfactory system the only sensory system that does not necessarily need to be routed through the thalamus

prior to cortical processing. 'Projection of olfactory information' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Disorders of the Olfactory System

Like other sensory systems, the structures involved in olfaction can be injured. An injury to the olfactory system can result in **hyposmia**, a reduced ability to smell, or **anosmia**, a complete loss of smell.

The most common insult to the olfactory system is simple nasal congestion, a temporary, physical blockage of the entry to the nasal cavity that decreases airflow and, therefore, the number of particles that reach the olfactory epithelium. Congestion can be caused by allergies, the common cold, upper respiratory bacterial or viral infections, or sinus infections.

Hyposmia is also one of the main neurological symptoms of COVID-19. Hyposmia is common among healthy, older adults, affecting about half of the population between 65 and 80 years old. As a person ages, spontaneous calcification causes the holes in the cribriform plate to shrink, which can impinge on and damage olfactory receptor neuron axons. Hyposmia can also be caused by abrupt head injuries. The olfactory receptor neuron

axons that project through the holes of the cribriform plate are particularly sensitive to blows to the head. Neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, contribute to smell deficiency. Usually, hyposmia precedes the major clinically observed symptoms of these disorders, hinting that smell deficiency may serve as an early diagnostic biomarker.

Another olfactory deficit, **phantosmia**, is when a person perceives "phantom" scents, or in other words, experiences an olfactory hallucination. Phantosmia may be triggered by a temporal lobe seizure or a stroke. It can also be caused by a brain tumor affecting the olfactory nerve (CN I), or the subsequent surgical removal of the tumor, leading to injury. Schizophrenia, a psychiatric condition characterized by auditory hallucinations, may also cause phantosmia.

Key Takeaways

- Odorants dissolve in the mucus of the olfactory epithelium and bind to odorant receptor proteins on olfactory receptor neurons.
- A single odorant can bind to multiple different odorant receptor proteins because the odorant receptor protein binds to a molecular feature of the odorant.
- Odorant receptor proteins are G protein-coupled receptors that cause accumulation of cAMP within the cell, and ultimately membrane depolarization of the olfactory receptor neuron.
- Olfactory information is carried from the olfactory receptor neuron axons through the cribiform plate and into the olfactory bulb where it synapses with the olfactory glomeruli. From there, the information travels through the olfactory tracts and can either be routed through the thalamus and then to olfactory brain areas, or can be

directly routed to olfactory cortical areas, bypassing the thalamus.

Test Yourself!

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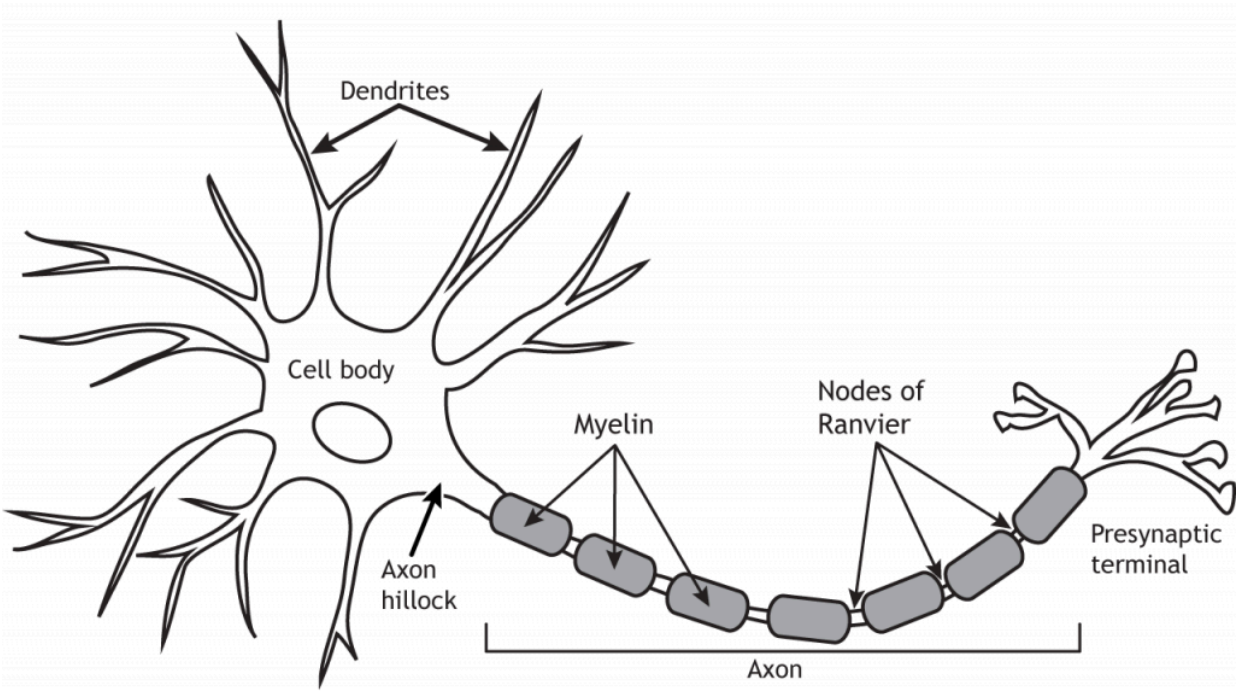
ADDITIONAL REVIEW ANSWERS

Chapter 1

Questions 1 and 2

The neuron is composed of a number of specialized structures that are critical for proper functioning. Dendrites branch out from the cell body or soma like a tree. The word dendrite comes from the word for tree in Greek. The dendrites are the primary input zone for the cell and receive information from other cells. The number of inputs a neuron receives depends on the complexity of the dendritic branching. The soma houses the nucleus and most organelles and is the location of gene transcription, protein synthesis, vesicle packaging, and other cellular machinery mechanisms. The axon hillock is located at the transition of the soma and axon. It is the location where action potential propagation begins. The axon transmits electrical signals, called action potentials, from the cell body to the presynaptic terminal. Some axons are covered by myelin sheath, which is an insulating material that allows the action potential to travel down the axon faster. Between the myelin segments are the Nodes of Ranvier where the axonal cell membrane is open to the extracellular space. Ions can flow across the membrane at the Nodes, which allows for regeneration of the action potential. Finally, the presynaptic terminal is the output zone. After the action potential reaches the terminal, neurotransmitters are released into the synapse to send messages onto the next cell.



Question 3

Myelin increases the speed at which action potentials flow down the axon. If myelin was lost, action potentials would propagate down the axon at a slower rate or possibly not at all. Normal sensory, motor, and cognitive functions would be dysfunctional, depending on the location of the demyelination.

Chapter 2

Question 1

Ions move from regions of high concentrations to regions of low concentrations by a process called diffusion. The concentration gradient will cause ions to diffuse across an impermeable membrane if there are open ion channels. Ions are also attracted to regions of opposite charge, so the electrical gradient will move cations toward a negative charge and anions toward a positive charge.

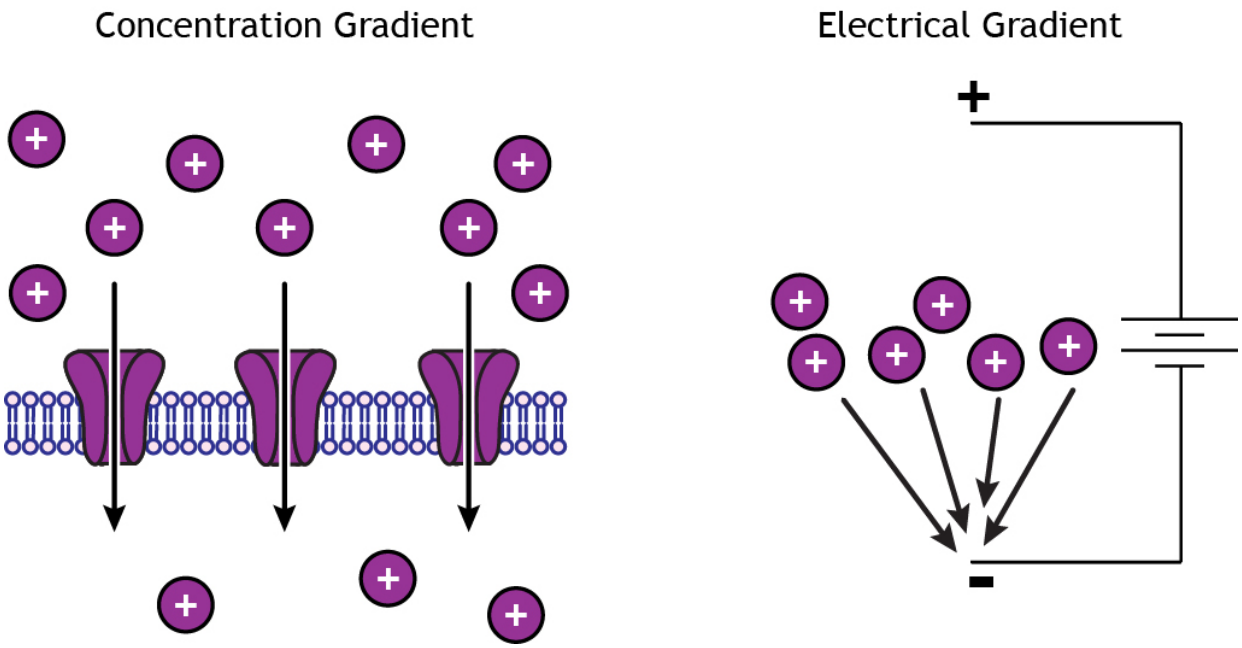


Figure 2.4. Concentration and electrical gradients drive ion movement. Ions diffuse down concentration gradients from regions of high concentration to regions of low concentration. Ions also move toward regions of opposite electrical charge. 'Gradients' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View animation of image.

Question 2

When an ion is at equilibrium, there will be no net ion flow in either direction. The ions will still move however, there will simply be an equal number of ions moving into the cell than are moving out.

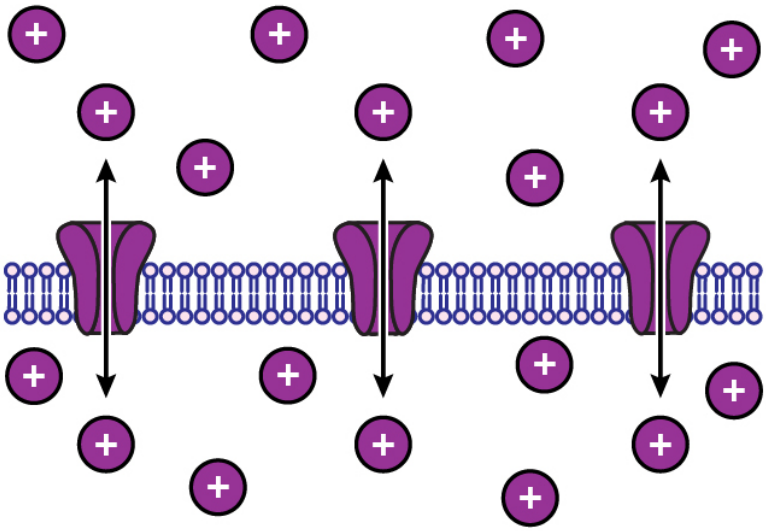


Figure 2.5. When an ion is at equilibrium, which occurs when the concentration and electrical gradients acting on the ion balance, there is no net movement of the ion. The ions continue to move across the membrane through open channels, but the ion flow into and out of the cell is equal . In this animation, 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 licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View animation of image.

Chapter 3

Question 1

The membrane potential is the difference in electrical charge between the inside and outside of a cell. The extracellular solution is the reference point, so you should think of that as having no charge. If a cell has a membrane potential of -70 mV, that means the inside of the cell is more negative than the outside. Active neurons can have drastic changes in their membrane potentials, but the resting membrane potential is the difference in charge when the cell is not active.

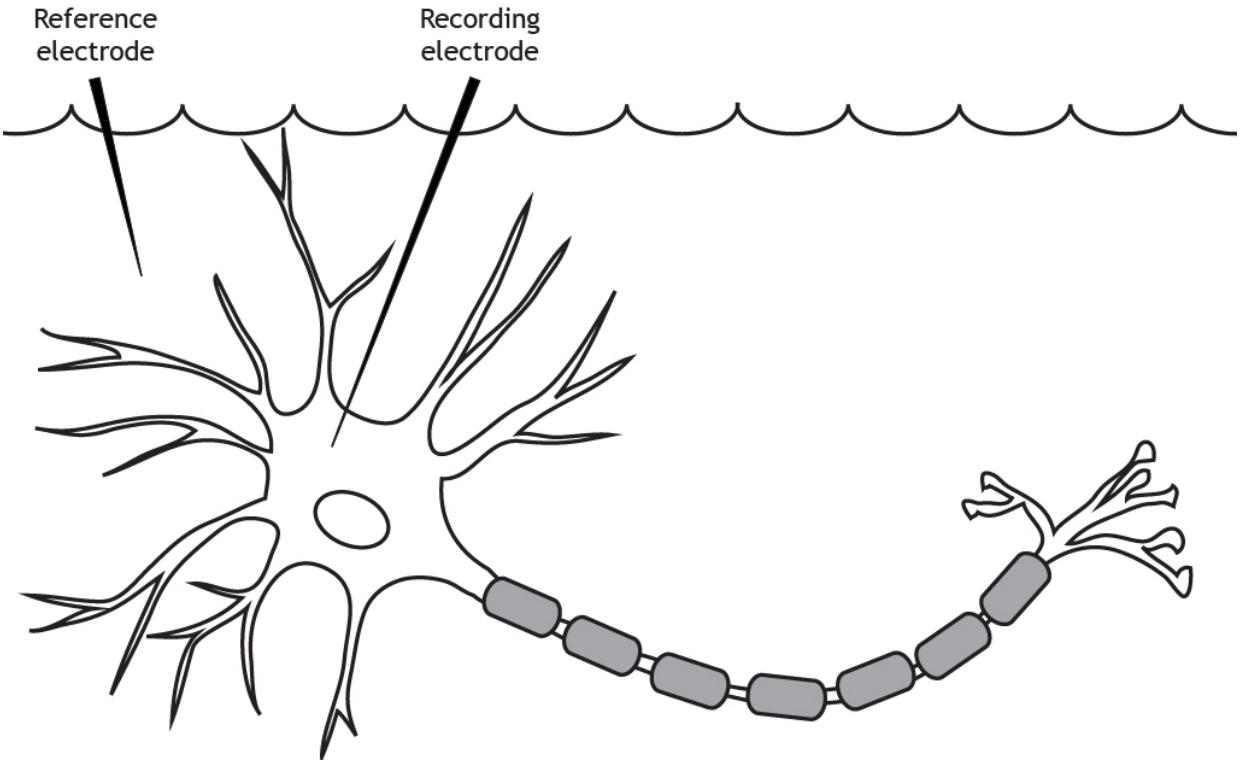


Figure 3.1. The membrane potential is measured using a reference electrode placed in the extracellular solution and a recording electrode placed in the cell soma. The membrane potential is the difference in voltage between these two regions. 'Measuring Membrane Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Question 2

The membrane potential is the difference in charge inside the cell relative to the outside, so it takes into account permeability and concentration of all charged molecules when the cell is at rest. It is calculated by the Goldman equation. Equilibrium potential is the membrane potential at which one specific ion is at equilibrium, meaning there is no net movement of that ion in either direction. A cell would reach the equilibrium potential of an ion if the membrane were permeable to only that ion. It is calculated by the Nernst equation.

Question 3

Nernst equation:

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

For Potassium:

z = 1

$[Ion]_{inside}$ = 125 mM

$[Ion]_{outside}$ = 15 mM

$$E_{ion} = \frac{61}{1} log \frac{15}{125} = -85mV$$

Chapter 4

Question 1

Goldman equation:

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

Increase extracellular potassium:

$$V_m = 61 * \log \frac{1[50] + 0.04[145] + 0.4[13]}{1[125] + 0.04[15] + 0.4[150]} = -29mV$$

Question 2

Decrease extracellular sodium:

$$V_m = 61 * \log \frac{1[5] + 0.04[100] + 0.4[13]}{1[125] + 0.04[15] + 0.4[150]} = -68mV$$

Question 3

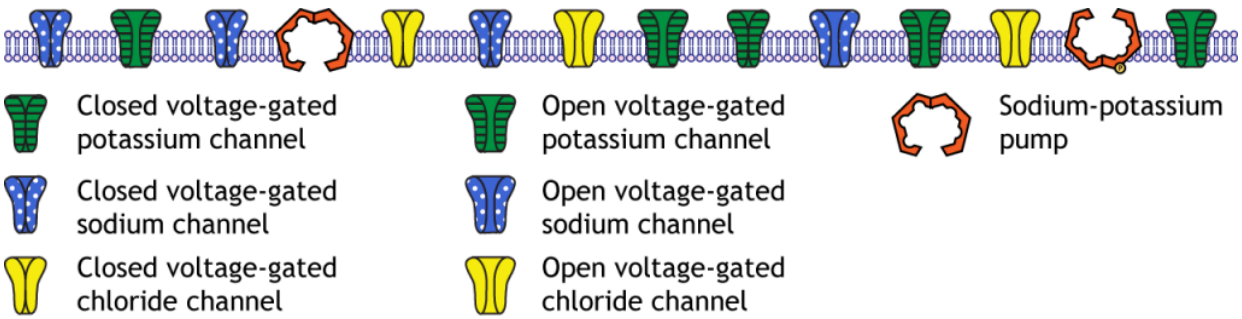
A change in potassium's extracellular concentration had a much larger effect on the resting membrane potential compared to changed sodium's extracellular concentration.

Question 4

The reason for this is because the membrane is significantly more permeable to potassium compared to sodium at rest. Since there are open channels, potassium can diffuse across the membrane and alter the resting membrane potential. Sodium may increase in concentration outside the cell, but without a way to cross the membrane, the membrane potential does not change.

Question 5

At rest, the neuronal membrane includes open non-gated potassium channels, fewer open chloride channels, very few open sodium channels, and sodium-potassium pumps.



Chapter 6

Question 1

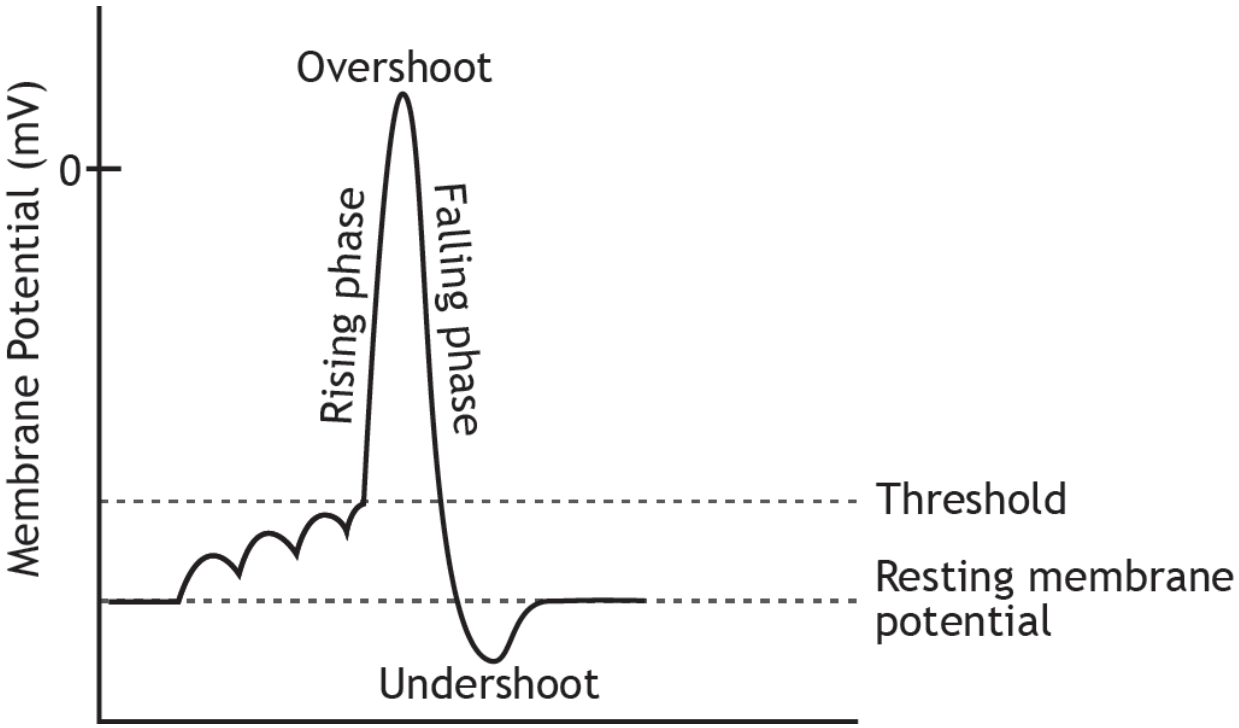


Figure 6.3. EPSPs that summate to reach threshold initiate the action potential. The depolarizing rising phase moves the membrane potential from threshold to above 0 mV. The overshoot is the peak of the action potential where the membrane potential is positive. The falling phase repolarizes the membrane potential, and the undershoot takes the membrane potential more negative than the resting membrane potential. After the undershoot, the membrane potential returns to rest. 'Action Potential Phases' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

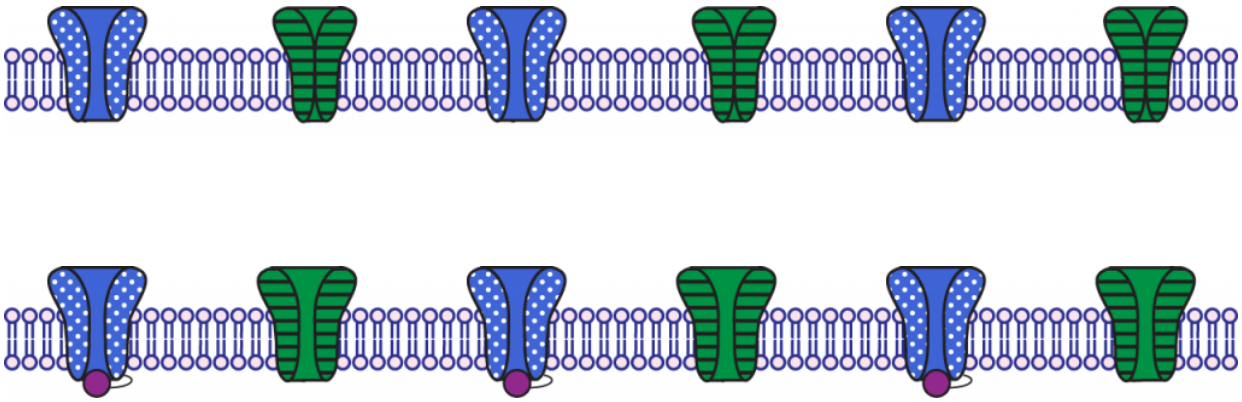
The rising phase is a depolarization. The voltage-gated sodium channels are open. The voltage-gated potassium channels are closed.

The falling phase is a repolarization. The voltage-gated sodium channels are inactivated. The voltage-gated potassium channels are open.

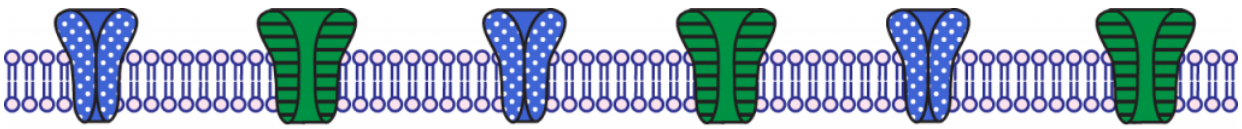
The undershoot is a hyperpolarization. The voltage-gated sodium channels are closed. The voltage-gated potassium channels close during the undershoot.

Question 2

The absolute refractory period occurs when the voltage-gated sodium channels are either open during the rising phase or inactivated during the falling phase.



The relative refractory period occurs when the voltage-gated sodium channels are de-inactivated during the undershoot, but the voltage-gated potassium channels are still open.



Question 3

The cell cannot fire a second action potential during the absolute refractory period. The voltage-gated sodium channels cannot reopen in response to a stimulus, regardless of the strength.

The cell can fire a second action potential during the relative refractory period, but the strength of the stimulus must be stronger than when the cell is at rest since the membrane potential is hyperpolarized. The cell will require more stimulus to reach threshold.

Chapter 7

Question 1

In this voltage-clamp experiment, the neuron is clamped at a membrane potential of 0 mV starting a the 1 msec time point. This depolarization is past threshold, so the voltage-gated sodium channels open transiently, increasing sodium permeability and allowing sodium ions to rush into the cell, shown by the inward ion flow on the graph. Briefly after opening, the voltage-gated sodium channels inactivate, preventing any further inward current. The delayed-rectifier voltage-gated potassium channels then open, increasing potassium permeability and allowing potassium ions to rush out of the cell, shown by the outward ion flow on the graph.

Chapter 10

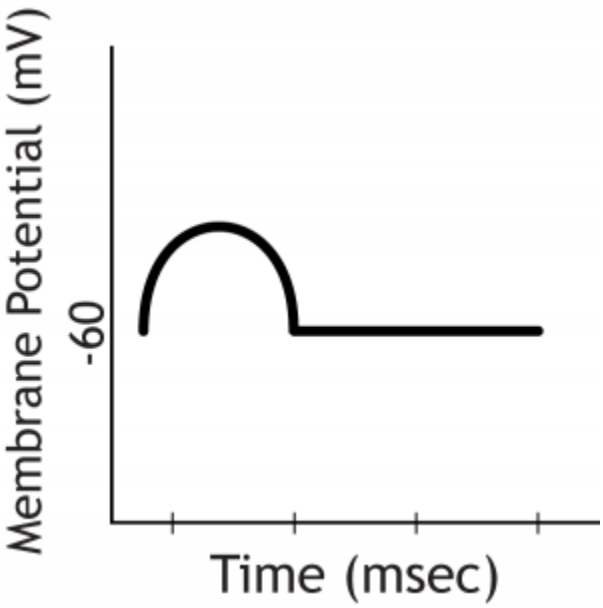
Question 1

1. An action potential arrives in the terminal
2. The depolarization opens voltage-gated calcium channels
3. Calcium interacts with synaptotagmin, a protein bound do synaptic vesicles
4. Synaptotagmin interacts with the SNARE proteins, causing the synaptic vesicle membrane to fuse with the cellular membrane
5. Neurotransmitters are released into the synaptic cleft via exocytosis.

Chapter 11

Question 1

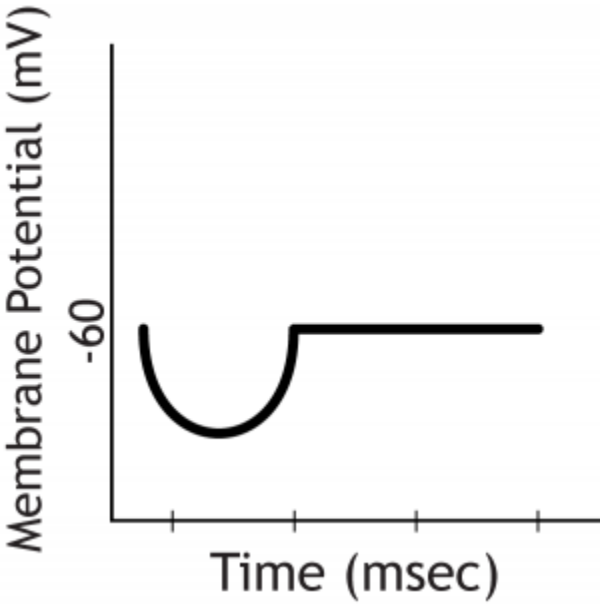
The postsynaptic cell would show an EPSP



A depolarization above rest at -60 mV.

Question 2

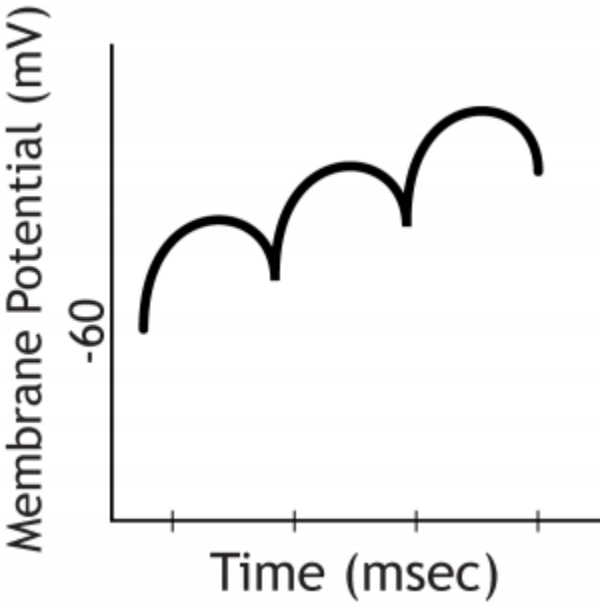
The postsynaptic cell would show an IPSP



A hyperpolarization below rest at -60 mV.

Question 3

With this repetitive firing comes a summation of individual EPSPs, which leads to an increase in depolarization. Once the depolarization reaches threshold, the cell will fire an action potential, but the recording electrode in this example is located in the cell body, not the axon, so action potentials will not be measured.



Summated EPSPs

Chapter 12

Question 1

Neurotransmitters can activate both ionotropic and metabotropic receptors.

Ionotropic receptors are themselves an ion channel, allowing direct ion flow after neurotransmitter binding. Action is immediate and rapid.

Metabotropic receptors do not form an ion channel, and if they affect ion flow it is done indirectly via G-proteins. The effects are slower than ionotropic receptors and have broader actions. Metabotropic receptors can open ion channels, but they can also send second messengers into the cell,

which have downstream cellular effect and can even alter gene transcription and protein translation.

Chapter 19

Question 1

Rods and cones play specialized roles in the perception of sight.

Physical appearance: Rods have an elongated, cylindrical outer segment; cones have a shorter, conical outer segment.

Light sensitivity: Rods are highly sensitive to light and therefore are specialized for low light levels. Cones, on the other hand, have lower sensitivity to light, so they are specialized for bright light conditions.

Location: Rods are almost completely excluded from fovea, but the fovea is the location of the majority of cones.

Convergence: Rods have high convergence on bipolar cells; cones have low convergence and can have a 1 to 1 pairing of photoreceptor to bipolar

Question 2

The fovea is the region of greatest vision acuity. It consists mainly of cone photoreceptors.

The optic disc is the region where the ganglion cell axons leave the retina as the optic nerve. It is responsible for our blindspot because of the absence of photoreceptors in the region.

Chapter 22

Question 1

Different areas of the body have different two-point discrimination thresholds. The more receptors that innervate an area, the smaller the receptive fields of those receptors, which leads to a smaller two-point discrimination threshold.

Chapter 23

Question 1

The primary somatosensory cortex is located in the postcentral gyrus – named because it is the gyrus just posterior to the central sulcus.

Question 2

Neurons traveling from brainstem will synapse in the ventral posterior nucleus of the thalamus before traveling to the primary somatosensory cortex.

IMAGES OF ANIMATIONS

Chapter 1

Animation 1

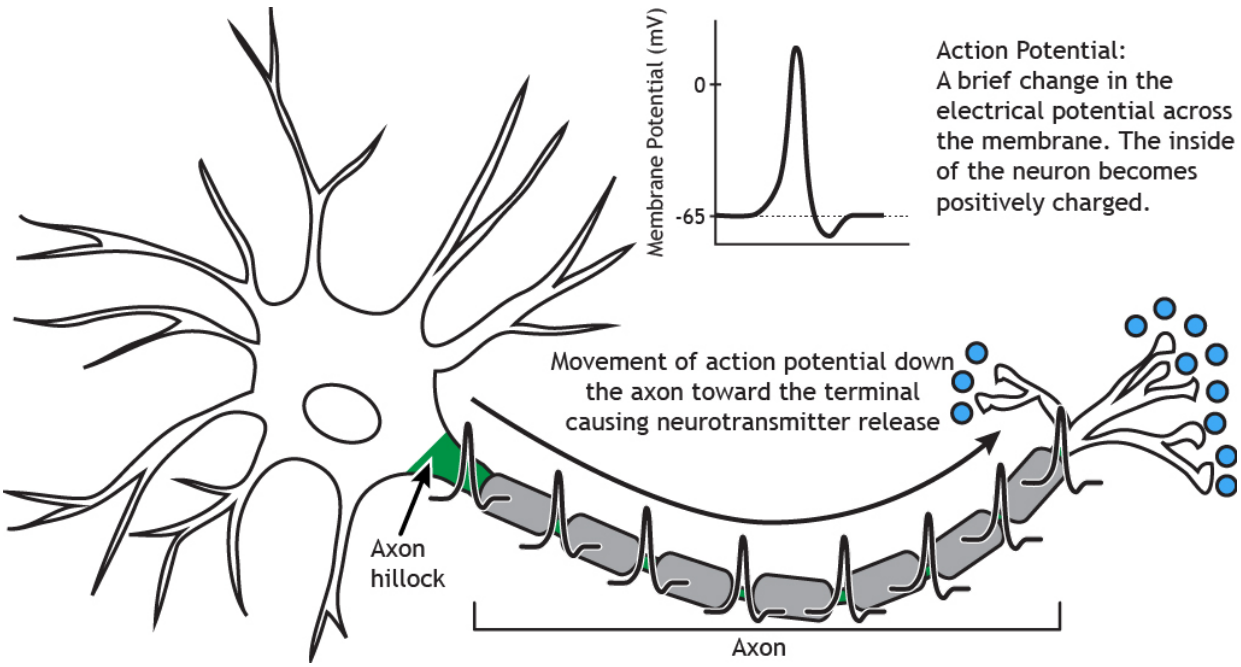


Figure 1.11. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. 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.

Chapter 2

Animation 1

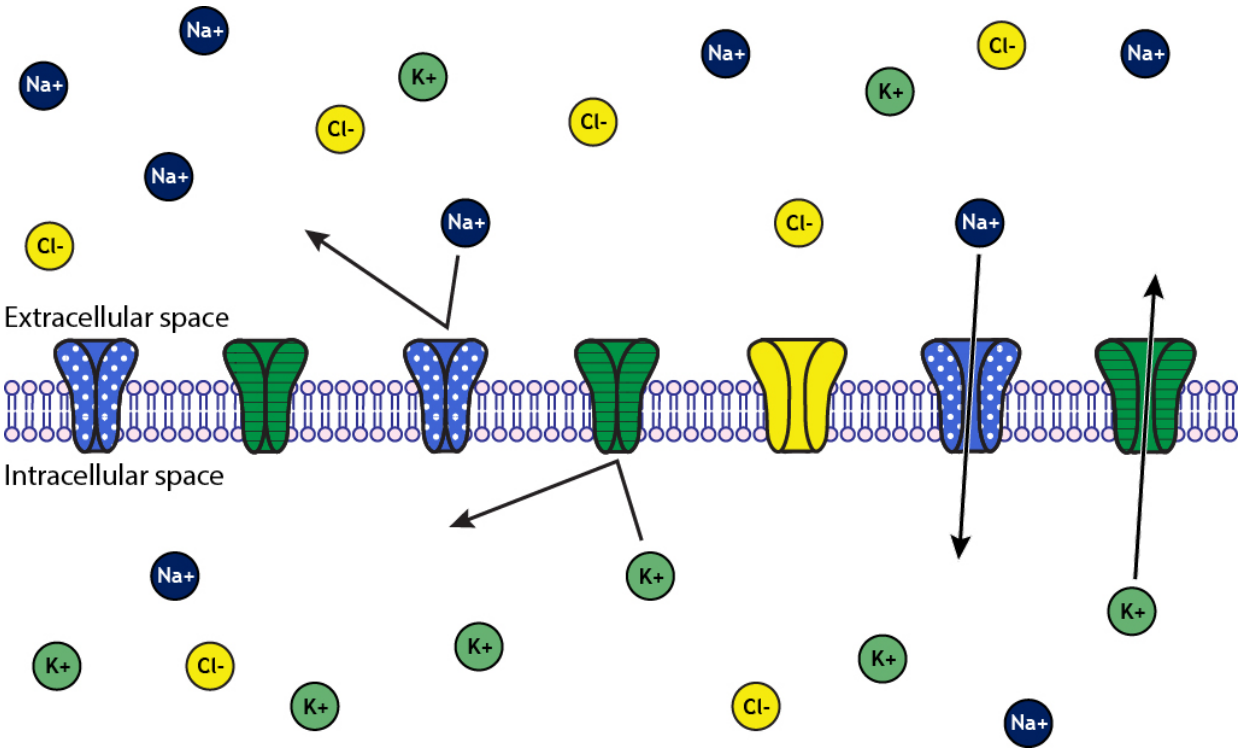


Figure 2.3. When ion channels in the membrane are closed, ions cannot move into or out of the neuron. Ions can only cross the cell membrane when the appropriate channel is open. For example, only sodium can pass through open sodium channels. The dotted, blue channels represent sodium channels; the striped, 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.

Animation 2

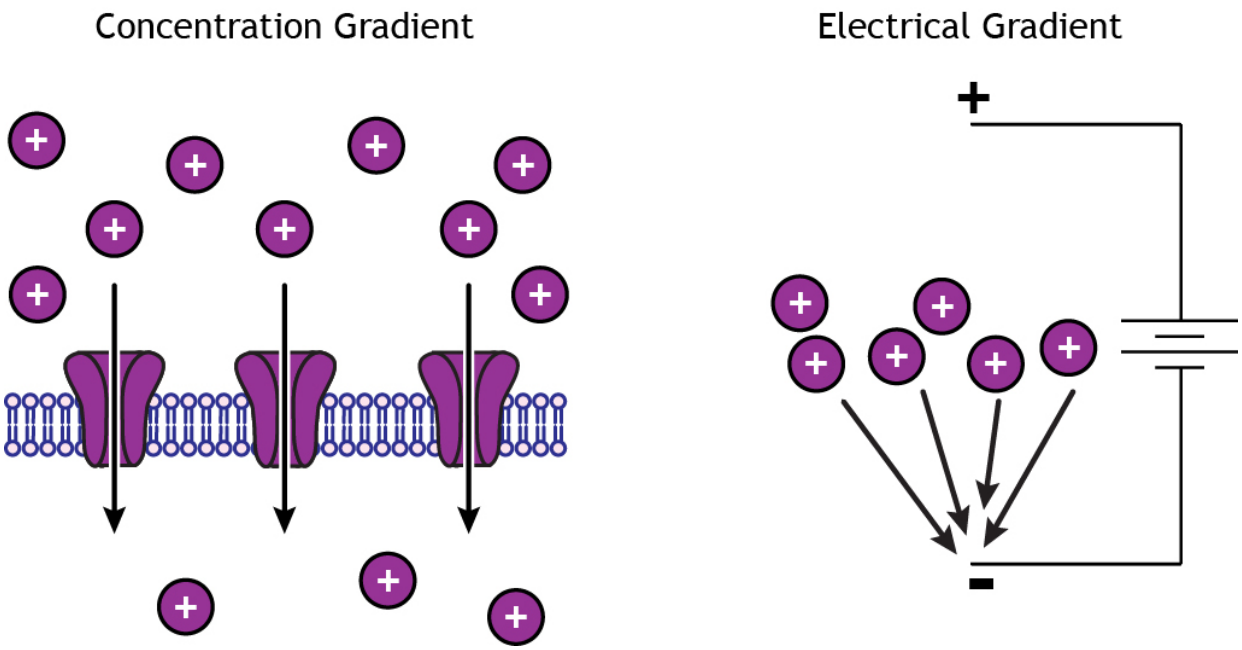


Figure 2.4. Concentration and electrical gradients drive ion movement. Ions diffuse down concentration gradients from regions of high concentration to regions of low concentration. Ions also move toward regions of opposite electrical charge. 'Gradients' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Animation 3

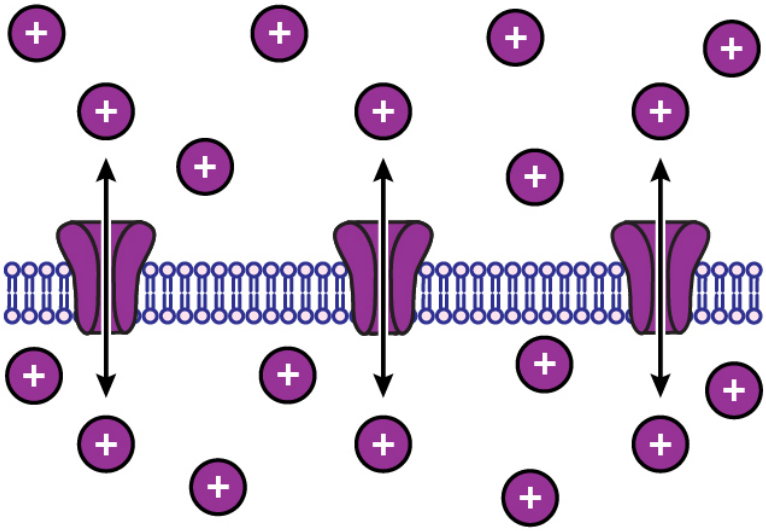


Figure 2.5. When an ion is at equilibrium, which occurs when the concentration and electrical gradients acting on the ion balance, there is no net movement of the ion. The ions continue to move across the membrane through open channels, but the ion flow into and out of the cell is equal . In this animation, 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 licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Chapter 3

Animation 1

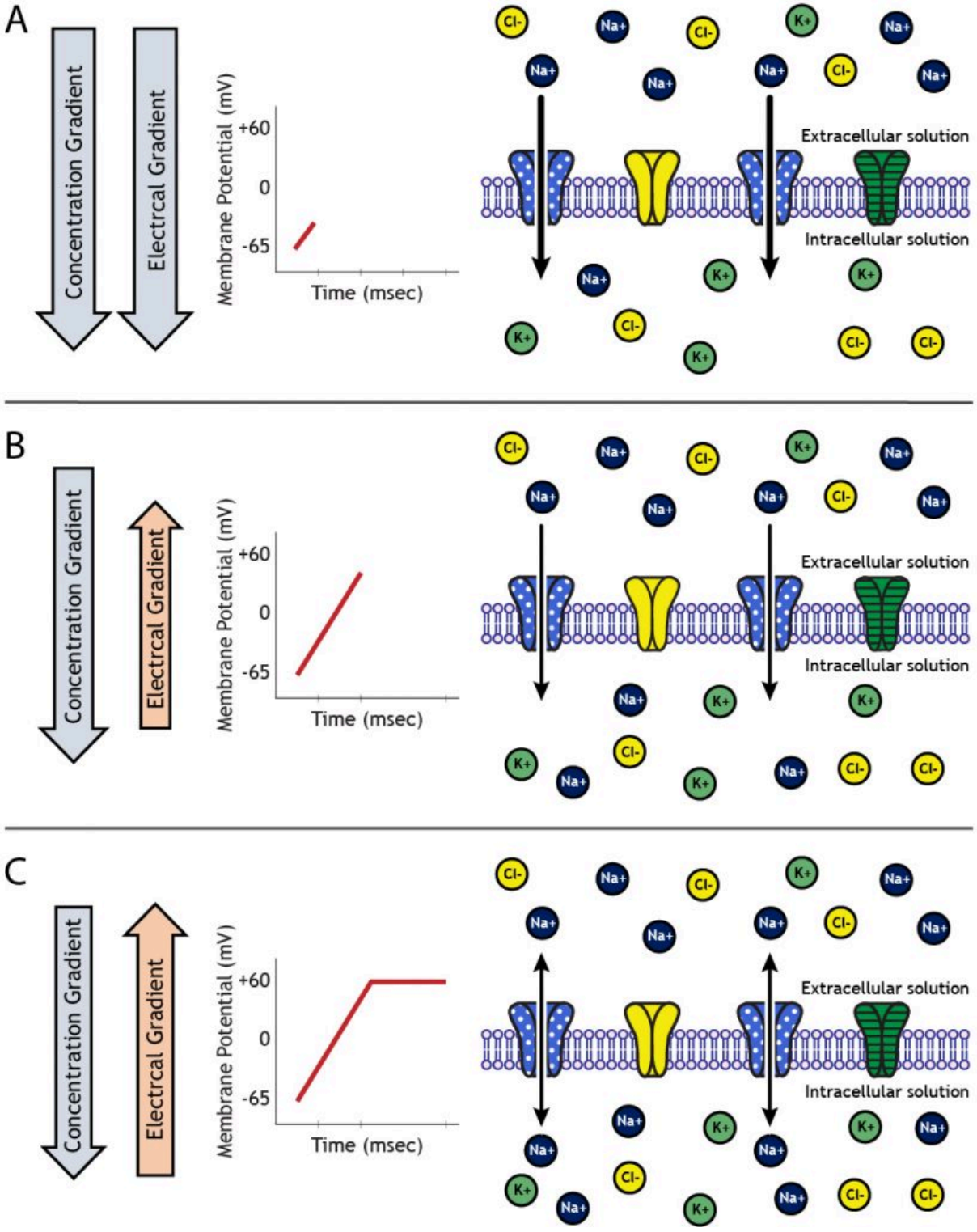


Figure 3.7. A) At rest, both the concentration and electrical gradients for sodium point into the cell.

As a result, sodium flows in. As sodium enters, the membrane potential of the cell decreases and becomes more positive. B) 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. C) 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.

Chapter 4

Animation 1

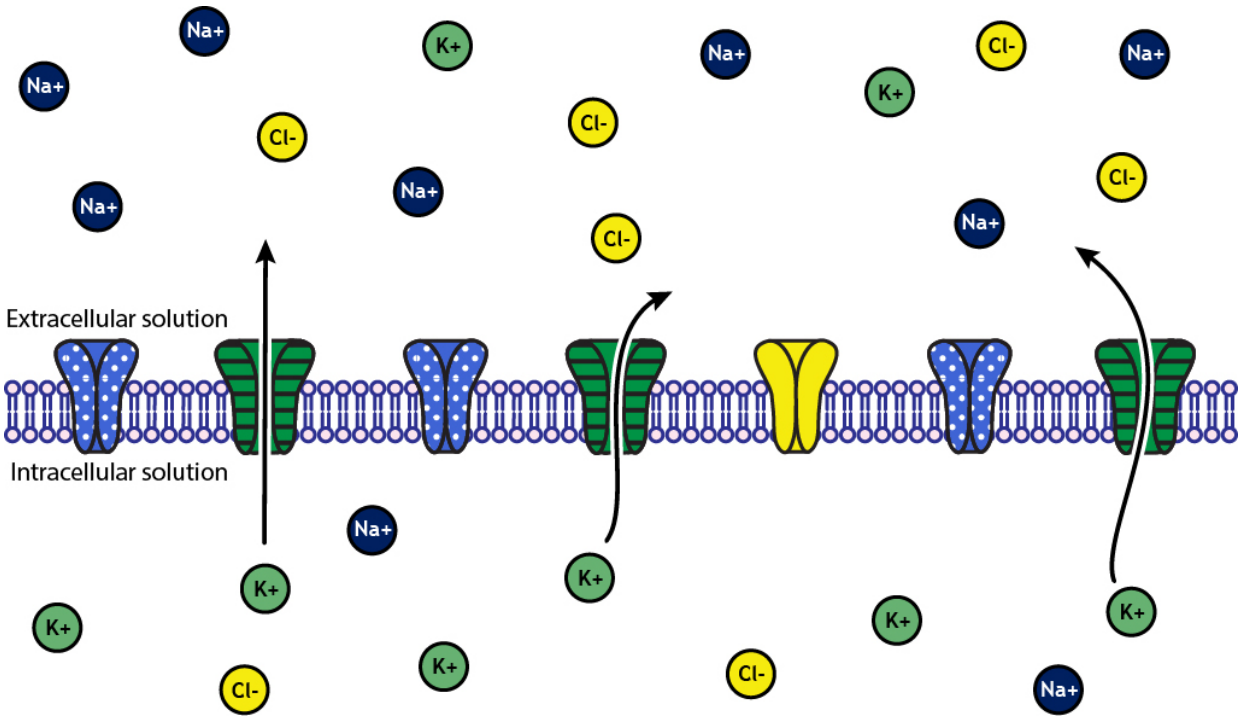


Figure 4.3. Electrochemical gradients drive potassium out of the cell, removing positive charge, making the cell's membrane potential more negative, in the direction of potassium's equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Potassium at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 2

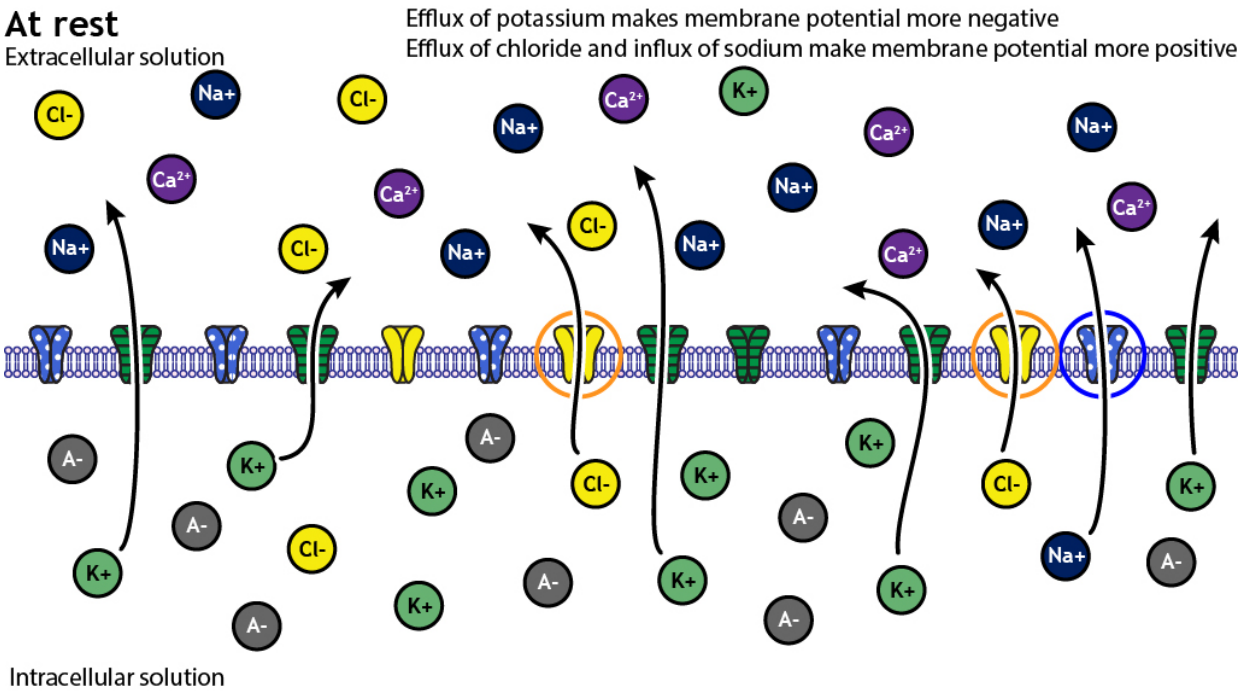


Figure 4.4. The membrane is most permeable to potassium at rest, and this leads to potassium efflux. However, the membrane is also permeable to chloride and sodium, and the flow of these ions keep the resting membrane potential more positive than potassium's equilibrium potential. The dotted, blue channels 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.

Animation 3

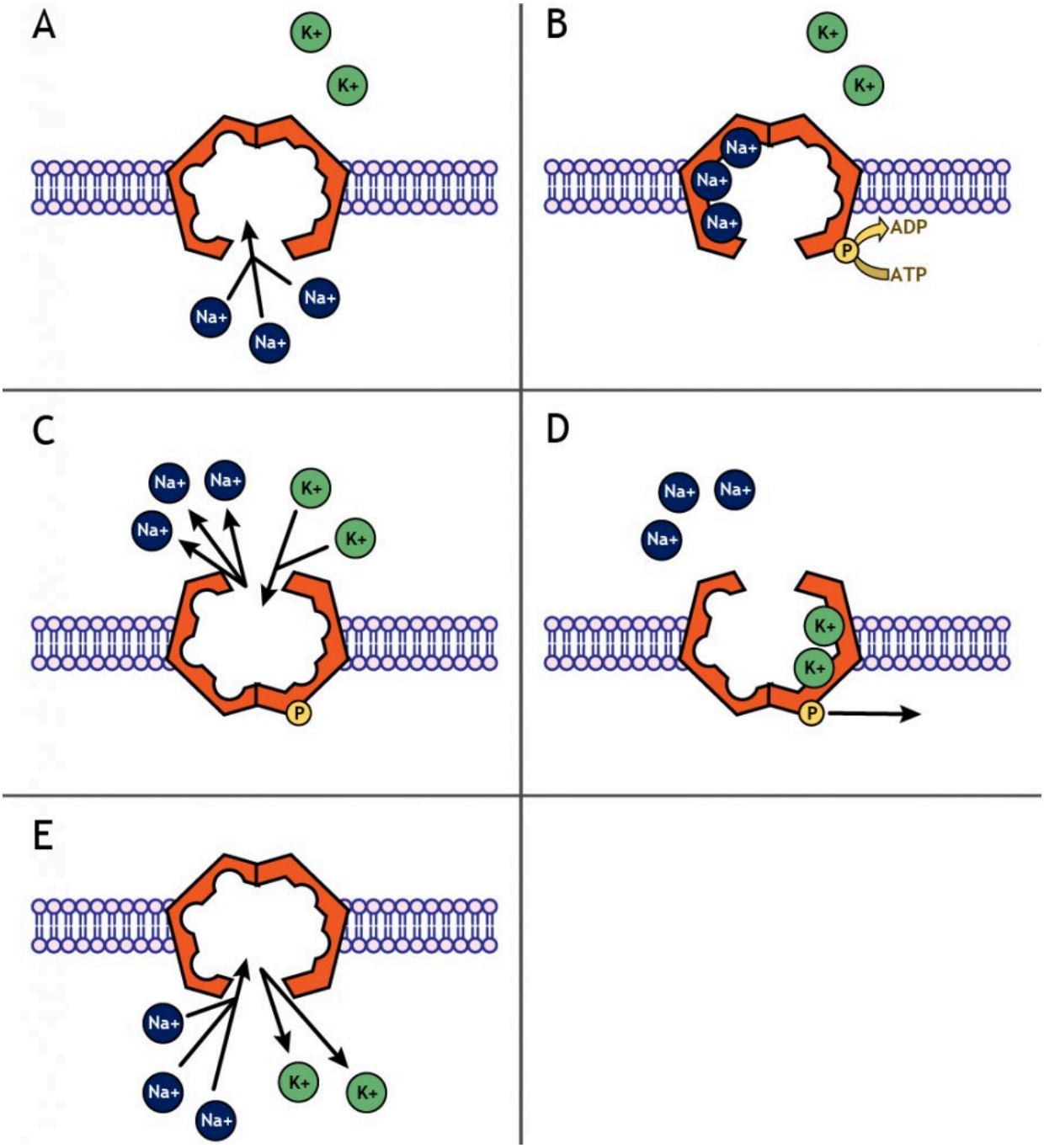


Figure 4.5. The sodium-potassium pump is embedded in the cell membrane and uses ATP to move sodium out of the cell and potassium into the cell, maintaining the electrochemical gradients necessary for proper neuron functioning. A) Three intracellular sodium ions enter the pump. B) ATP is converted to ADP, which leads to a conformational change of the protein, closing the intracellular side and opening the extracellular side. C) The sodium ions leave the pump while two extracellular potassium ions enter. D) The attached phosphate molecule then leaves, causing the pump to again

open toward the inside of the neuron. E) The potassium ions leave, and the cycle begins again.

Chapter 5

Animation 1

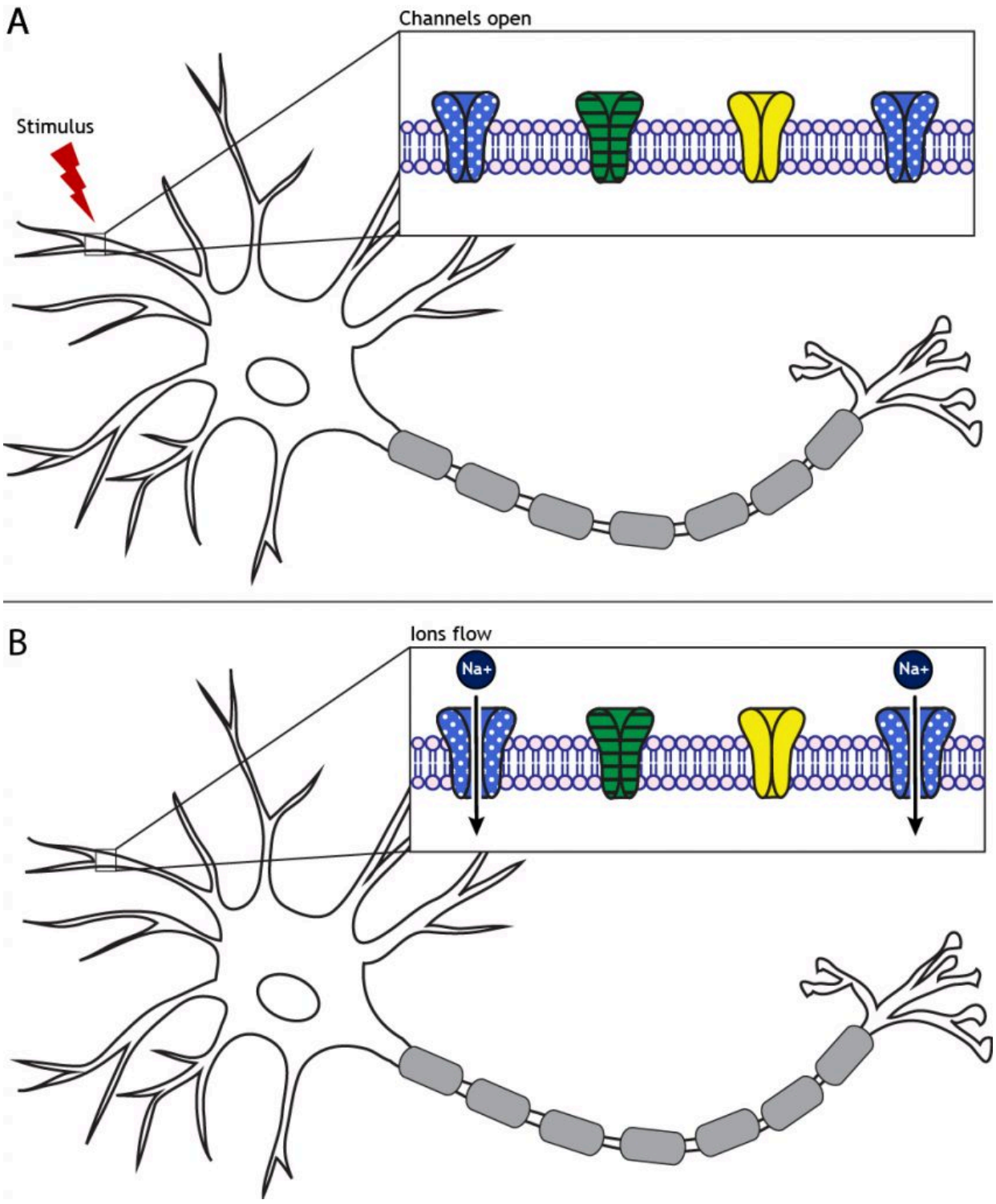


Figure 5.3. Top panel: A stimulus can cause ion channels in the membrane of the cell body or dendrites to open. Bottom panel: The open ion channels allow ion flow across the membrane. The

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.

Animation 2

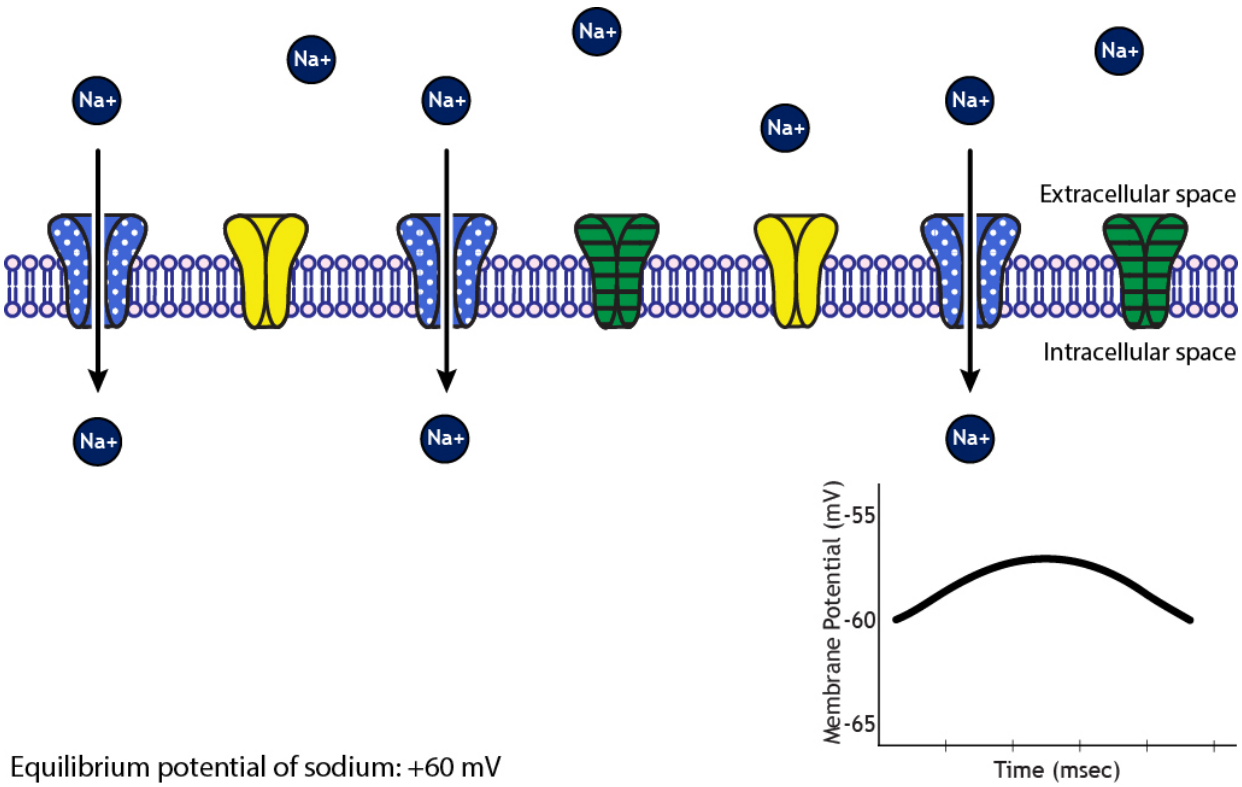


Figure 5.4. When a stimulus opens sodium channels, sodium rushes into the cell because the equilibrium potential of sodium is +60 mV. This causes an excitatory depolarization called an excitatory postsynaptic potential (EPSP). After the stimulus, the ion channels close, and the membrane potential returns 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.

Animation 3

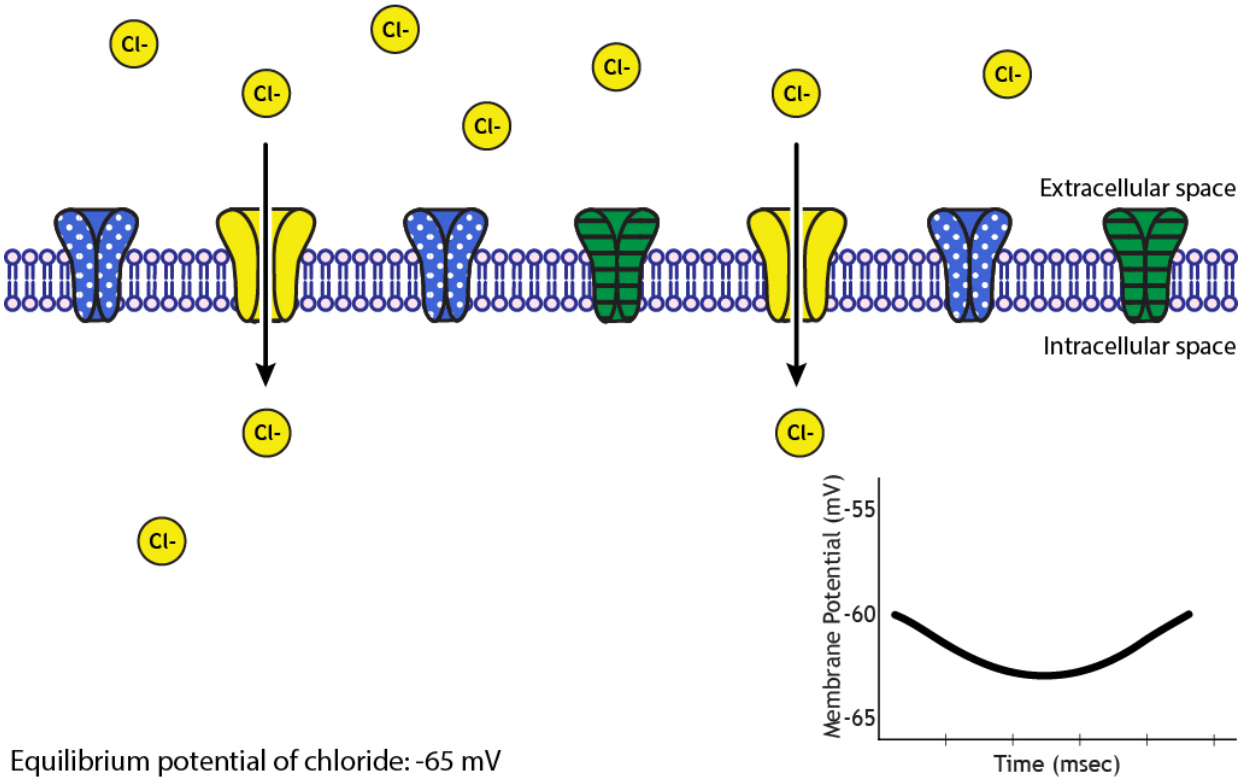


Figure 5.5. When a stimulus opens chloride channels, and the resting membrane potential is more positive than chloride's equilibrium potential of -65 mV, chloride rushes into the cell. This causes an inhibitory hyperpolarization called an inhibitory postsynaptic potential (IPSP). After the stimulus, 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.

Animation 4

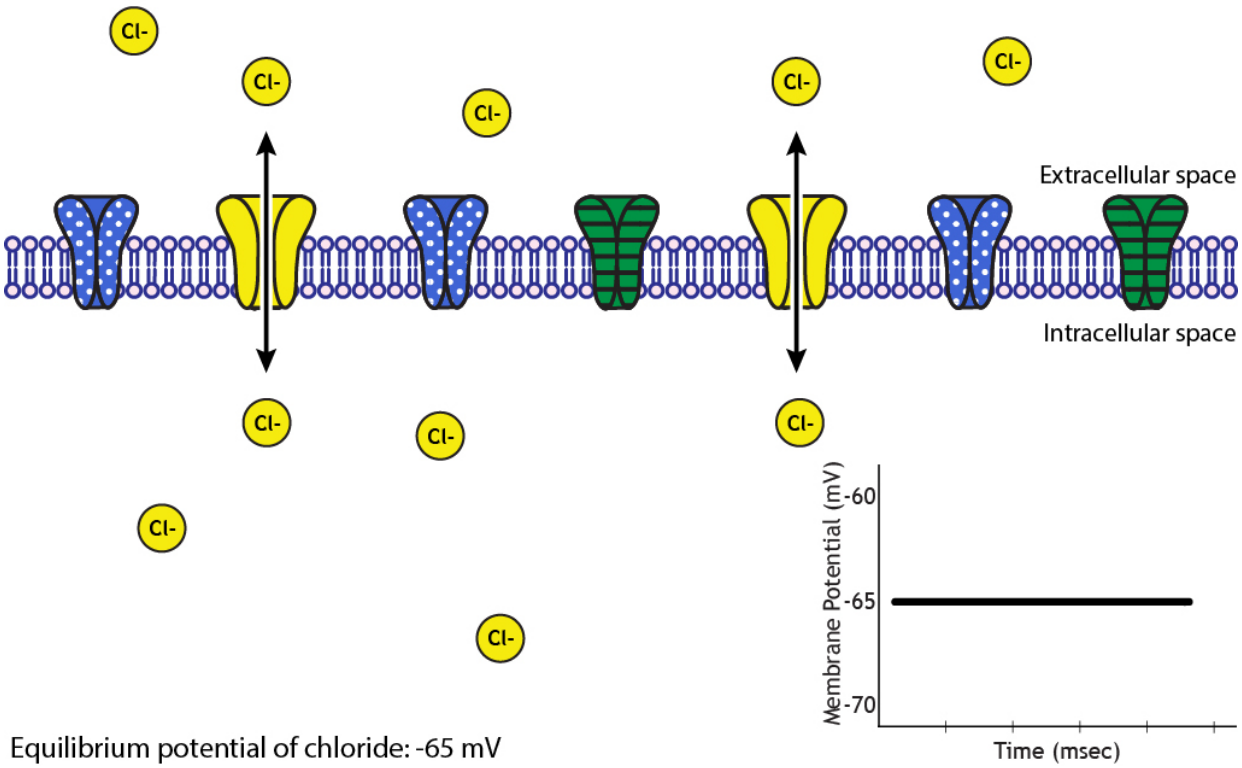


Figure 5.6. If the cell is at rest at chloride's equilibrium potential, when a stimulus opens the chloride channels, there will be no net movement of chloride in either direction because chloride will be at equilibrium. Since there is no net movement, there will also be no change in membrane potential 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.

Animation 5

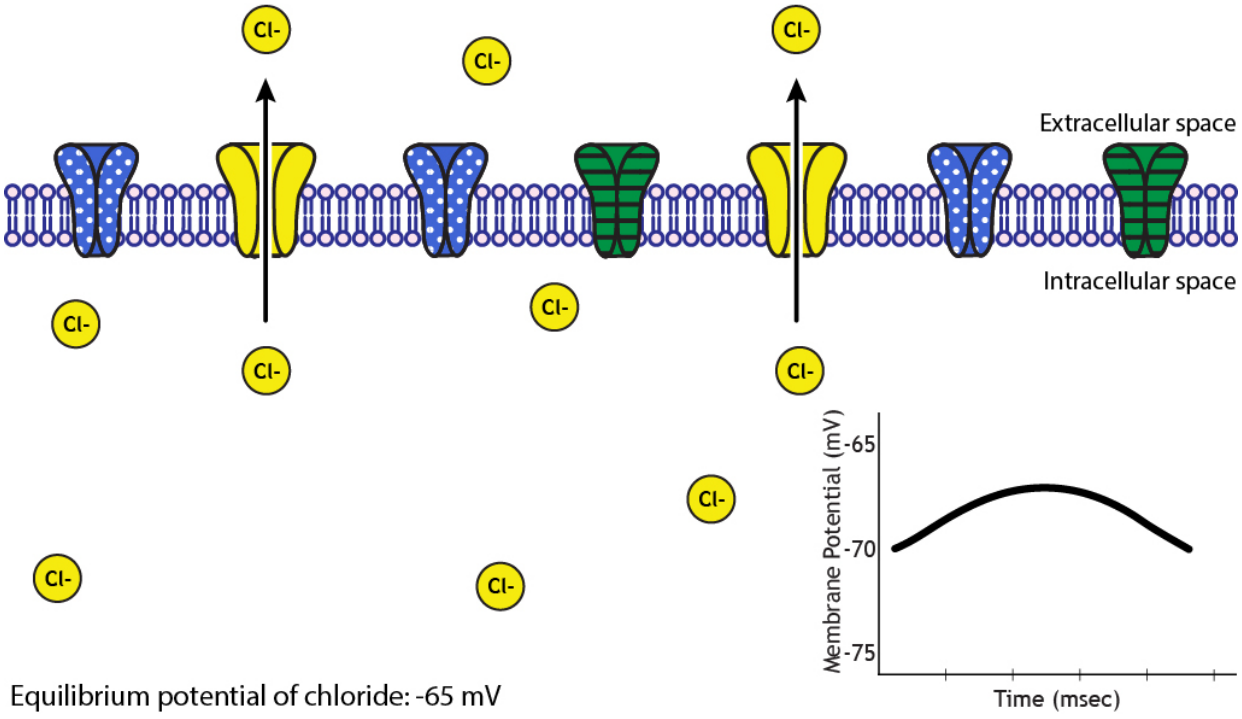


Figure 5.7. If the cell is at rest at chloride's equilibrium potential, when a stimulus opens the chloride channels, chloride will leave the cell, removing its negative charge. This causes a depolarization in the membrane potential, but it is still inhibitory since chloride movement will try to keep 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.

Animation 6

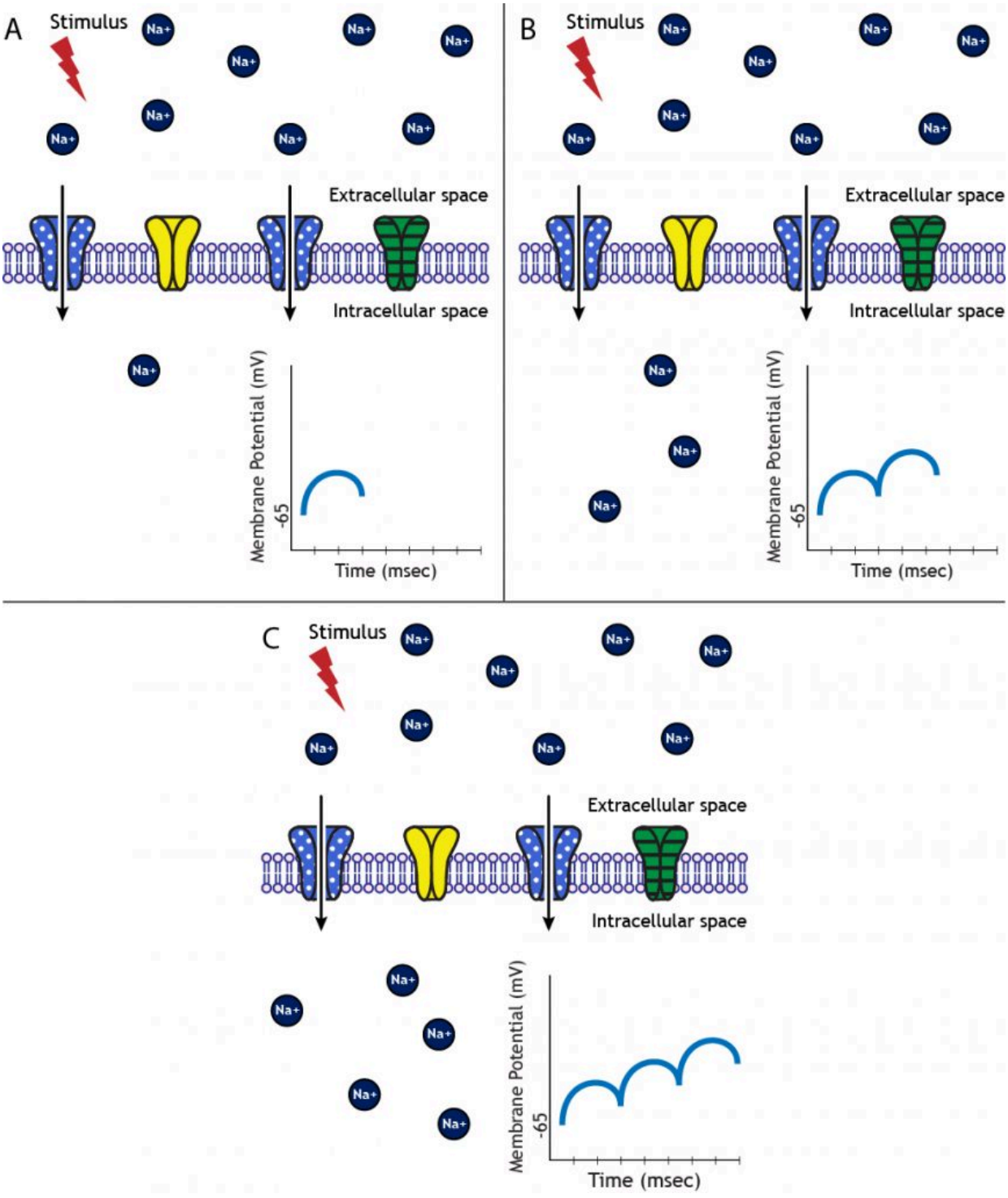


Figure 5.8. Excitatory stimuli that occur quickly in succession lead to summation of EPSPs. This leads to increased depolarization of the membrane potential compared to a single EPSP. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the

solid yellow channels represent chloride channels. 'Summated EPSPs' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 7

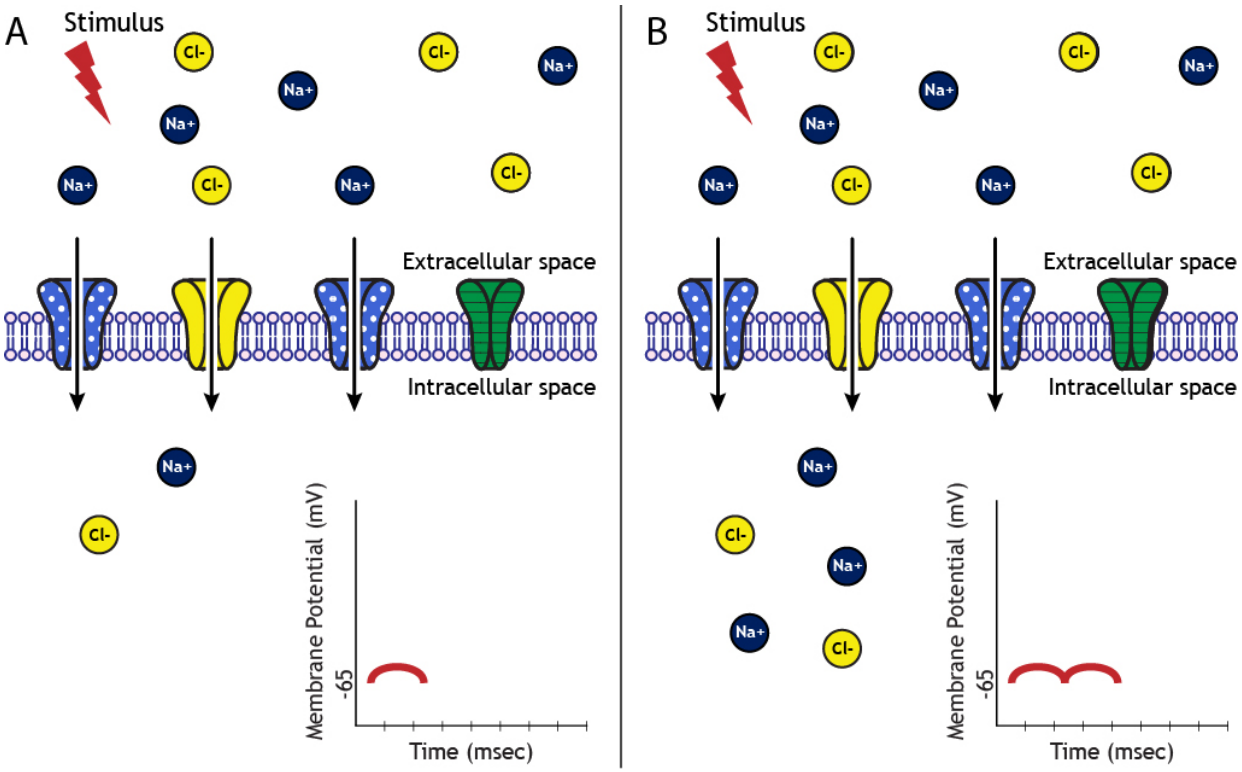
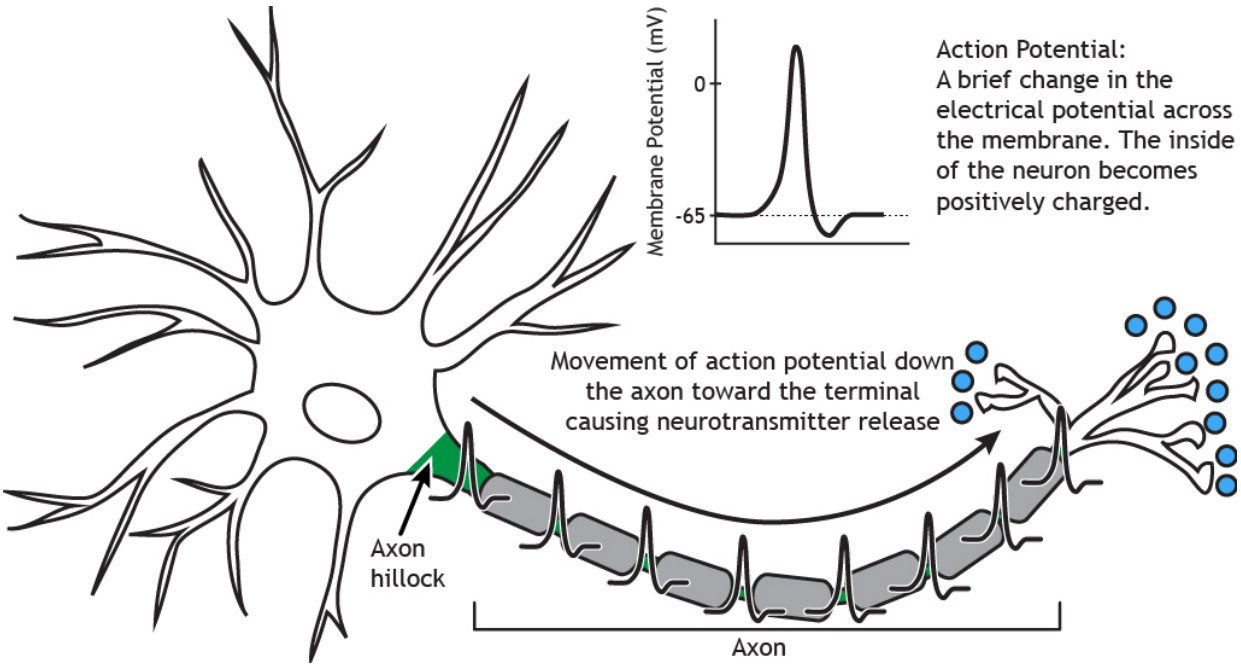


Figure 5.9. When an inhibitory input and an excitatory input stimulate a postsynaptic neuron at the same time, chloride and sodium channels open. Due to the equilibrium potentials of the two ions, both will flow into the cell. Sodium tries to depolarize the cell, whereas chloride tries to keep the cell 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.

Chapter 6

Animation 1



Animation 6.9. 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 is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 2

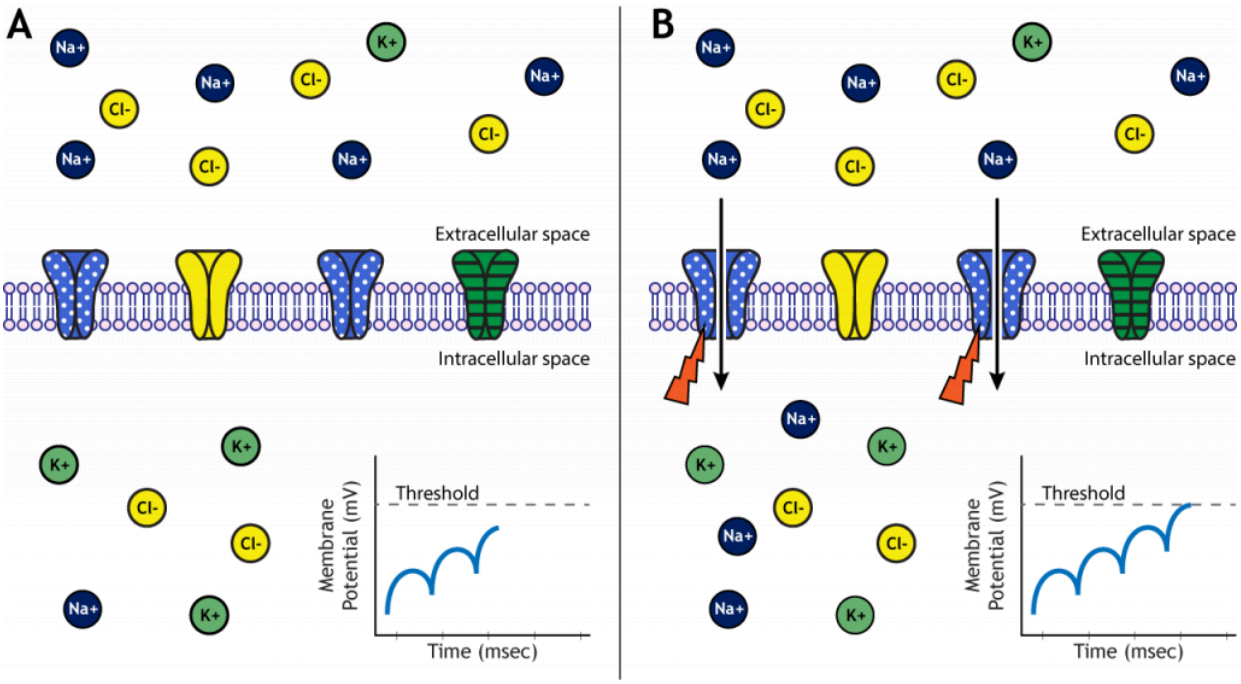


Figure 6.10. A. As EPSPs summate, a result of ion movement not shown in the figure, the cell's membrane potential will depolarize. B. Reaching threshold causes voltage-gated ion channels to open. Once the channels are open, ions will move toward equilibrium. In the figure, sodium ions flow inward. The 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.

Animation 3

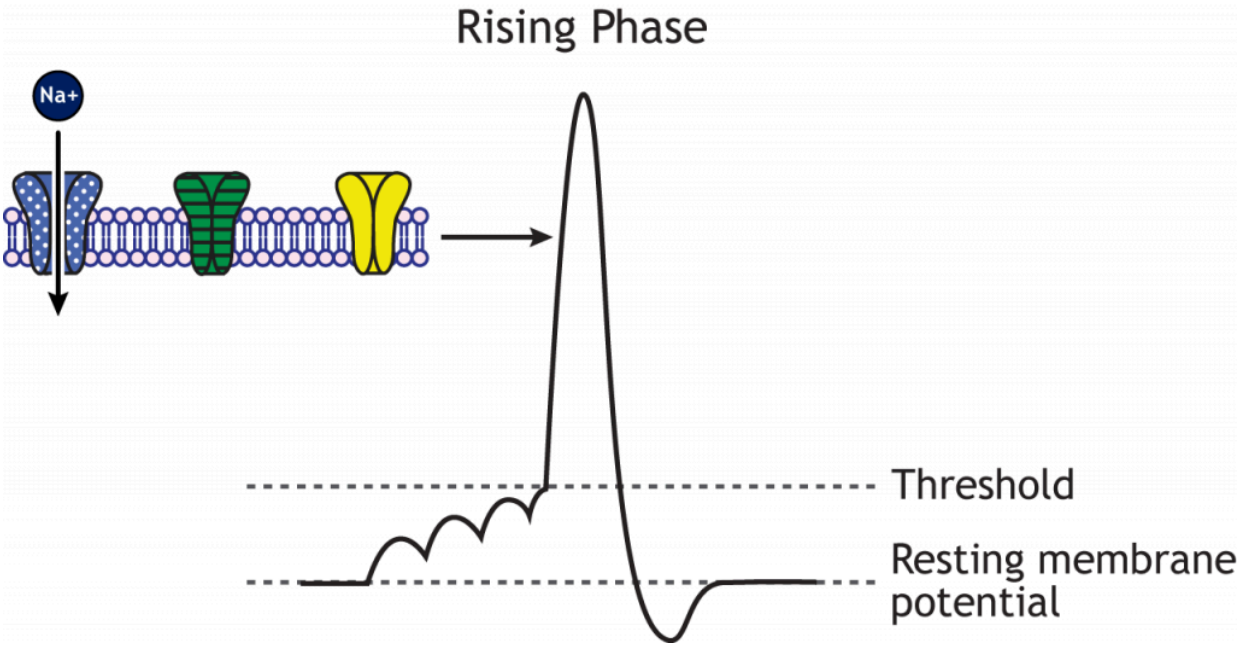


Figure 6.11. Voltage-gated sodium channels open once the cell's membrane potential reaches threshold. The rapid influx of sodium results in a large depolarization called the rising phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated 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.

Animation 4

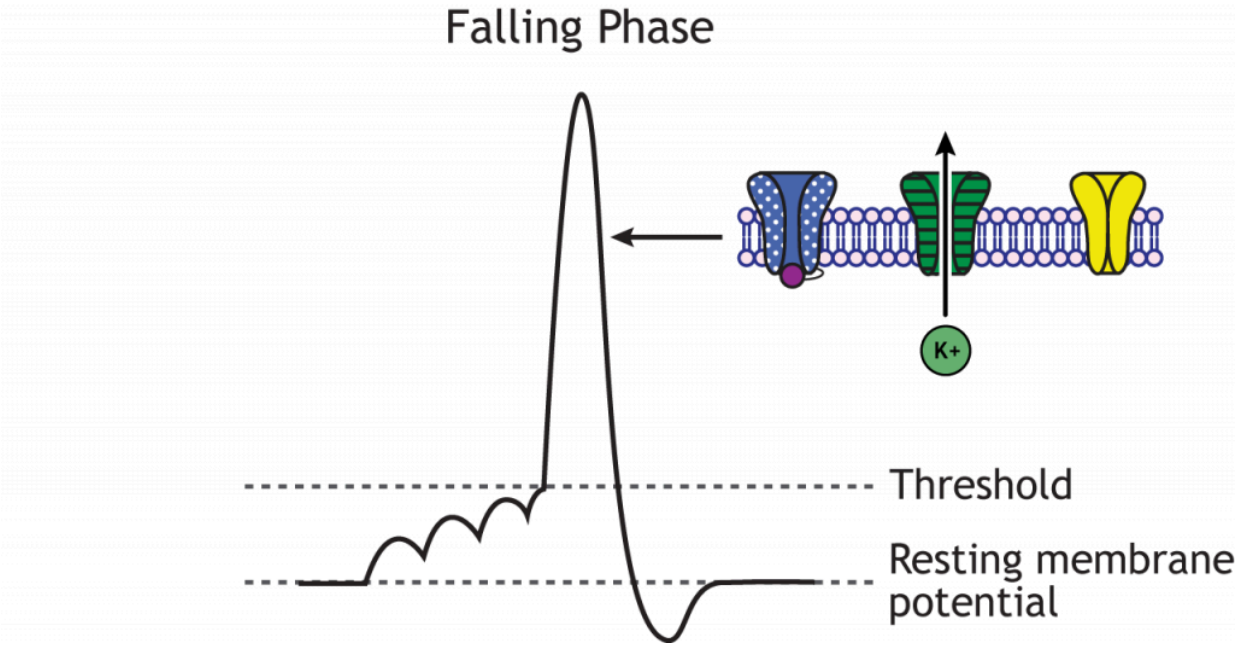


Figure 6.12. After approximately 1 msec, the voltage-gated sodium channels inactivate, which prevents any further ion flow into the cell. Although the voltage-gated potassium channels are activated in response to the cell reaching threshold, their opening is delayed and occurs alone with the sodium channel 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 chloride channels. 'Falling Phase" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 5

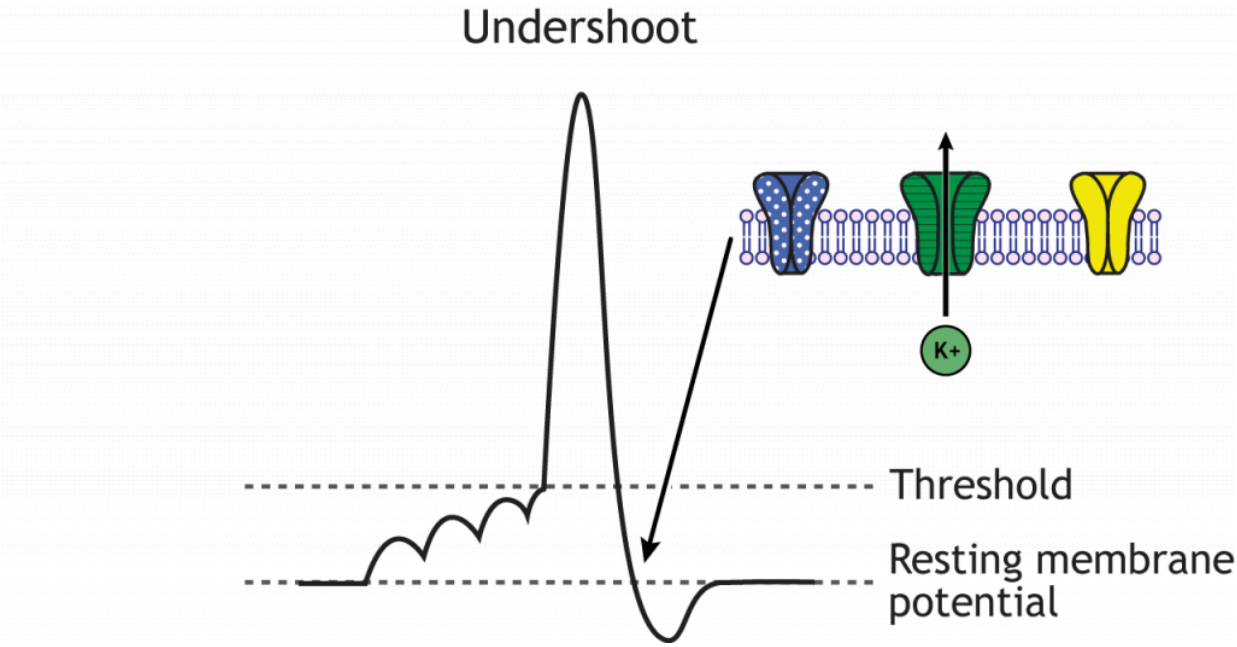


Figure 6.13. Once the cell's membrane potential repolarizes, the voltage-gated sodium channels de-inactivate and return to their closed state. The voltage-gated potassium channels remain open long enough for the undershoot to occur as potassium continues to flow out of the cell. The dotted, blue channels 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.

Animation 6

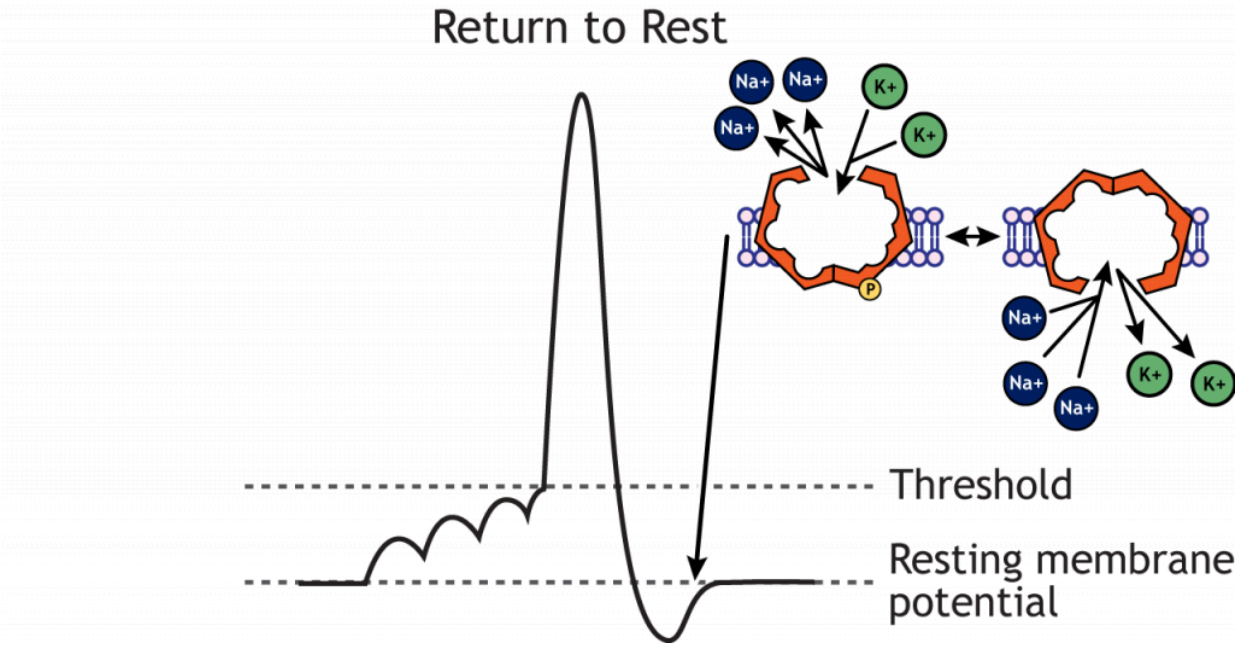


Figure 6.14. Once the voltage-gated potassium channels close, the sodium-potassium pump will work to re-establish the electrochemical gradients and return the cell to its resting membrane potential. 'Return to Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 7

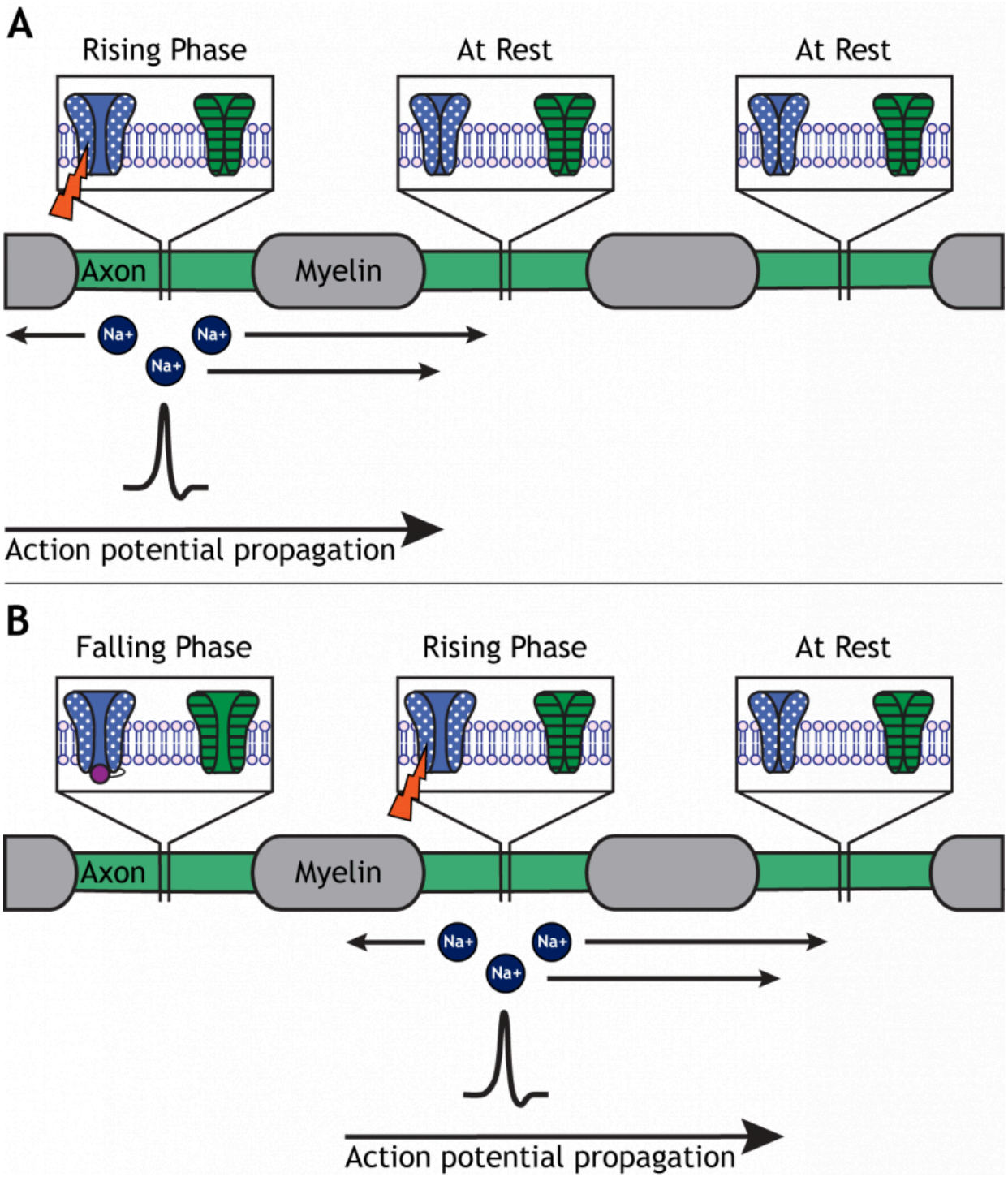


Figure 6.15. A) A voltage change that reaches threshold will cause voltage-gated sodium channels to open in the axonal membrane. The influx of sodium causes the rising phase of the action potential, but the ion flow also depolarizes nearby axon regions. B) As the depolarization reaches threshold,

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.

Animation 8

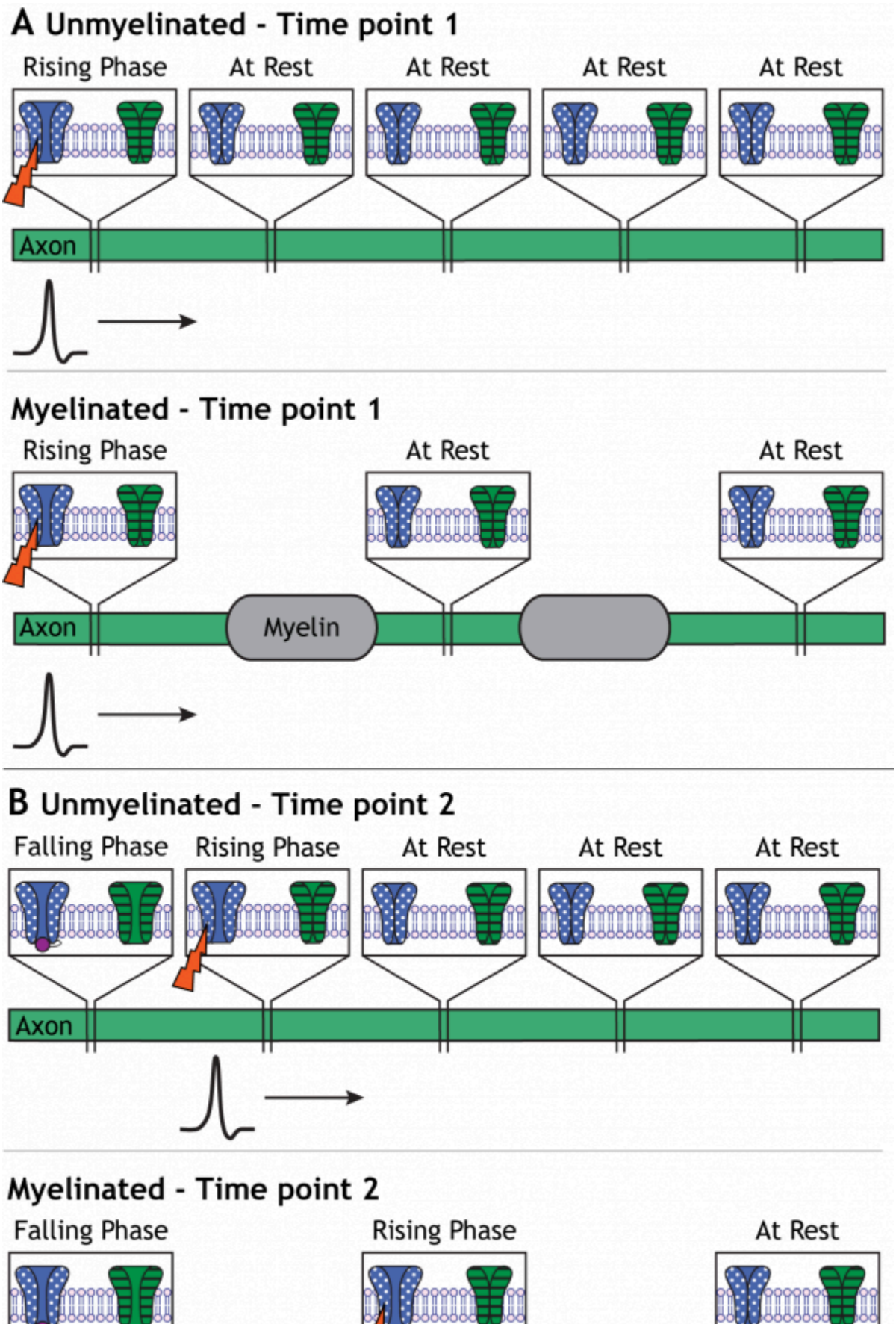

A Unmyelinated - Time point 1
Rising Phase
At Rest
At Rest
At Rest
At Rest
Axon
Myelinated - Time point 1
Rising Phase
At Rest
At Rest
Axon
Myelin
B Unmyelinated - Time point 2
Falling Phase
Rising Phase
At Rest
At Rest
At Rest
Axon
Myelinated - Time point 2
Falling Phase
Rising Phase
At Rest

Figure 6.16. 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.

Chapter 7

Animation 1

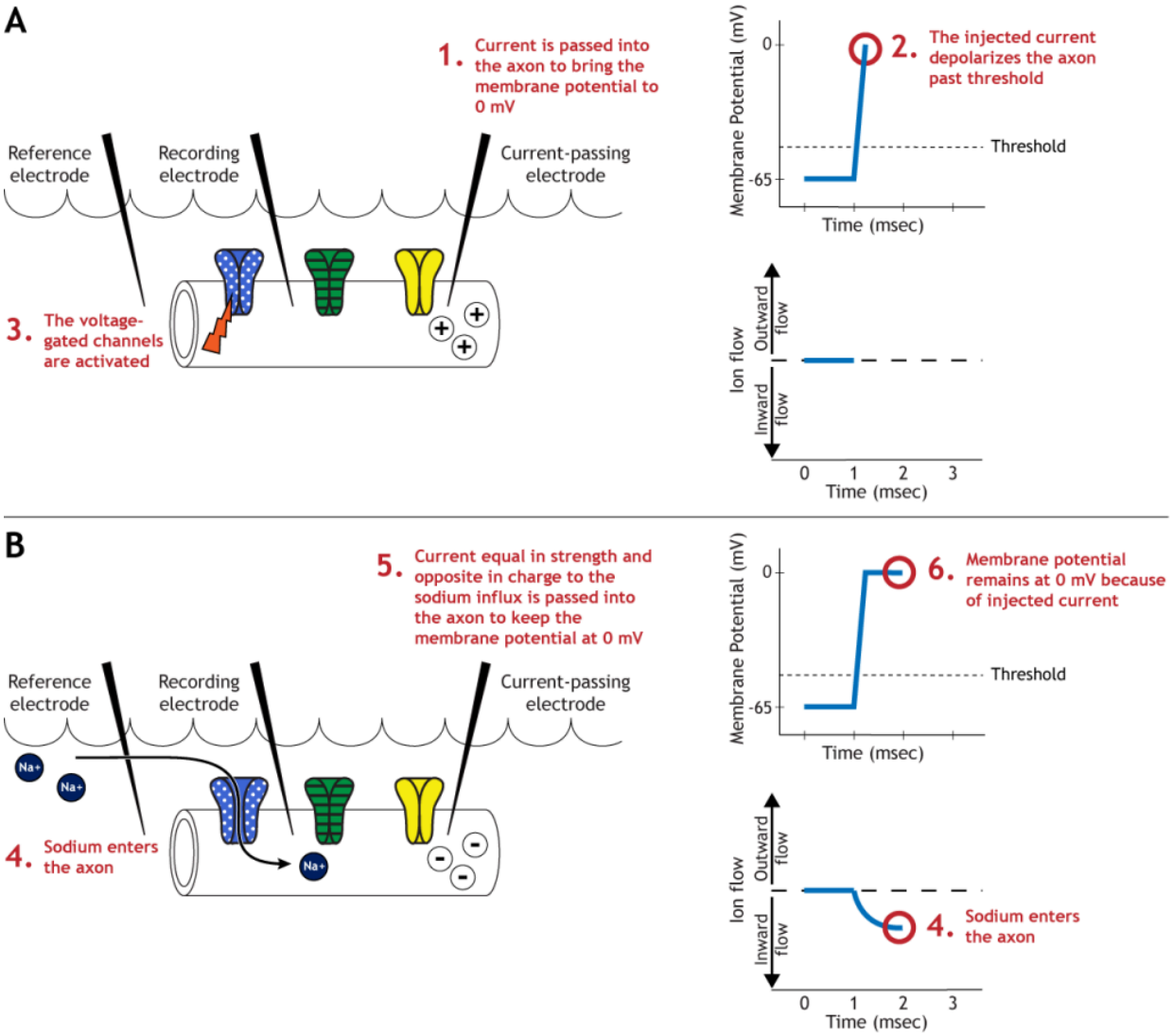


Figure 7.9. A) Clamping the cell at 0 mV will result in current being passed into the axon to depolarize the membrane potential. This depolarization is above threshold, so the voltage-gated ion channels in the membrane will be activated. B) Sodium will enter the axon through the open sodium channels. 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.

Animation 2

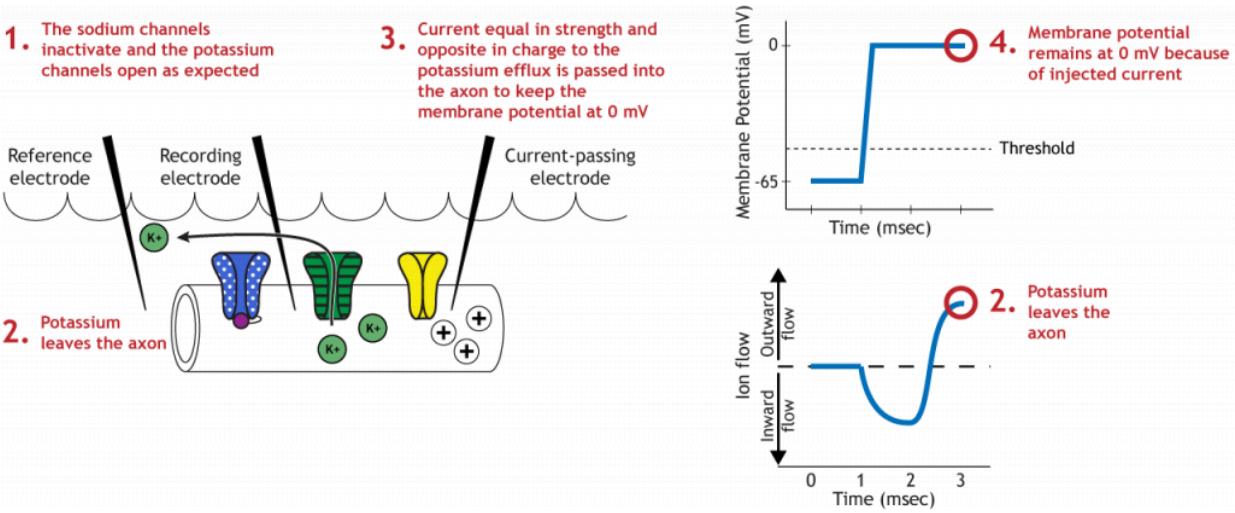


Figure 7.10. The voltage-gated sodium channels will inactivate, and the potassium channels will open. Potassium will then flow out of the axon. Similar to the sodium influx, the voltage clamp equipment will inject current equal in strength and opposite in charge to the potassium efflux in order to keep 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.

Chapter 8

Animation 1

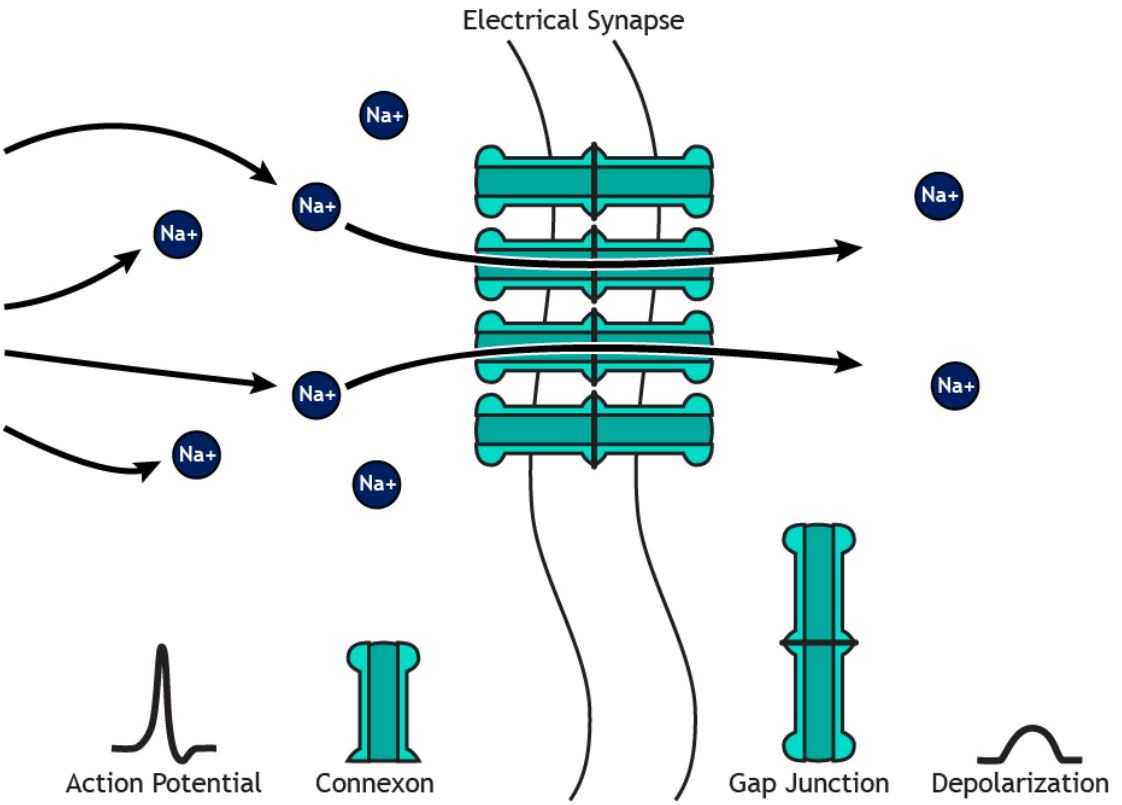


Figure 8.4. Membrane-bound proteins called connexons form gap junctions between presynaptic and postsynaptic neurons. This allows for direct exchange of ions between neurons. An action potential in the presynaptic neuron will cause an immediate depolarization of the postsynaptic membrane because the 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.

Animation 2

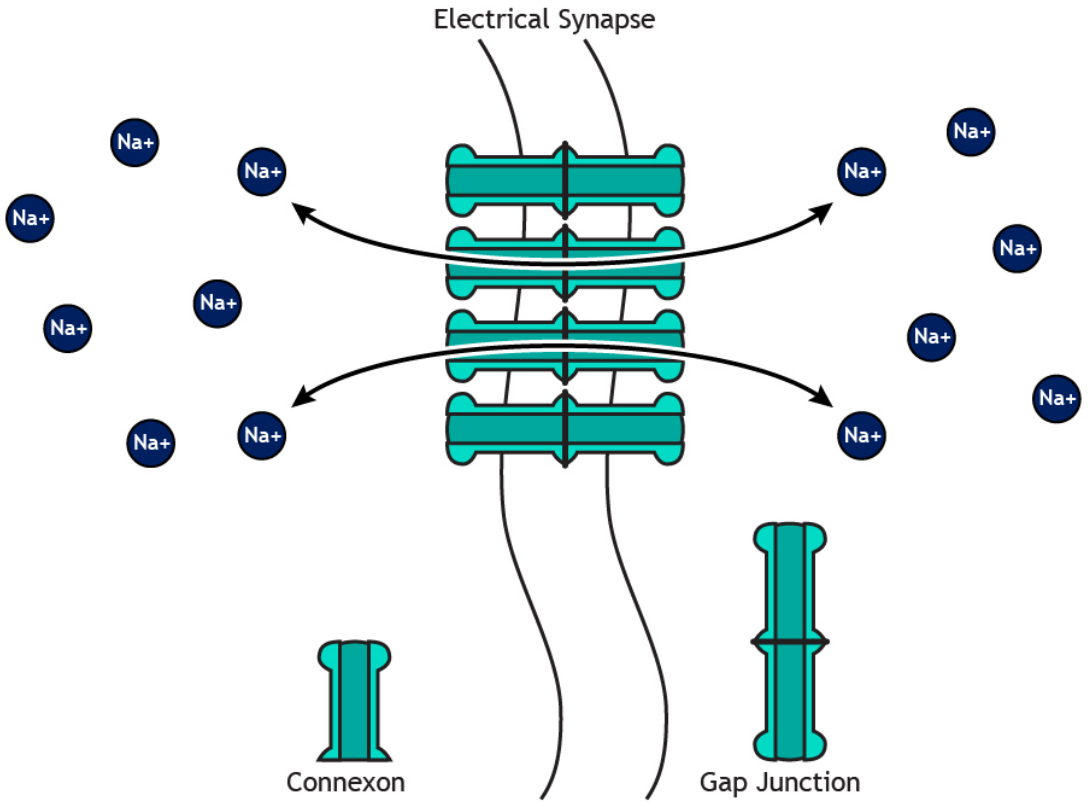


Figure 8.5. Since an electrical synapse is a direct, physical connection between two neurons, ions are able to flow either direction across the gap junction. 'Bidirectional Electrical Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 3

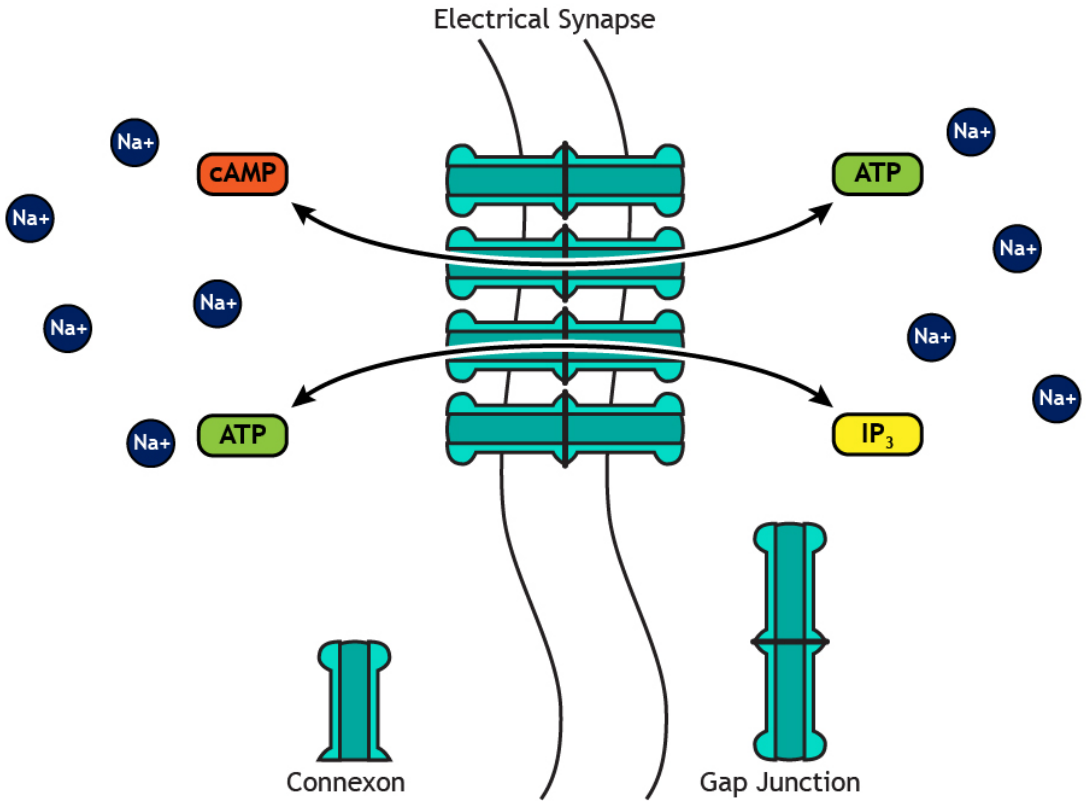


Figure 8.6. Gap junctions are large enough to allow the flow of small cellular molecules like ATP or second messengers. 'Electrical Synapse – Small Molecules' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 4

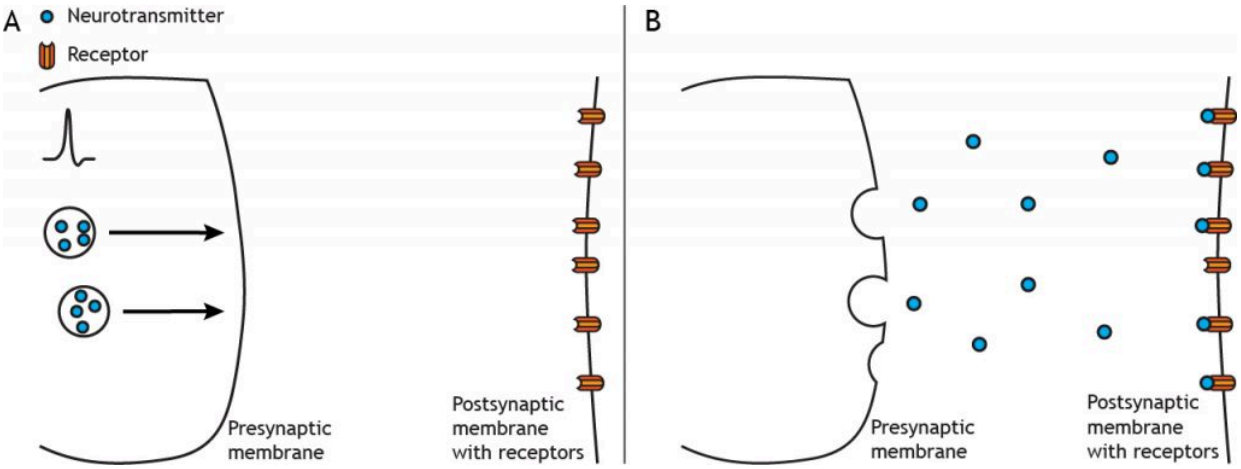
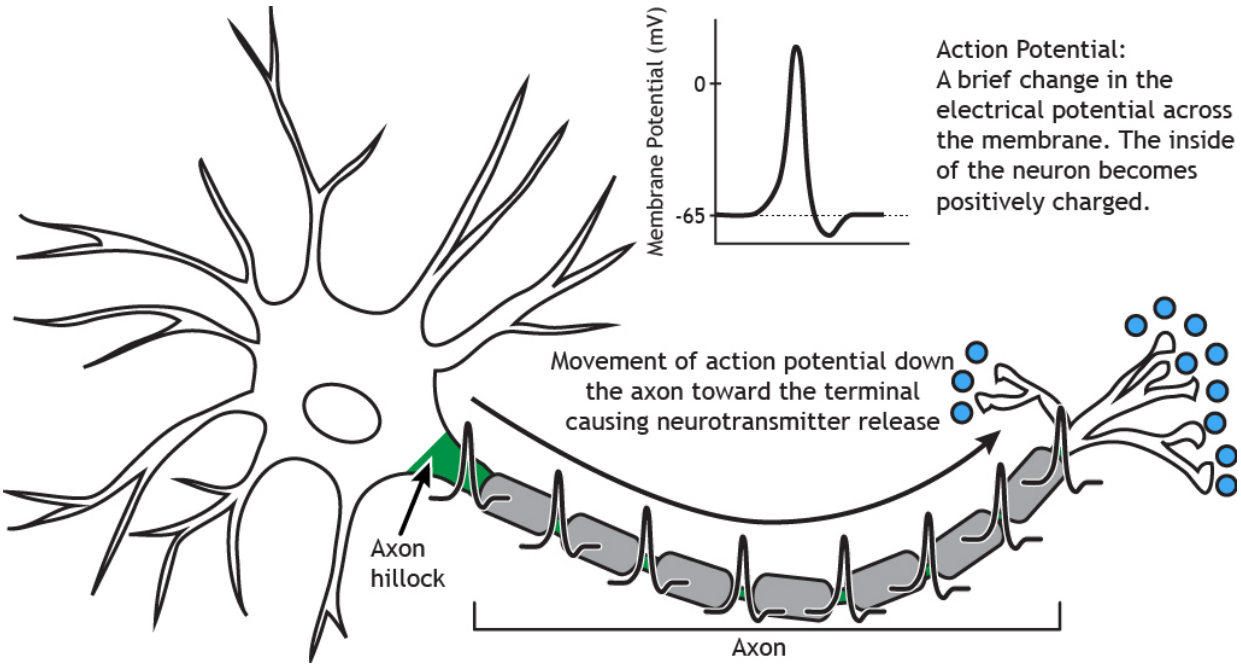


Figure 8.7 When an action potential arrives in the presynaptic terminal, neurotransmitters are released into the synaptic cleft where they can act on neurotransmitter receptors in the postsynaptic membrane. 'Chemical Synapse – Neurotransmitter Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 10

Animation 1



Animation 10.5. 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.

Animation 2

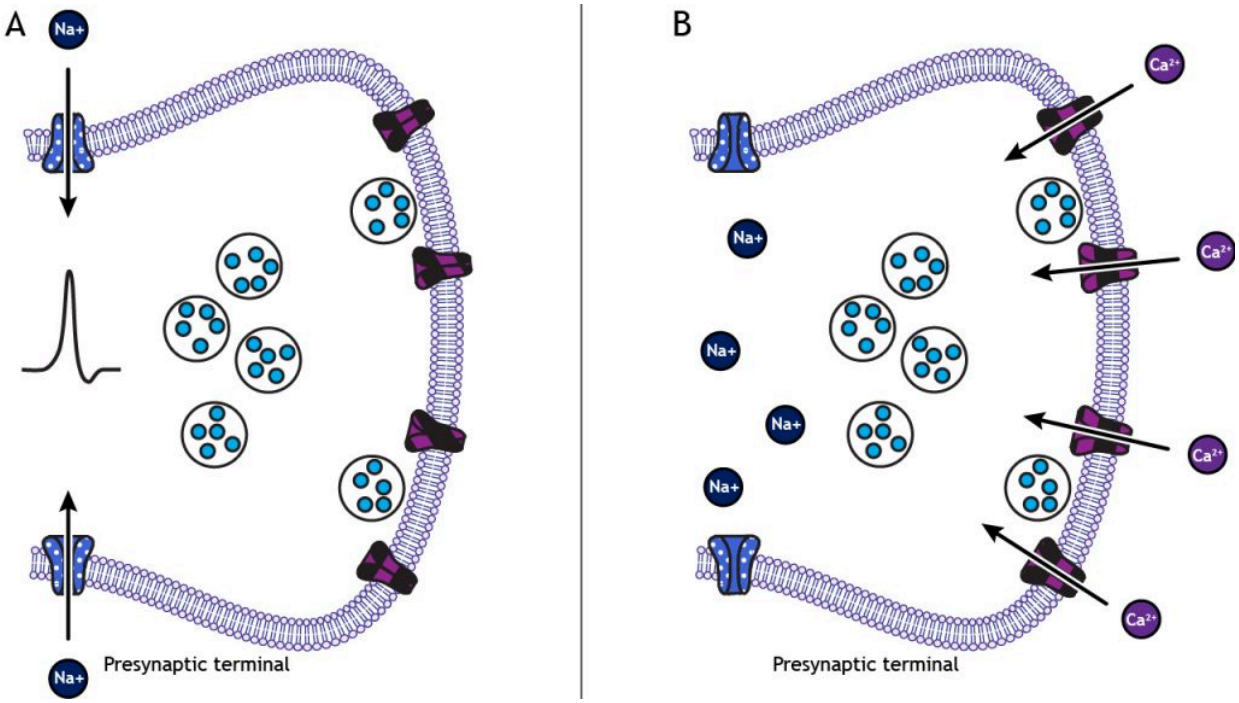


Figure 10.6. A) An action potential causes an influx of sodium in the terminal. B) The depolarization opens voltage-gated calcium channels, and calcium ions flow into the terminal down their electrochemical gradient. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped 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.

Animation 3

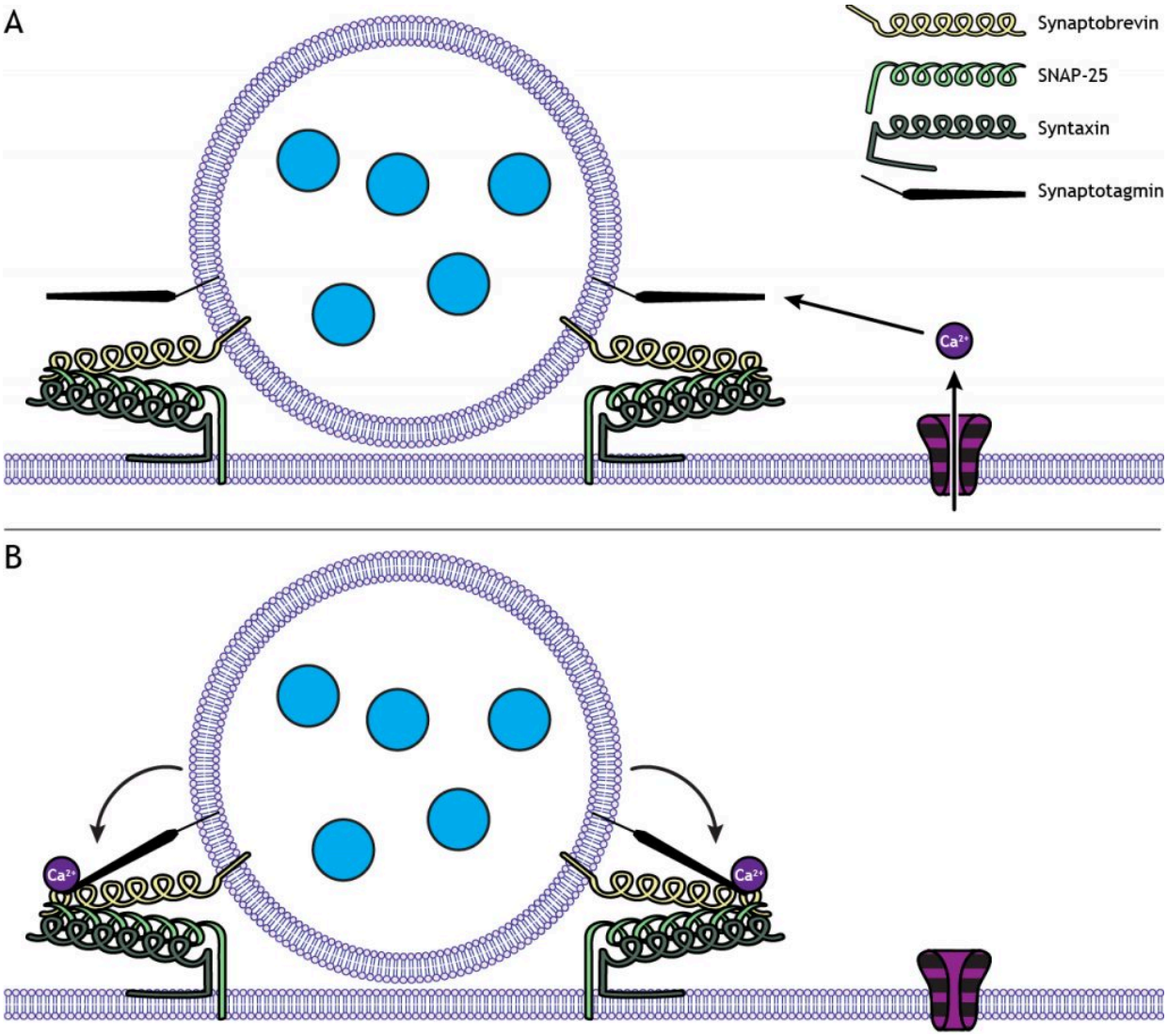


Figure 10.7. A) Calcium enters the cell when the voltage-gated channels open. B) In the presence of calcium, synaptotagmin, a protein bound to the vesicular membrane interacts with the SNARE proteins. The purple, striped channels represent voltage-gated calcium channels. 'Synaptotagmin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 4

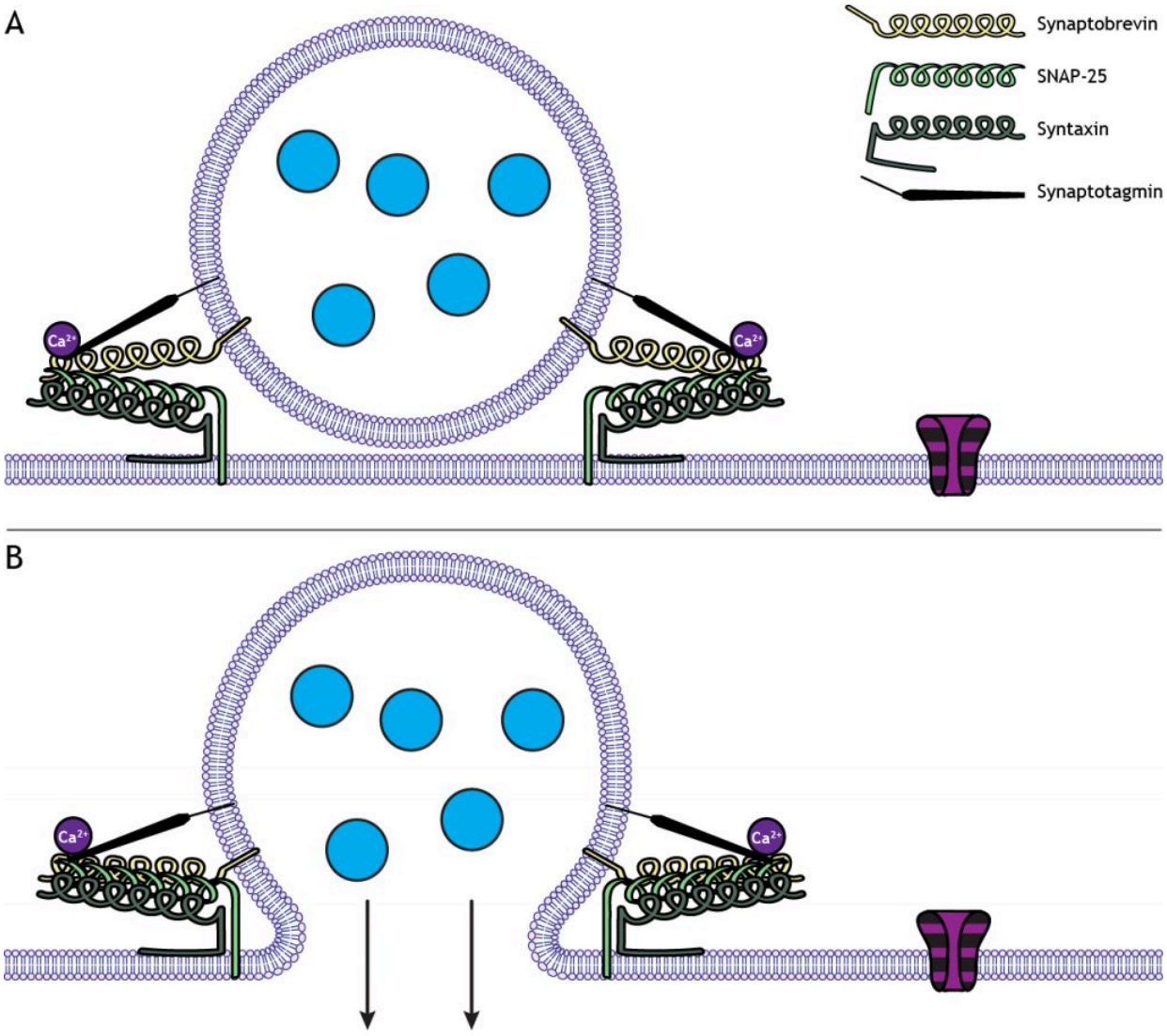


Figure 10.8. Once the synaptotagmin-SNARE protein complex forms, the synaptic vesicle membrane fuses with the terminal membrane, and the neurotransmitters are released into the synaptic cleft through exocytosis. The purple, striped channels represent voltage-gated calcium channels. 'Transmitter Exocytosis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Chapter 11

Animation 1

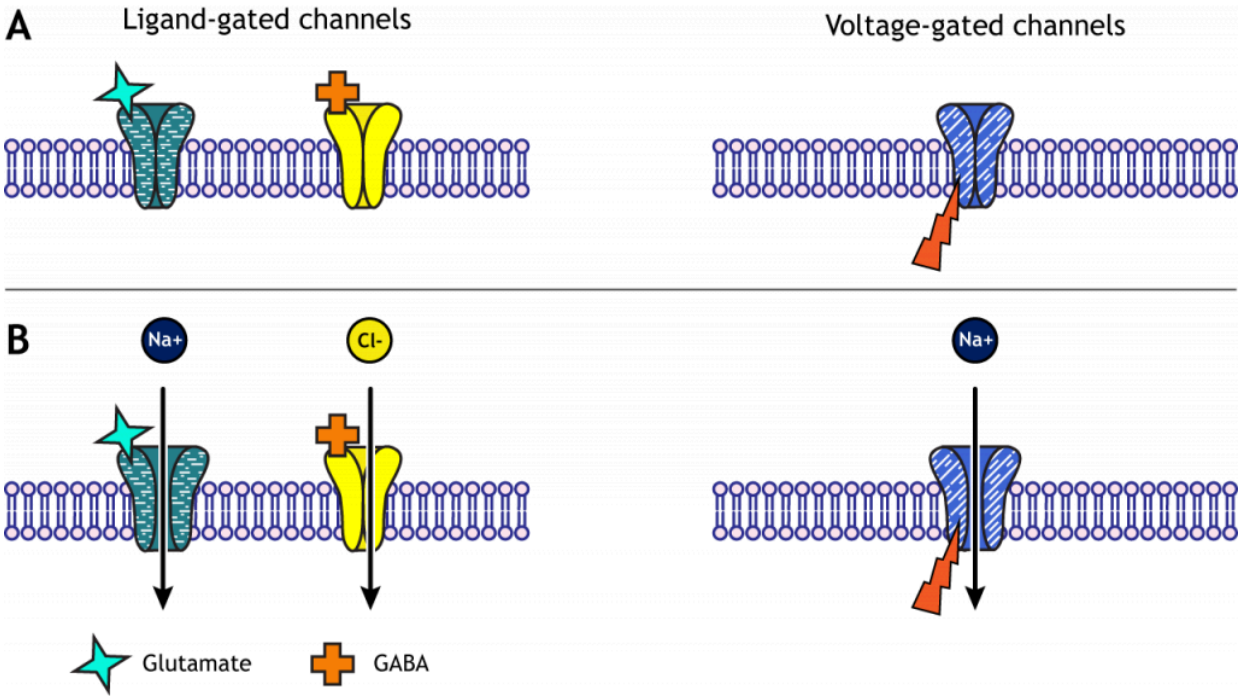


Figure 11.2. A) Ionotropic receptors, also called ligand-gated channels, are ion channels that are opened by the binding of neurotransmitters. Voltage-gated channels are opened by the membrane potential of the cell reaching threshold. B) Both types of channels allow ions to diffuse down their electrochemical 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.

Animation 2

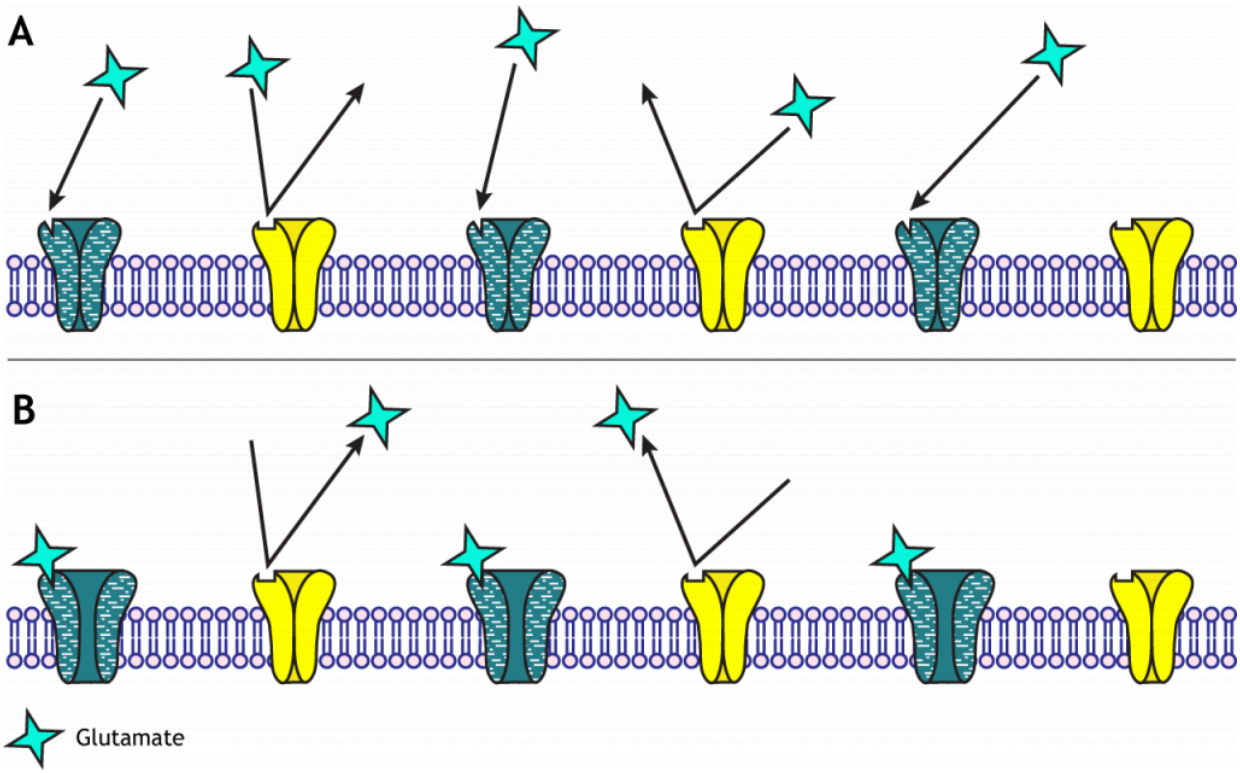


Figure 11.3. Since neurotransmitter receptors can only bind specific neurotransmitters. glutamate binds to (A) and opens (B) glutamate receptors but has no effect on GABA receptors. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors. 'Ligand and Receptor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 3

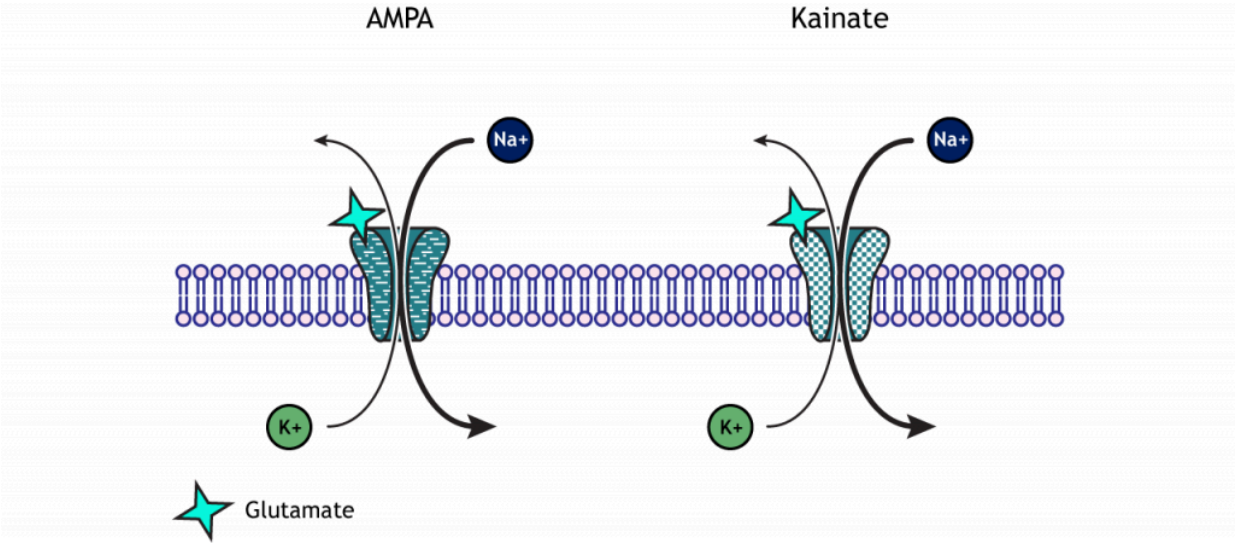


Figure 11.4. AMPA and kainate glutamate receptors are non-selective ion channels that allow both sodium and potassium to flow across the membrane. When glutamate binds, sodium flows in and potassium flows out. The lined, teal channel represents AMPA receptors; the checkered, teal channel represents kainate 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.

Animation 4

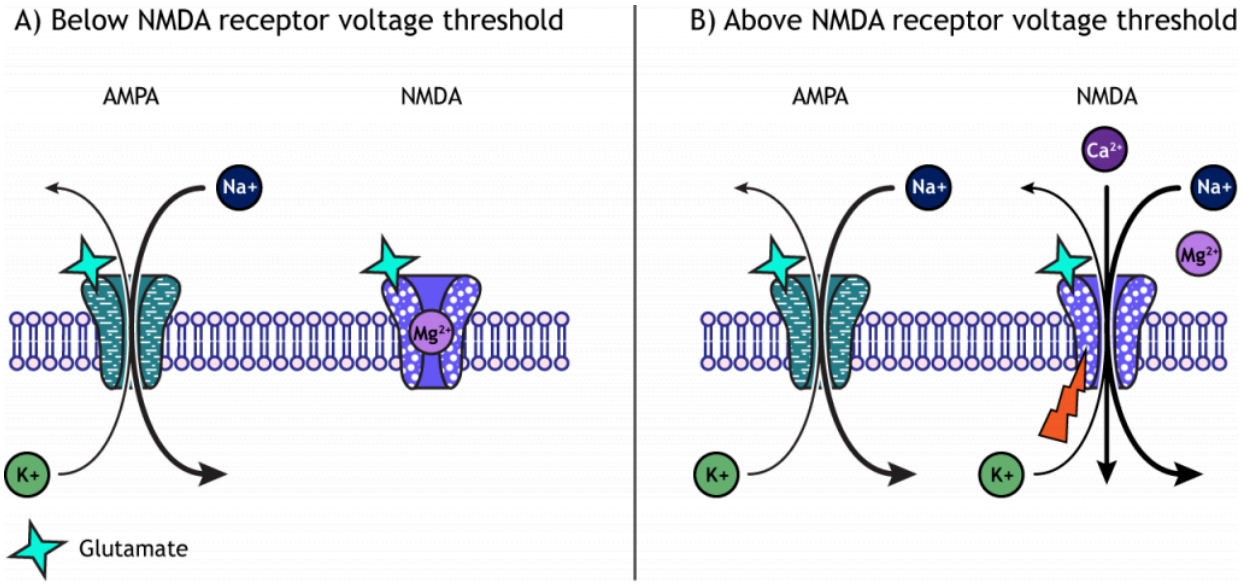


Figure 11.5. NMDA receptors are opened by a combination of glutamate binding and a voltage trigger. A) At low levels of stimulation when the the membrane potential is near rest and below the NMDA receptor voltage threshold, a magnesium ion blocks the open NMDA receptor channel preventing ion flow. Ions can flow through open AMPA receptors, which begins to depolarize the membrane. B) Once the NMDA receptor voltage threshold has been reached, the magnesium ion is expelled from the channel, allowing sodium, potassium, and calcium to cross the membrane. The lined, teal channels represent AMPA receptors; the dotted, violet channels represent NMDA receptors. 'AMPA and NMDA' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 5

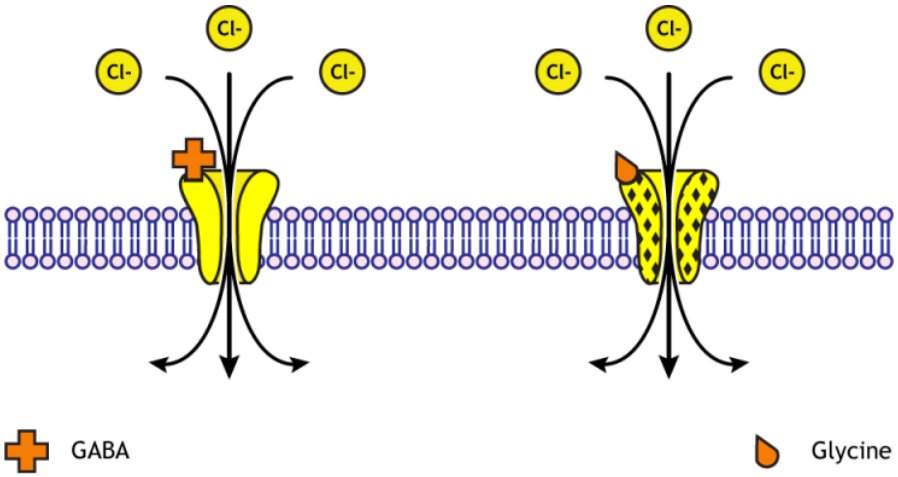


Figure 11.6. GABA and glycine are inhibitory receptors that are selective to chloride. The solid yellow channel represents a GABA receptor; the patterned, yellow channel represents a glycine receptor. 'GABA and Glycine' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 6

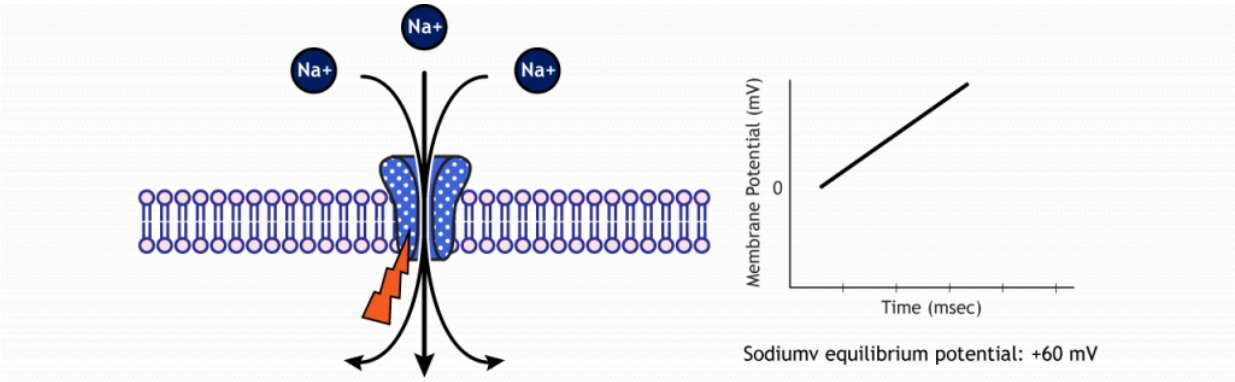


Figure 11.7. Ions move through open voltage-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the ion's equilibrium potential. In the figure, a voltage-gated sodium channel opens, and sodium flows in until the membrane potential 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.

Animation 7

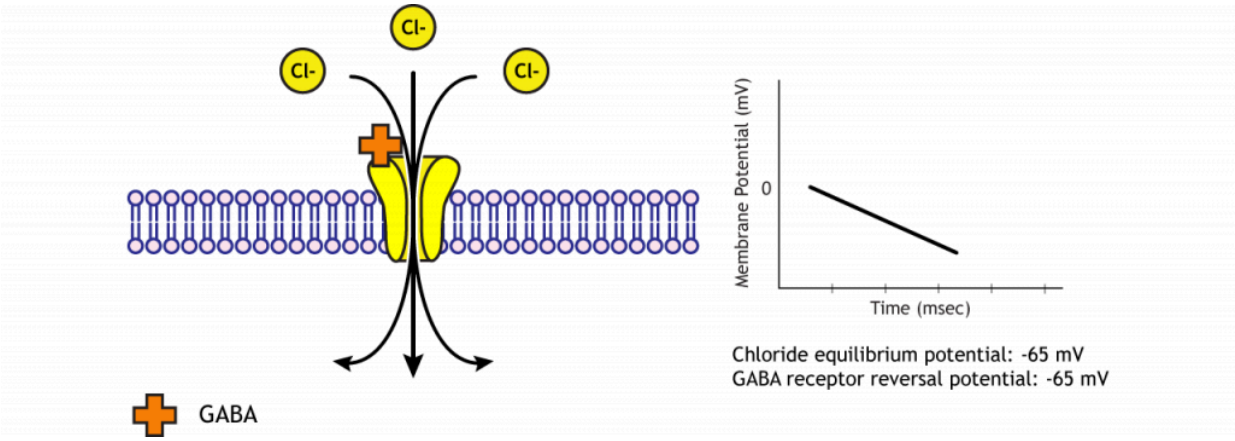


Figure 11.8. Ions move through open ligand-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the receptor's reversal potential. When the ionotropic receptor only increases permeability for one ion, the receptor's reversal potential 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. 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.

Animation 8

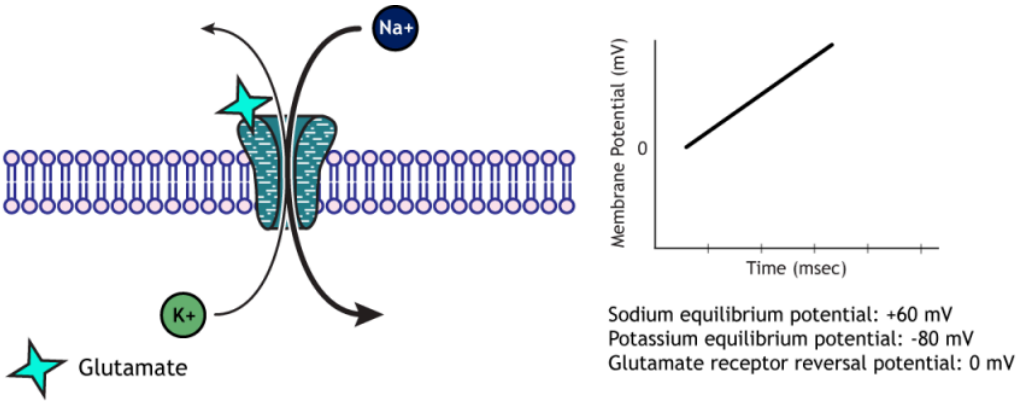


Figure 11.9. The reversal potential of an ionotropic receptor that is not selective to one ion will fall between the equilibrium potentials of the permeable ions. Glutamate receptors allow the flow of both sodium and potassium ions, so the reversal potential for the receptor is approximately 0 mV. More 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.

Animation 9

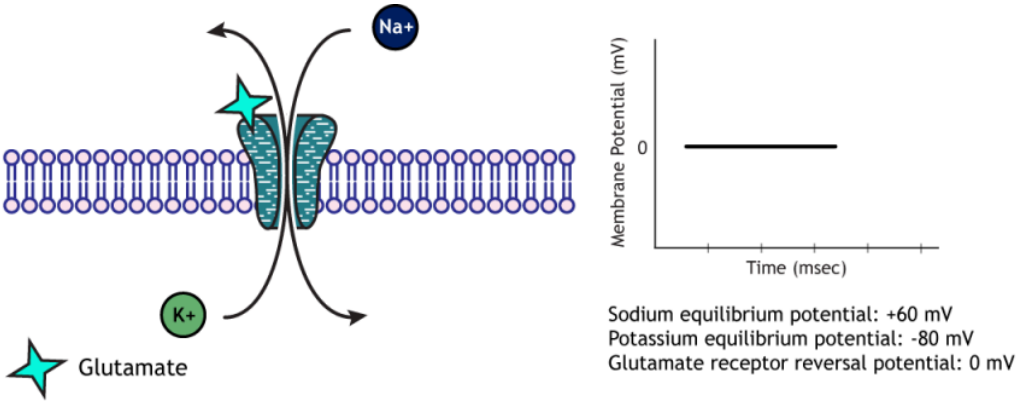


Figure 11.10. At the reversal potential, there is no net ion flow in either direction. An equal number of sodium ions enter the cell as potassium ions leave. Since there is no change in voltage at the reversal potential, if the receptor remained open, the membrane potential would stay at 0 mV. 'Glutamate 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.

Chapter 12

Animation 1

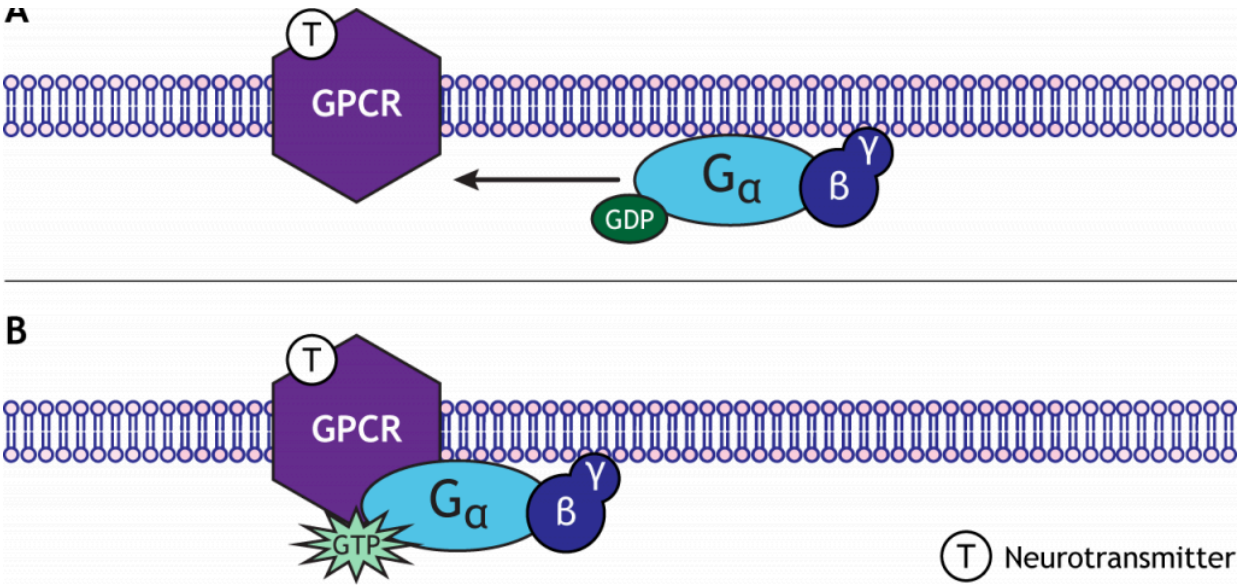


Figure 12.5. A) Neurotransmitter binding to a G-protein-coupled receptor causes the inactivated G-protein complex to interact with the receptor. B) The GDP molecule is then exchanged for a GTP molecule, which activates the G-protein complex. 'G-protein Binding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 2

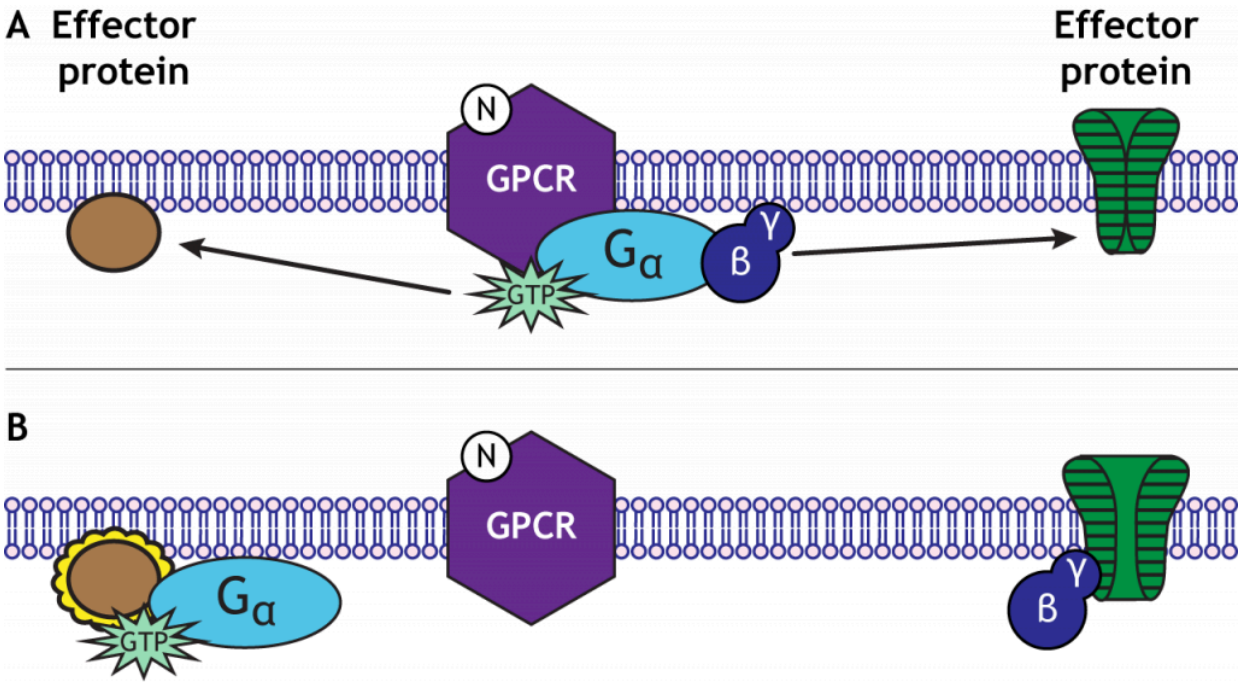


Figure 12.6. A) Once activated, the G-protein complex will separate into the alpha-GTP subunit and the beta-gamma subunit. B) These subunits can stimulate or inhibit effector proteins within the cell. 'G-protein Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 3

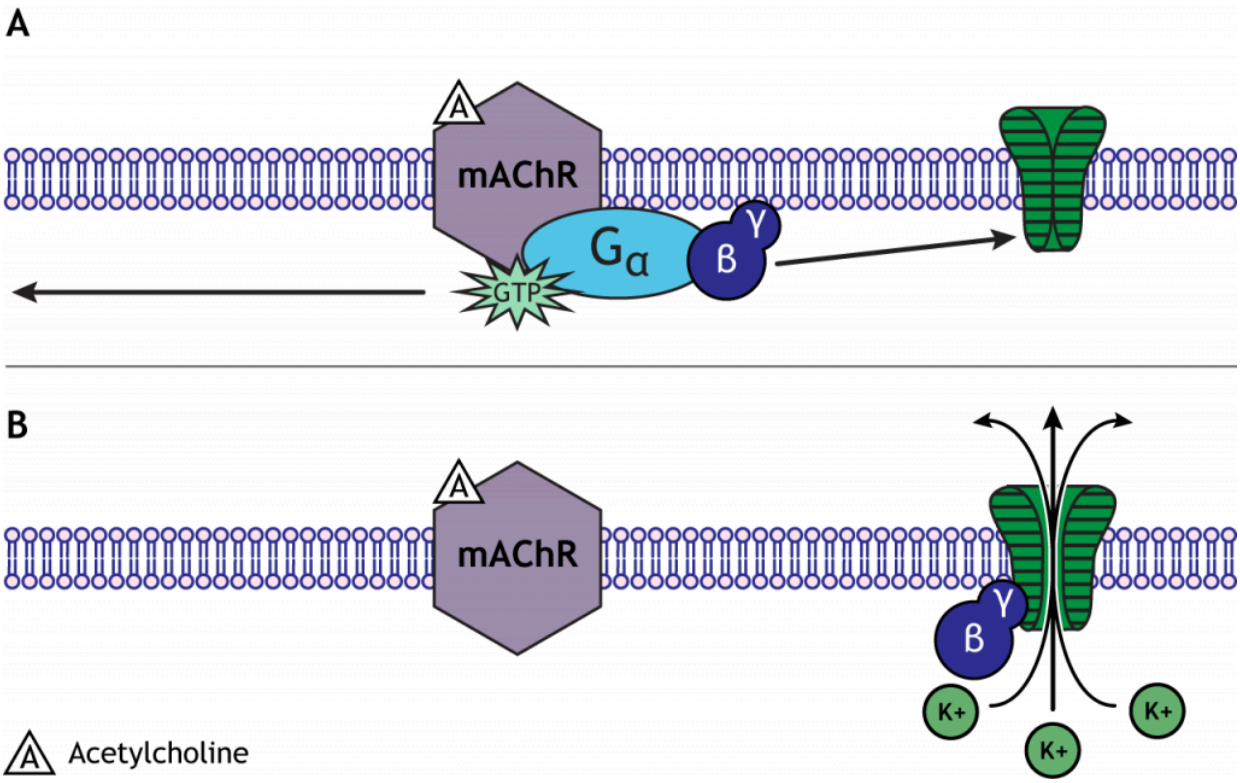


Figure 12.7. Some GPCRs, like the muscarinic acetylcholine receptors in the heart, alter cellular permeability by opening ion channels. The activated beta-gamma subunit of the muscarinic receptor (A) opens GIRK potassium channels and allows the efflux of potassium (B). 'Beta-Gamma Ion Channels' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 4

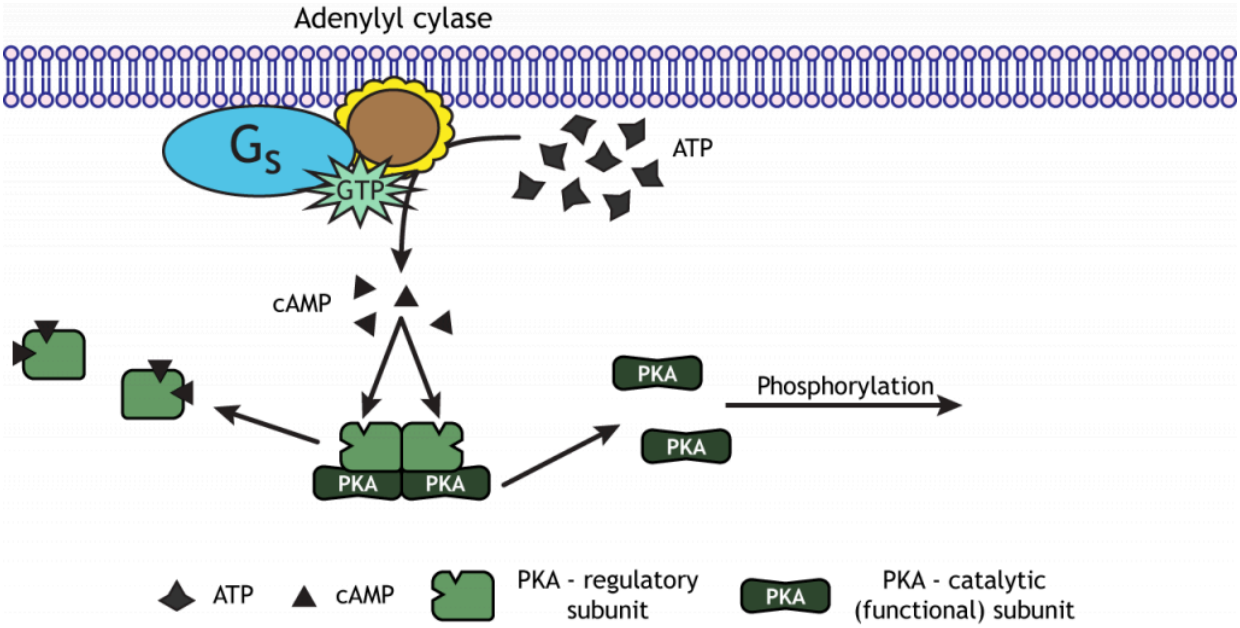


Figure 12.8. GPCRs that couple to the Gs alpha subunit initiate the adenylyl cyclase / cAMP pathway. The Gs subunit activates adenylyl cyclase, which then converts ATP to cAMP. cAMP binds to and activates protein kinase A (PKA), which phosphorylates proteins in the cell. 'Adenylyl Cyclase Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 5

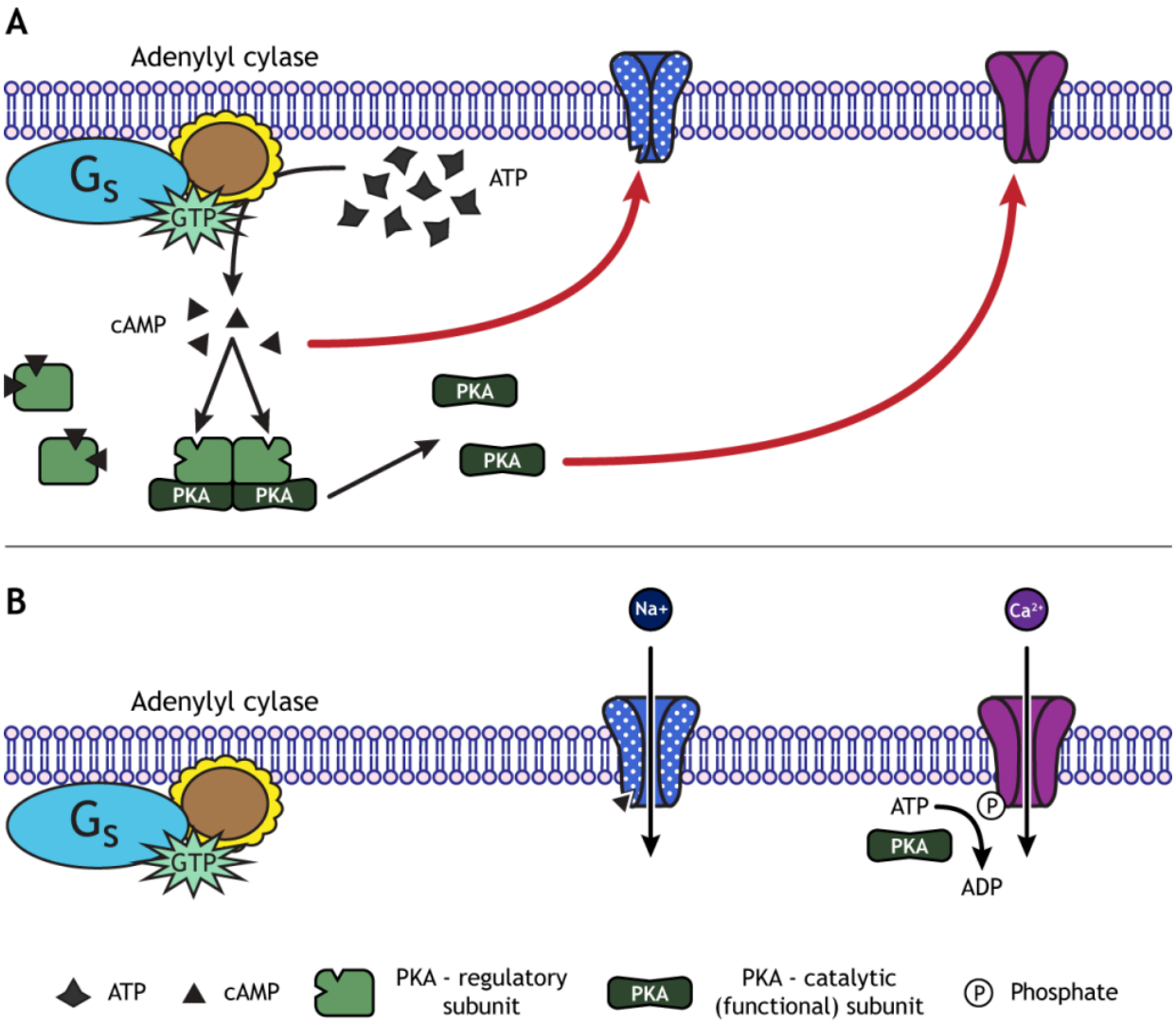


Figure 12.9. A) The adenylyl cyclase / cAMP pathway can alter many cellular functions. One example is that both cAMP and PKA can open ion channels. B) Like ligand-gated channels, there are also cAMP-gated channels, which open after cAMP binding. PKA is able to phosphorylate and modulate ion channel function 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.

Animation 6

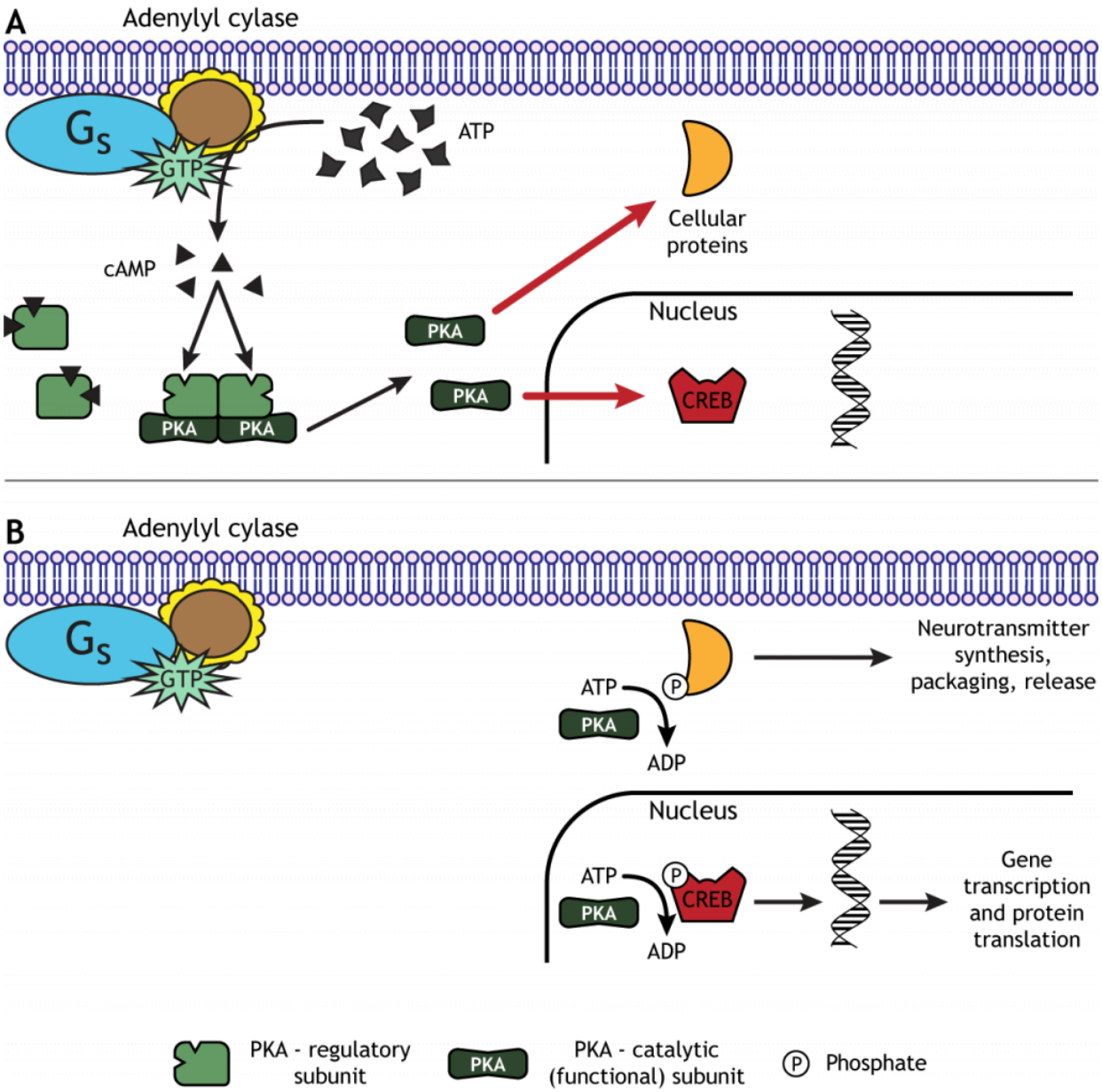


Figure 12.10. A) PKA can phosphorylate a number of proteins involved with neuron function. B) It can target proteins involved with neurotransmitter synthesis, packing, and release, or it can enter the nucleus and phosphorylate CREB, a transcription factor that can initiate gene transcription and protein 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.

Animation 7

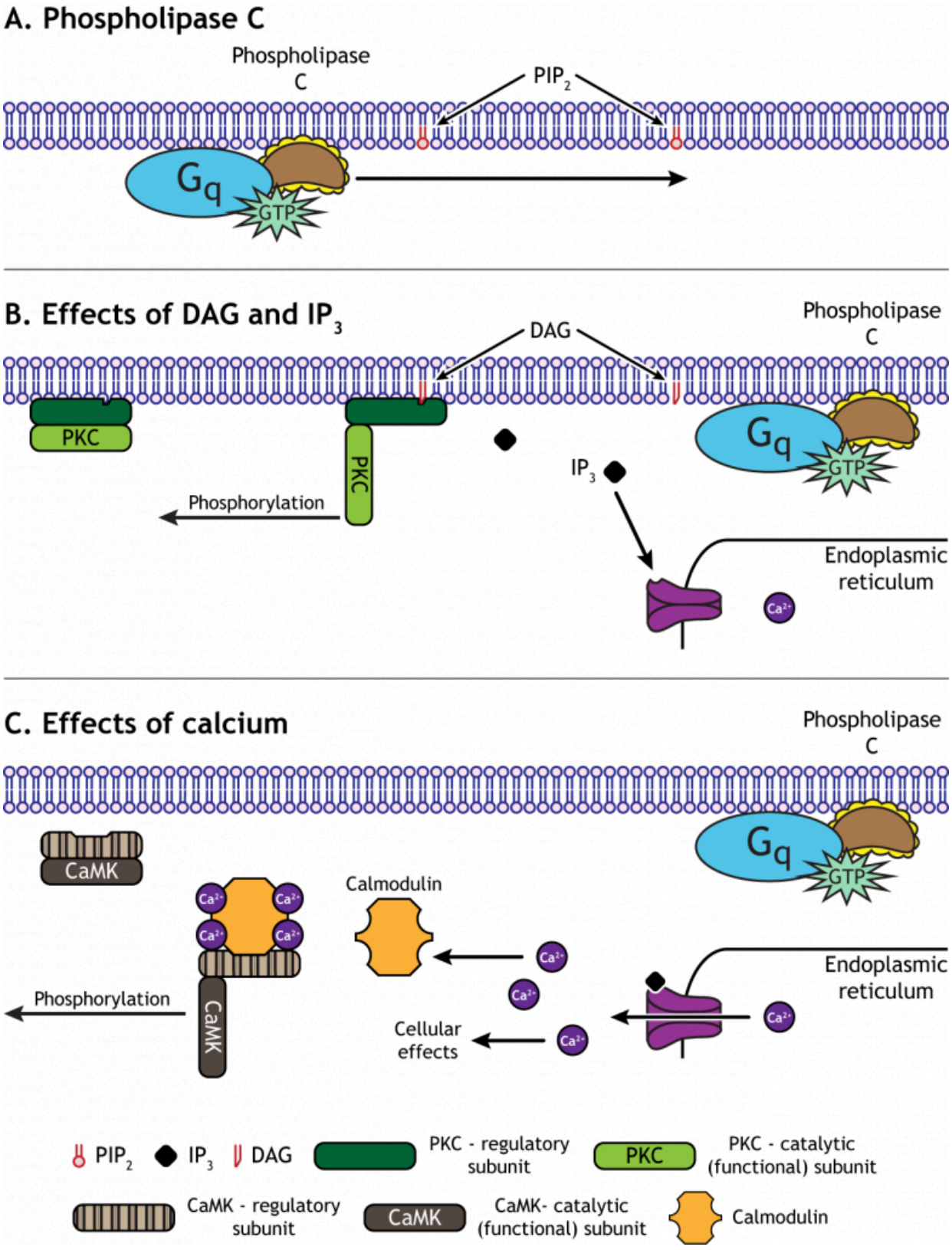

A. Phospholipase C
Phospholipase C
PIP2
Gq
GTP
B. Effects of DAG and IP3
DAG
Phospholipase C
PKC
PKC
Phosphorylation
IP3
Gq
GTP
Endoplasmic reticulum
Ca2+
C. Effects of calcium
Phospholipase C
CaMK
Calmodulin
Ca2+
Phosphorylation
CaMK
Gq
GTP
Endoplasmic reticulum
Cellular effects
PIP2
IP3
DAG
PKC - regulatory subunit
PKC
PKC - catalytic (functional) subunit
CaMK - regulatory subunit
CaMK
CaMK- catalytic (functional) subunit
Calmodulin

Figure 12.11. A) The Gq G-protein subunit activates phospholipase C, which converts the phospholipid PIP2 in the cell membrane into DAG, another membrane-bound molecule, and IP3, a cytoplasmic molecule. B) DAG can interact with PKA, initiating phosphorylation of cellular proteins. IP3 opens calcium channels in the endoplasmic reticulum, allowing calcium to flow into the cytoplasm. C) Calcium, another second messenger can have many cellular effects. It can bind to calmodulin, which then activates CaMK, causing phosphorylation of more protein targets. 'IP3-DAG Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 19

Animation 1

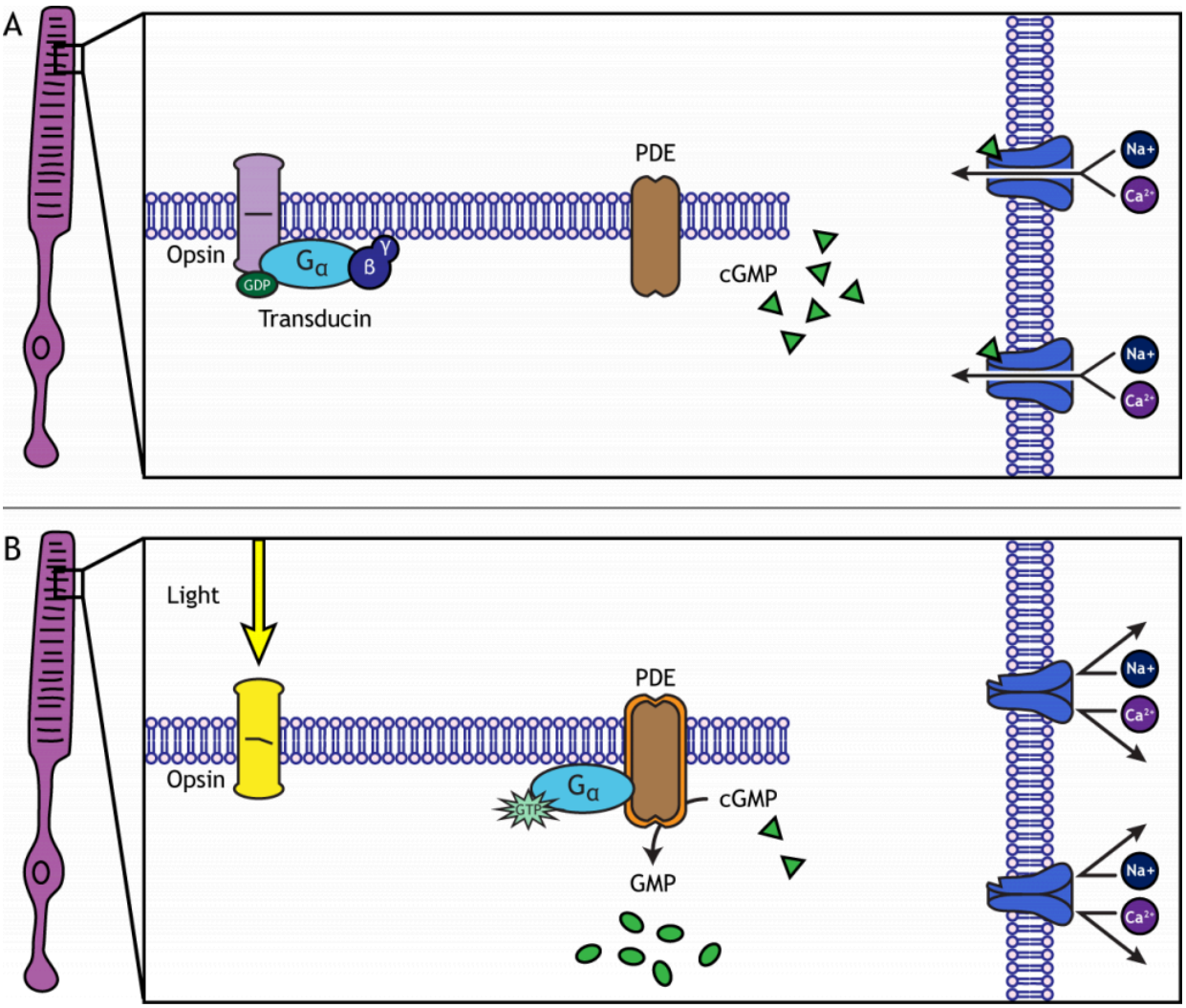


Figure 19.16. A) In the dark, the photoreceptor is depolarized due to an influx of sodium and calcium through open ion channels that are gated by cGMP. The photoreceptor has high levels of cGMP when it is in the dark. Additionally, the opsin proteins, the G-protein transducin, and phosphodiesterase (PDE) are all inactivated. B) Light reaching the photoreceptor causes a conformational change in the opsin protein, which activates the G-protein transducing. Transducin activates phosphodiesterase (PDE), which converts cGMP to GMP. Without cGMP, the cation channels close, stopping the influx of positive ions. This results in a hyperpolarization of 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.