The Nervous System

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The underlined headings correspond to the five Nervous system videos.

1. Introduction and cell types

Like the endocrine system, the nervous system responds to the environment and regulates the body. However in contrast to the endocrine system, the nervous system is much more rapid and targets cells more specifically. In addition, the nervous system is able to integrate more types of information from the environment and to respond with a broader range of reactions compared to the endocrine system.

A sizable portion of the nervous system is involved in collecting information about our environment. The information is integrated and interpreted by the central nervous system (brain, spinal cord) and used to cause a response often by stimulating muscles or glands.

Cell Types

Despite the fact that the nervous system is extremely complicated, there are relatively few cell types present.

Neurons

Neurons are the cells of the nervous system that communicate and integrate information. They communicate with one another with their processes, or cell extensions, that emanate from the cell body. **Dendrites** are processes which usually receive information from other neurons while **axons** are processes that usually pass information on to other neurons or cells. Neurons use electrical signals to communicate along their length and often use chemical signals to communicate with one another. The morphology of neurons can differ widely depending on their role in the nervous system. Some neurons that receive signals from many other neurons can have thousands of dendrites. However, most neurons have only a single axon. Axons can branch to form many axon terminals that can be used to communicate with many neurons downstream.

Glial Cells

Several types of **glial cells** support neurons in the nervous system. The axons of many neurons have a covering of specialized plasma membrane called **myelin** that makes the electrical signals that travel along axons faster and more efficient. In the **central nervous system** (the brain and spinal cord), **oligodendrocytes** use their processes to wrap many layers of myelin around each axon. Each oligodendrocyte insulates many axons. In the **peripheral nervous system** (outside of the brain and spinal cord), a single axon is coated by many **Schwann cells** that wrap themselves around a portion of a single axon to cover it with myelin.

Astrocytes are another type of glial cell that function to support neurons in the central nervous system. Astrocytes provide metabolic support to neurons and maintain the extracellular environment so that neuronal signaling can occur. Some astrocytes

have processes that coat the outside of blood vessels in the brain and help to form a tight **blood-brain barrier** that protects the brain from toxic substances in the blood.

Microglial cells are scavenger cells of the nervous system that can take up cellular debris as well as serve other immune functions for the brain.

2. Membrane potentials

Signaling Along Neurons

The speed and efficiency of the nervous system is contributable to the electrical and chemical signals that travel along and between neurons, respectively. Neurons use electric currents that can travel along their lengths in a very efficient manner. The current is generated by the flow of ions across the plasma membrane through ion channels.

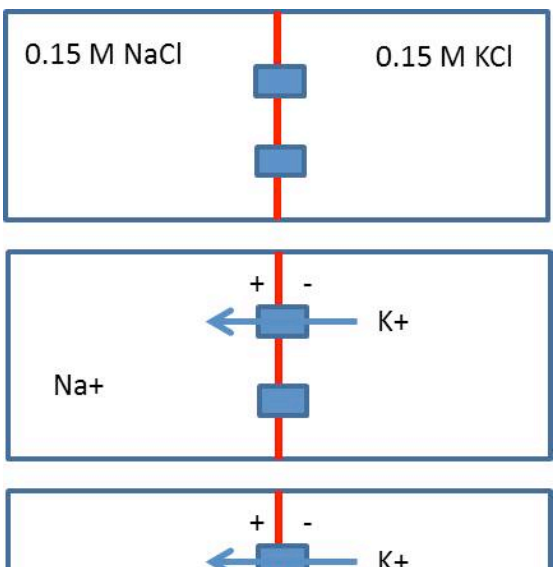
Electrochemical Gradient

In order for a neuron to generate a current, or flow of electrical charge, the cell spends energy to establish a concentration and electrical gradient of ions across the plasma membrane. The gradient is primarily established by affecting the concentration of three ions in the cell, Na^+, Cl^- and K^+ (Fig. 1).

Ion	ECF (Plasma)	ICF (Cytosol)
Na^+	140.0	15.0
K^+	4.4	140.0
Cl^-	105.0	7.0

Equilibrium potentials

Due to the concentration gradient of ions across the plasma membrane of cells, the intracellular fluid has a small excess of negative charge compared to the extracellular fluid. The separation of charge has the potential to do work. As a result, the magnitude of the charge difference between the inside and outside of the cell is referred to as the **membrane potential** and measured in **millivolts**. If there is an excess of negative charges on the inside of the cell, the membrane potential is negative. If the excess charge on the inside of the cell is positive, the membrane potential is positive. The membrane potential of a cell under specific conditions is determined by the concentration of ions inside and outside of the cell and by the permeability of the membrane for those ions.



The simplest case is to consider a system that is permeable to only one ion (Fig. 2). In Figure 2, there are two solutions separated by a membrane that differ in their Na^+ and K^+ concentrations. In the top compartment, the ion channels in the membrane are not open. Since the number of positive and negative charges is equal on both sides of the membrane, the membrane potential is 0 mV. In the 2nd compartment, if K^+ selective ion

channels are opened, K^+ will travel down its chemical concentration gradient into the left compartment which will cause an excess of positive charges on the left and an excess of negative charges on the right. In the 3rd compartment, there is still a chemical concentration gradient for K^+, but the increase in negative charges on the right is causing some K^+ to be pulled back into the solution on the right. Finally in the bottom compartment, the number of K^+ leaving the compartment on the right because of the concentration gradient equals the number that are being pulled back into the compartment because of the excess of negative charge. This potential difference between the two compartments is the equilibrium potential for K^+ in this system. In a cell, the equilibrium potential for an ion is determined by the concentration of the ion inside the cell versus the concentration outside the cell. **Using the concentrations from the table in Figure 1 the equilibrium potential for K^+ in a typical neuron is -90 mV (E_K) and for Na^+ is +60 mV (E_{Na}).** The E_{Na} is positive while E_K is negative because Na^+ and K^+ accumulate on opposite sides of the plasma membrane.

Membrane potential

If a cell at a given time is permeable to only one ion, the membrane potential will become equal to the equilibrium potential for that ion. However, if ion channels open for more than one ion, then the membrane potential will be determined by the concentration of the ions inside and outside of the cell as well as the permeability of the cell to those ions.

Under resting conditions, there are pumps and channels that collectively contribute to the resting membrane potential. The Na^+/ K^+-ATPase is a pump that uses the energy from ATP to transport three Na^+ out of the cell and two K^+ into the cell. This maintains the concentration gradients across the plasma membrane (Fig. 1) and causes the inside of the cell to have an excess of negative charges. In addition, there are some K^+ channels that allow K^+ to leave the cell which makes the inside of the cell even more negative. There are also some Na^+ channels (fewer than the K^+ channels) that let a little Na^+ into the cell. Once the system reaches steady-state the Na^+/ K^+-ATPase is pumping the same number of Na^+ and K^+ as the channels are letting through and they balance each other. When taking into account the action of the Na^+/ K^+-ATPase and the K^+ and Na^+ channels, the resting membrane potential (-70 mV) is between the equilibrium potential for K^+ and Na^+ but closer to the equilibrium potential for K^+ because the membrane is more permeable to K^+.

The membrane potential can change quickly and dramatically when the cell is excited. When the membrane potential increases but still remains negative, the membrane is **depolarizing**. An **overshoot** is when the membrane potential becomes positive. When the membrane potential decreases towards the resting potential it is **repolarizing**. If the membrane potential goes below the resting potential then it is **hyperpolarized**.

Graded Potentials

Changes in membrane potential produce the electrical signals that neurons use to communicate. A change in membrane potential at a location on the plasma membrane of a neuron results from opening of ion channels. The change in membrane potential can then travel along the length of the neuron due to neighboring ion channels

that are gated by electrical stimuli. A **graded potential** is a transient change in the membrane potential that decreases in magnitude as it spreads out along the plasma membrane of the neuron and is proportional to the intensity of the stimulus. If ion channels in a specific part of the membrane are activated (for instance by a ligand like a neurotransmitter) and that portion of the membrane is depolarized, the positive charges that have entered the cell will diffuse along the inside of the membrane. This area of depolarization will continue to spread but will decrease in intensity over distance. If the stimulus is more intense, more ion channels will open and the change in potential will be greater. This will result in the graded potential traveling a further distance. Graded potentials signal over small distances since the intensity of the signal decreases over distance. However, they can also be additive if they occur in rapid succession. Graded potentials can stimulate or inhibit neurons and have no refractory period, or time period when the cell can not respond to a stimulus after the first change in potential.

3. Action potentials

Most neurons use action potentials as the most efficient and quickest way to convey electrical currents along the length of their axon. An **action potential** is an electrical signal like graded potentials but they differ in several ways. Action potentials are large changes in membrane potential that have a similar pattern of membrane potential change. In this way, an action potential is an all-or-none phenomenon because either there is a large change in membrane potential if the stimulus was adequate or there is little change in membrane potential. In addition, action potentials have the same intensity as they travel along a membrane – they do not diminish over distance. Cells that are capable of producing action potentials are excitable due to the expression of the voltage-gated ion channels required to form an action potential.

At the beginning of an action potential the cell which was at resting membrane potential has a graded potential that causes the membrane to be depolarized. If the depolarization from the graded potential reaches a certain voltage, called the threshold, then enough voltage-gated Na^+ channels will be opened to start an action potential. Once enough Na^+ channels are open, Na^+ starts rushing into the cell due to the net negative charge inside the cell and the excess of Na^+ outside the cell. This causes the membrane potential to increase and surpass 0 mV due to the concentration gradient of Na^+. The cell is so permeable to Na^+ that the membrane potential quickly comes close to the equilibrium potential for Na^+. Right before the membrane potential reaches the equilibrium potential for Na^+, the Na^+ channels inactivate and the slower opening voltage-gated K^+ channels open. When the K^+ channels open, there is an excess of positive charge and K^+ inside the cell (a positive membrane potential) so K^+ leaves the cell and travels down its concentration and electrical gradients. This lowers the membrane potential and it approaches the equilibrium potential for K^+, which is below the resting membrane potential. The K^+ channels start to close and the membrane returns to the resting potential.

Once the Na^+ channels have inactivated, the membrane must repolarize before the channel returns to the closed state and can be opened again. This means that there is a refractory period that prevents another action potential from occurring before the first one has ended. Once an action potential occurs in one portion of the axon, the adjacent area will experience a depolarization from the spread of Na^+ just like in a

graded potential as long as the proper channels are expressed. This will be above threshold and will cause an action potential in the adjacent area which allows the action potential to travel along the axon. However, because of the refractory period, the action potential travels in one direction along the axon and not in two directions. In addition, each action potential that is produced down the axon will be identical and will not diminish over time or distance.

Neurons relay signals along their length using graded potentials and action potentials. However, certain parts of neurons are specialized to facilitate certain kinds of potentials. Some sensory neurons receive their signals from their processes that are embedded in a tissue sensing changes in the environment. These changes cause graded potentials to travel down the process toward the cell body. In other neurons, the source of the graded potential comes from a neuron that is contacting a dendrite or the cell body. In either case, the graded potentials can start in the dendrites or cell body and if it is strong enough travel to the axon **initial segment**, where the neuron has the highest concentration of voltage-gated ion channels and the lowest threshold, to start an action potential. The initial segment is the beginning of the axon that connects to the neuronal cell body at the **axon hillock**. Once an action potential is started at the beginning of the axon, due to the refractory period, it will travel down the axon to the end of the neuron. Because a neuron can have many dendrites and have many other neurons contacting the dendrites or cell body, the axon hillock and initial segment can integrate those signals by requiring that signals reach a threshold before an action potential is formed. The strength, frequency and location of a stimulus received by a neuron will determine if threshold is reached because graded potentials are formed, not action potentials.

Saltatory conduction

In the human body, axons can be quite long (from the spinal cord to the toe). In order for an action potential to travel quickly along an axon that may be three meters long, some axons are myelinated. **Myelin** is an insulator that is made up of many layers of specialized plasma membrane that is formed by Schwann cells in the peripheral nervous system and oligodendrocytes in the central nervous system. The Schwann cells and oligodendrocytes lay the myelin along the axons with regularly spaced gaps called **nodes of Ranvier**. The myelin speeds conduction along an axon by insulating it and preventing leaking of ions in the area around an action potential. This allows the effects of the action potential, or the change in membrane potential, to be detected further down the axon in the neighboring node where there is a concentration of ion channels. In a myelinated axon, the action potential jumps from node to node allowing it to travel more quickly and more efficiently.

The diameter of an axon also determines how quickly action potentials travel down its length. Larger diameter axons have less resistance so action potentials travel more quickly along their length. This is exploited by the body. Neurons that sense touch have large diameter axons while pain and itch neurons have small diameter axons.

4. Methods of communication

Neurons signal to one another through a specialized junction called a **synapse**. The synapse is where the electrical signal from one neuron (presynaptic neuron) is

transmitted to another neuron (postsynaptic neuron). Depending on the role of a particular neuron, it can receive signals from many presynaptic neurons (convergence) or it can send signals to many postsynaptic neurons (divergence).

The presynaptic neuron causes a graded potential to occur in the postsynaptic neuron. The graded potential can depolarize the postsynaptic membrane, which makes the potential closer to threshold, and is called an **excitatory postsynaptic potential**. Alternatively, the graded potential can hyperpolarize the postsynaptic membrane, which makes the membrane potential farther from threshold, and is called an **inhibitory postsynaptic potential**. Since presynaptic neurons cause graded potentials in postsynaptic neurons, spatial and temporal summation of signals from multiple synapses can occur so the postsynaptic neuron can integrate information.

One example of neurons integrating information is during **lateral inhibition** of sensory neurons. In order to discern the exact point of contact of a stimulus such as a pencil, neighboring neurons must be inhibited. For instance, a pencil which is depressing the skin may cause three sensory neurons to fire. However, the neuron in the middle may fire more frequently because the pencil is in the middle of its receptive field. Branches from the axons of all three neurons **converge** on neighboring neurons. However, since the middle neuron is firing action potentials most frequently, its firing is affected the least by the inhibition. Lateral inhibition leads to reduction of the firing of the neighboring neurons so the resulting sensation is that the pencil is depressing only the field of the middle neuron. This allows for more precise determination of the stimulus site and type.

Chemical synapses

Most synapses in the mammalian nervous system transmit between the presynaptic and postsynaptic neurons using chemicals called **neurotransmitters**. As the action potential from the presynaptic neuron travels to the end of the axon, calcium is released from voltage-gated calcium channels and causes vesicles full of neurotransmitters to fuse with the plasma membrane and dump their contents into the space between the two neurons called the **synaptic cleft**. The neurotransmitters diffuse across the synaptic cleft and often directly or indirectly activate ion channels on the postsynaptic neuron to cause a graded potential. In an excitatory synapse, ion channels are opened that let positive ions into the cell causing a graded potential that depolarizes the membrane and may or may not be sufficient to reach threshold (**excitatory postsynaptic potential**). In an inhibitory synapse, chloride enters the cell or potassium leaves the cell causing a graded potential that hyperpolarizes the membrane and moves the membrane potential farther from threshold (**inhibitory postsynaptic potential**).

Since there are many steps in synaptic transmission, there are many ways that drugs can alter the process and affect the nervous system. Drugs can affect neurotransmitter synthesis, release and degradation. They can also inhibit or activate the receptors and signal transduction machinery of the postsynaptic cell. The effects of drugs that affect the nervous system are complicated by the ability of the nervous system to adapt to the changes that the drugs have caused.

The nervous system contains many types of neurotransmitters along with their respective receptors. There are two main types of synapses that are not only found in the central nervous system but also in the periphery. In **cholinergic** synapses the

presynaptic neuron releases **acetylcholine** as the neurotransmitter and it is received by one of two main types of receptors in the postsynaptic neuron or cell. Skeletal muscle and brain express **nicotinic** receptors which are ion channels that are gated by acetylcholine. In heart, smooth muscle and glands, **muscarinic** receptors bind acetylcholine which starts a signal transduction pathway that regulates ion channels.

Adrenergic synapses release either **norepinephrine** or **epinephrine** into the synaptic cleft. The norepinephrine or epinephrine bind to one of two classes of receptors, alpha-adrenergic or beta-adrenergic receptors. Both types of receptors use signal transduction to affect the postsynaptic cell which can be in the heart, smooth muscle, or a gland.

5. Organization

The nervous system collects information from the environment, processes the information obtained, and then reacts in an appropriate manner. This is accomplished as a concerted effort between both the central and peripheral nervous systems. **Afferent** neurons are sensory neurons that lead from their sensory receptors in the periphery to the central nervous system which processes the information. **Efferent** neurons lead from the central nervous system back out to the periphery to cause the response to the stimulus. There are two different classes of efferent neurons in the peripheral nervous system, **somatic motor neurons** and **autonomic neurons** (Fig. 3). Somatic motor neurons excite only skeletal muscle and are responsible for most of our voluntary movements. The somatic nervous system and autonomic nervous system also differ in their anatomy. In the somatic nervous system, neurons with cell bodies in the central nervous system send axons to the skeletal muscle they innervate. In the autonomic nervous system, a neuron with a cell body in the central nervous system synapses with a second neuron whose cell body is in a **ganglion**, or cluster of neuronal cell bodies in the periphery. The second neuron sends an axon to the target organ.

Within the autonomic nervous system there are three divisions. The enteric neurons connect to neurons in the wall of the intestinal tract that control many processes there. The **sympathetic** and **parasympathetic** divisions are important for controlling many processes for body homeostasis (Fig. 3).

Sympathetic and Parasympathetic Systems

The sympathetic and parasympathetic divisions of the autonomic nervous system differ in their anatomy. Both utilize two neurons in series to lead from the central nervous system to the target organ. However, the ganglia for the sympathetic system are for the most part next to the spinal cord while the ganglia for the parasympathetic system are usually very close to or within the target organs. The sympathetic and parasympathetic systems both use acetylcholine and nicotinic receptors at the synapses in their ganglia. In the target organs in the parasympathetic system, acetylcholine and muscarinic receptors are usually present at the synapse. In the sympathetic system, norepinephrine is usually the neurotransmitter that binds to adrenergic receptors on the target organ. One exception is in the adrenal gland where the postsynaptic cells don't release neurotransmitter into a synapse. Instead, they

release a mixture of epinephrine and norepinephrine into the bloodstream that can bind adrenergic receptors all over the body.

Many organs are innervated by the parasympathetic and sympathetic **nerves**, or bundles of axons. In most cases this allows one system to activate the organ and the other system to inhibit it. In general, the parasympathetic system is activated during periods of rest or digestion while the sympathetic system is most active during the fight or flight situations. The sympathetic system prepares us for fighting by increasing the heart rate, releasing glucose from the liver, and dilating our pupils. In addition, the sympathetic system can divert blood from the skin and digestive system to the heart, brain and skeletal muscles. The sympathetic branch of the autonomic nervous system can be thought of as the gas pedal on a car while the parasympathetic branch is like the brake. If you want to slow down you can press the brake or let up on the gas. This dual control of systems that cause opposing actions allows for fine control of an organ's activity and overall body homeostasis.