Section One: Chapter 7: Membrane Potential and Neurophysiology

Overview

This last part of Section One culminates by bringing together all of the elements we have considered so far. From homeostasis, to solutions, plasma membrane, membrane transports, enzymes, etc. Now we will consider the details of the **membrane potential** – this is how signals get sent and how action takes place!

Recall from the end of the previous chapter that the **resting membrane potential** (RMP) is created by the **uneven** distribution of charged particles (ions) and chemicals (concentrations) between the inside and the outside of the cell. This creates the electrochemical gradient that allows the cell to do **work**, which is 'moving things'. The focus in this chapter will be on how the membrane potential (which is a voltage) changes the activity in **neurons**, which are the communication cells of the nervous system. This area of study is called **neurophysiology**.

Two Cells of the Nervous System

There are two general types of cells in the nervous system: **Neurons** and **Glial cells**. The glial cells are considered support cells for the neurons and are covered at the end of this chapter. Some important differences between neurons and glial cells are that neurons can generate **action potentials**, whereas glial cells cannot. Neurons communicate via **synapses** that use neurotransmitters, and glial cells do not have chemical synapses. Glial cells, like all living cells, do have a resting membrane potentials in order to carry on their vital functions.

The Two Control Systems of the Body

This chapter of physiology introduces the two **Control Systems** of the body, which covers **Local Control** and contrasts that with what is termed **Long Distance Control**. In general terms, there are two basic forms of long distance control in the body: **The Nervous System** and **the Endocrine System**. The very basic details of each are covered below as a brief introduction. Then the focus will intensely be on the examination of cell communication using the neurons as an example, so the focus will be on the nervous system control and particularly on **neurophysiology**. As we go further into membrane potentials in this chapter, it will further rely on the knowledge of the plasma membrane presented in the previous chapter.

Neurons are critical cells in the orchestration of complex long distance communication throughout the body. Therefore, we will examine in detail the dynamic actions across the plasma membrane of neurons.

The Plasma Membrane allows Work to occur across it

Form the previous section we know that the plasma membrane is an excellent insulator and this helps it to facilitate work (moving things) across it. The separation of electrical charges and chemical concentrations across the lipid bilayer creates gradients and this is a very powerful arrangement. This *electrochemical disequilibrium* is also referred to as the **electrochemical gradient**. This gradient is created and maintained by active transport mechanisms (such as the Na^+/K^+ pump) and by selective membrane permeabilities to certain ions. The membrane is selectively permeable, yes, but each system sets up mechanisms that permit the passage of the molecules they need to pass through, and in doing so information is communicated.

The "Control Systems" of the Body

The two broad categories of control systems in the body are **Local** and **Long Distance**. All forms of 'control' are about communication and maintaining function and stability, or homeostasis.

Local Control

This occurs in local surroundings and typically involves one cell or a few cells in the same vicinity. It involves signal molecules being released and binding to receptors. It includes autocrine and paracrine control.

Autocrine. This is a type of signaling where a cell releases a signal molecule that targets **itself** (auto). When the signal binds to receptors on its own surface, it causes a change in the cell's activity (see **Fig. 7.1** top).

Paracrine. This is a type of signaling where a cell releases a signal molecule that targets a neighboring or nearby cell. The prefix para means next to. When the signal binds to receptors on the neighboring cell's surface, it causes a change in that cell's activity. The signal molecule released by the cell can diffuse a short distance to adjacent cells (see **Fig. 7.1** bottom).

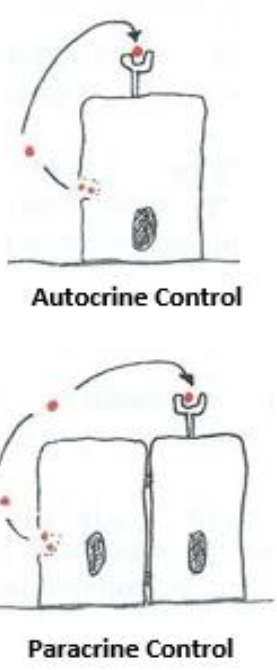


Figure 7.1 Drawing cells engaging in autocrine control (top) and paracrine control (bottom).

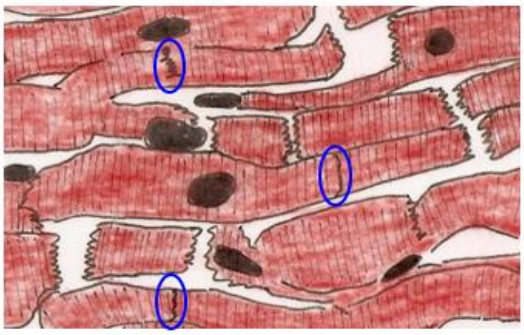


Figure 7.2 Drawing of myocardiocyte (heart muscle cell) histology showing the intercalated discs (blue circles).

Another type of communication occurs between neighboring cells that are connected by **gap junctions**, which are like protein channels connecting neighboring cells. Although this is a type of local control it is not placed in the same category as paracrine because of the different signaling mechanisms used. The adjacent cells connected by gap junctions allow charged ions to pass through to the neighboring cells and this generates electrical signals as they move across cell membranes. A perfect example of how gap junctions help adjacent cells to communicate extremely effectively is seen in myocardiocytes (heart cells). The myocardiocytes in **Figure 7.2** above shows intercalated discs (in blue circles) where the gap junctions are located. This form of communication is called **functional syncytium**, which allows individual cells within a tissue to function as a single, coordinated group. It is common in muscle tissue and critical to the functioning of the heart as a coordinated orchestrator of blood flow. More on the amazing talents and complexities of heart in chapters ahead.

Long Distance Control

This is the type of control that spans long distances in the body and may integrate multiple systems for an action or a process. The two basic long distance control systems in the body are the **Nervous System** and the **Endocrine System**. Both systems involve feedback and reflex control loops within the body.

The nervous system uses electrical signaling (neural impulses) and chemical signals (neurotransmitters) to communicate, while the endocrine system uses long distance chemical signal molecules (hormones, produced by glands) to communicate.

The Nervous System - In general this system is **faster** in its response, **more specific**, and usually **very brief** in comparison to the endocrine system. Neurons in the central and peripheral nervous system fire electrical impulses and release **neurotransmitters** to communicate throughout the body. The signal transmission of the nervous system is fast because neurons are interconnected, but many functions are more short-lived. See **Figure 7.3** below for the basic arrangement and function of this system.

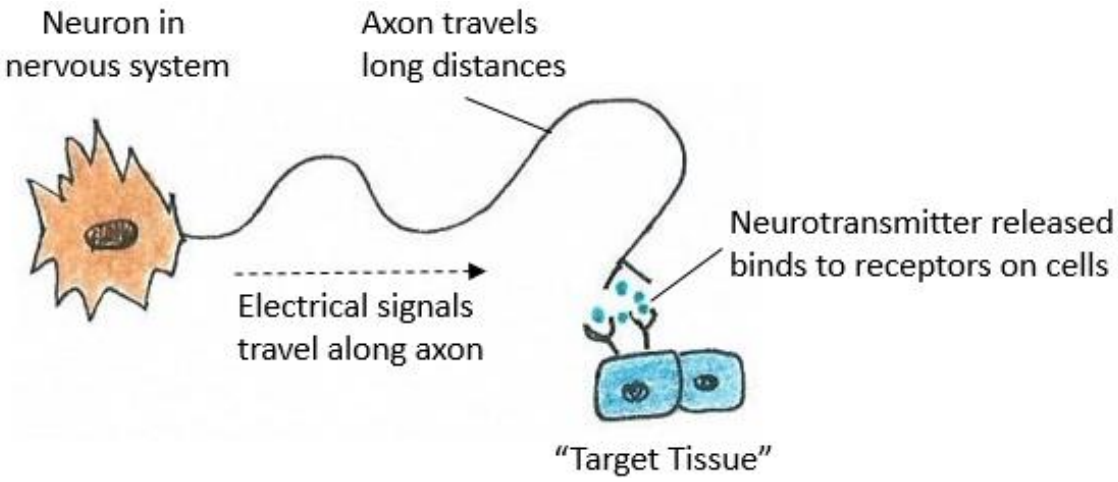


Figure 7.3 The neuron sends an electrical signal along its axon, it is converted into a chemical signal at the synaptic end bulb and signal molecules called neurotransmitters are released to bind with receptors on the target tissue.

The Endocrine System – In general this system is **slower** in its response, **broader**, and **longer lasting** in comparison to the nervous system. The chemical messengers in the endocrine system are **hormones**, which are released from endocrine glands into the bloodstream. They can go practically anywhere the blood goes but they only have an effect on "target tissue", those cells that have receptors for that specific hormone. See **Figure 7.4** below for the general schematic of how the endocrine system operates.

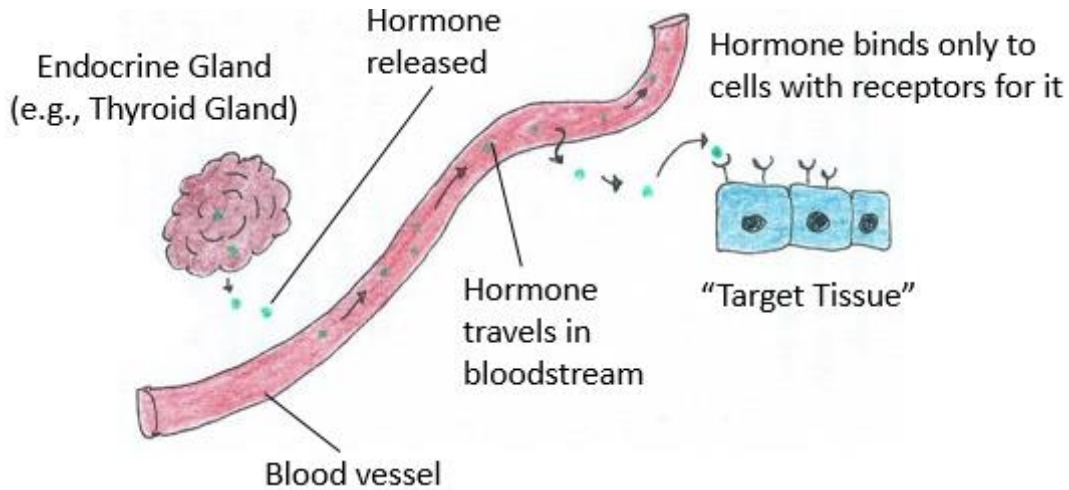


Figure 7.4 The endocrine gland releases a chemical signal called a hormone into the interstitium which goes into the bloodstream. It travels in the bloodstream and can bind with target tissue that has receptors for that hormone on it, which will change the activity of the cell receiving the signal.

Neurons and the Nervous System (NS)

Very briefly, let's examine the anatomy of neurons since we need to understand how information flows through them. For the drawing of the generalized neuron below (**Fig. 7.5**), some of the basic structures of a typical motor neuron have been labeled. Information (stimulus) is received at the **dendrites** that branch off the cell body. It is processed by the **soma** (cell body) and if the stimulus is strong enough, it triggers an electrical signal (an action potential) to be propagated down the elongated process called the axon and to the **synaptic end bulbs**. Here, the electrical signal is converted into a chemical signal with the release of neurotransmitters from synaptic vesicles (via exocytosis).

As will become more clear, a single neuron can be viewed as a ***microcosm*** (a smaller encapsulation of a larger system) for the more complex **feedback loops** already discussed in the introduction, which involves many different neurons.

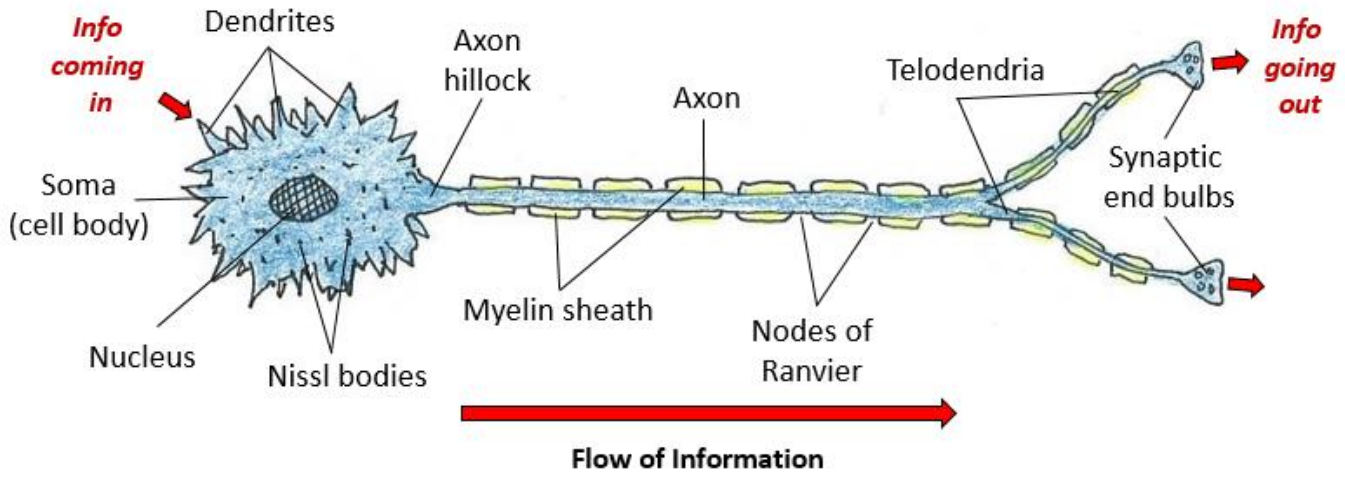


Figure 7.5 This is a labeled drawing of a typical motor neuron to show the key structures involved in receiving (dendrites), processing (soma) and sending out information (axon and synaptic end bulbs). The direction of information flows in this order, from the dendrites through to the synaptic end bulbs to the target tissue.

The Membrane Potential of Neurons

The place where we will begin our closer examination is at the plasma membrane of a neuron where the incoming signal starts everything off, that is, at the dendrites and soma. We will build the story out and describe the action potential and neurotransmitter release as we move through the material. At the end of this section, all of this will be presented together as signal transduction at the synapse - which is the site of communication between two neurons. Each step along the way is vital and we need to be familiar with the all of the processes in order to see the big picture.

As we know from our introduction to physiology, potential energy (PE) is stored energy, it is energy that exists by virtue of its position. As any energy, it has the capacity to be converted into other forms of energy (like kinetic energy), and it can be used or exchanged for work. **Energy** is the capacity to do **work**, and work is moving things. The amazing thing about living cells is that at rest they all have the potential to do work because they have an arrangement where potential energy exists across their plasma membranes due to the electrochemical gradient that is maintained by all of those Na^+/K^+ pumps. This potential to do work across a cell membrane at rest is called the **Resting Membrane Potential** (**RMP**). This is a normal and necessary arrangement for cells to function properly, and effectively communicate in a healthy human body.

The membrane potential of a cell has a slight imbalance in electrical charge across the plasma membrane, that is, the cell is slightly negative on the inside and slightly positive on the outside. Also, the relative concentrations of various ions and molecules are notably different on the outside of the cell (ECF) compared to the inside of the cell (ICF). As seen in **Figure 7.6** below, there is equipment in a lab that can measure the difference in electrical change (voltage) across a membrane. This is like an indication of the magnitude of potential energy across the plasma membrane.

Measuring the Voltage of Neuron at Rest

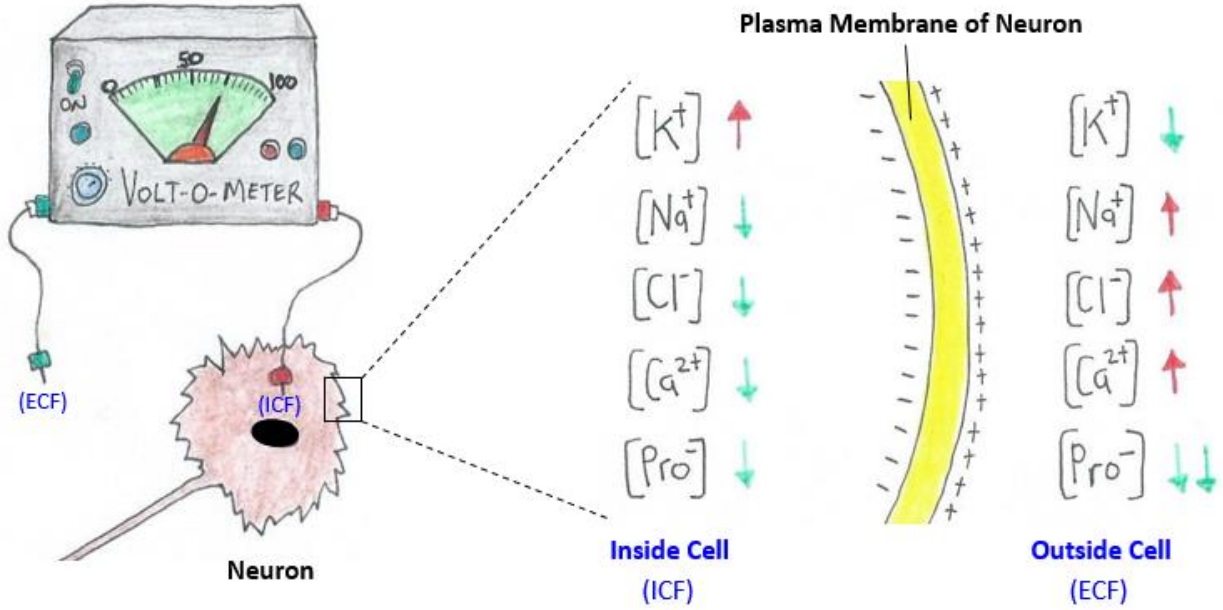


Figure 7.6 This diagram shows the voltage of the neuron being measured (left), and a zoom in of what exists across the plasma membrane of the neuron (right). Shown at the right are the relative concentrations of five key substances across the plasma membrane: K^+, Na^+, Cl^-, Ca^{2+}, proteins (Pro^-). Notice how the inside of the cell (ICF) is negatively charged compared to the outside of the cell (ECF). The difference in concentrations and charge creates the potential energy across the plasma membrane.

The Ions Responsible for the RMP

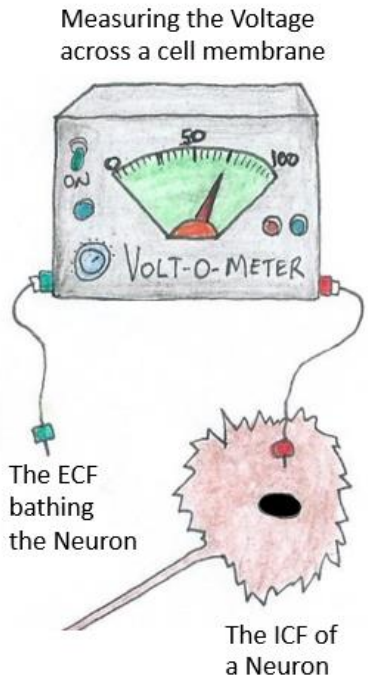
The major ions responsible for the maintenance of the RMP are K^+ and Na^+. Knowing what we already know about these busy ions, that is not surprising. However, the relative ion concentrations of other ions and substances are also very important; they are Cl^-, Ca^{2+} and proteins (Pro^-). Proteins usually have a slight negative charge and are therefore abbreviated as Pro^-s. From **Figure 7.6** above, we can see there is a difference between the inside of the neuron and the outside, showing the electrical and chemical gradients.

There is a useful pattern to note about the ions on the inside versus the outside of a cell, because in cells at rest it is essentially always the same. It is this: **K^+** is the only ion with a **high concentration inside** the cell. Also note that the Na^+ ions are exactly the opposite of K^+. At rest **Na^+** is kept at a very **low concentration inside**. And all the other three ions follow the Na^+ levels both inside and outside of the cell. So, if you are not sure what the Cl^- levels are in the ECF, relatively speaking it's the same as Na^+. That will come in handy later. The proteins are moderately low inside the cell but very low outside in the interstitium. We know that from the transcapillary dynamics of colloid osmotic pressure. The intracellular Ca^{2+} is usually very low, except in muscle tissue, but even there it is not free in the cytosol, but is compartmentalized and stored in the *sarcoplasmic reticulum* (SR) in high concentrations.

Neurophysiology

In examining how cells communicate, the first type of cell we examine in detail is the **neuron** (nerve cells), these are the communication cell of the nervous system. **Neurophysiology** is the study of how neurons receive and transmit information. All cells communicate, but this initial section focuses on neurons because much is known about how they signal, transmit and receive information.

We'll now see how important knowing about ions, channels and carriers in the plasma membrane is. Recall, at 'rest' the cell maintains an **electrochemical disequilibrium** (imbalance) and this creates the **Resting Membrane Potential** (RMP). The difference in charge across the plasma membrane can be measured in a lab with instruments that might look similar to the '*Volt-O-Meter*' on the left. One probe measures the inside of the cell and the other probe measures the outside of the cell. The difference between the two sides registers in **millivolts** (mV). For neurons the RMP = **-70 mV**. The value of 70 indicates that the magnitude of the voltage across the cell is 70 mV. The minus sign indicates that this measurement is in reference to the inside of the cell, which at rest is slightly negative relative to the immediate outside of the cell. When looking at graphs of the voltage of resting neurons it will be steady on -70 mV until something occurs to change that. Understanding this will play an important role understanding graded and action potentials.



The major ions (e.g., K^+, Na^+, Cl^-, and Ca^{2+}) play a big role in how cells communicate, but as **Table 7.1** below shows, K^+ is the most permeable ion of the plasma membrane. The Na^+ ion is much less permeable than K^+ and therefore in this way, K^+ is the most influential ion in establishing the RMP. Although their concentration gradients are similar, their permeabilities are not. That value of the RMP of -70 mV is mostly due to the permeability of K^+. That is not to say that Na^+ is not important. It is because Na^+ is kept out of the cell so vigorously that makes it a powerful force when channels open and let the Na^+ come flooding in! The exploration of the equilibrium potentials for both Na^+ and K^+ next should shed some light on why we need to know about their permeabilities and the two gradients they need to contend with.

Figure 7.7 Shows how lab equipment can measure the change in voltage that exists across the plasma membrane of a neuron. The difference in voltage, at rest, is about -70 mV.

Table 7.1 A comparison of the permeabilities of ions responsible for creating the membrane potential.

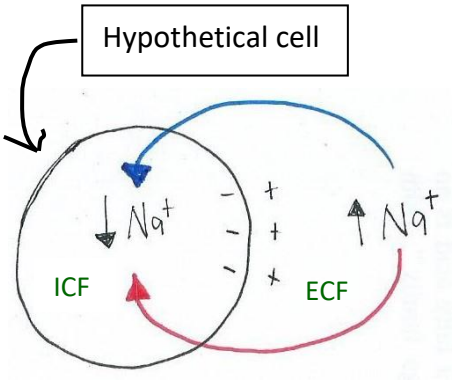
Ion	ICF Concentration (mM)	ECF Concentration (mM)	Permeability	Comparison
K^+	150	5	50-75	Most permeable
Na^+	15	150	1	Much less permeable
Pro-	65	0	0	Not very permeable

Equilibrium Potentials, the Na^+/K^+ pump and the RMP

If we examine the **equilibrium potential** of the important ions Na^+ and K^+, it nicely illustrates how the differences in permeabilities of these two ions contribute to the value of the RMP. To understand the equilibrium potentials for Na^+ and K^+ ions, we must examine a hypothetical cell and assume in each case (separately) that the Na^+ and K^+ ions are *freely permeable*, thus can cross the cell membrane freely.

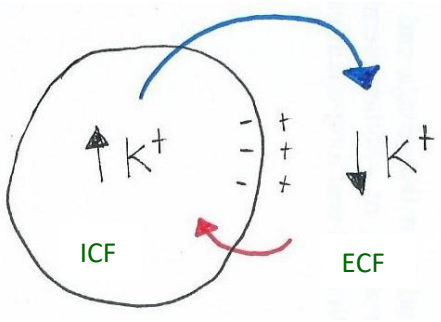
1) The movement of Na^+ ions alone:

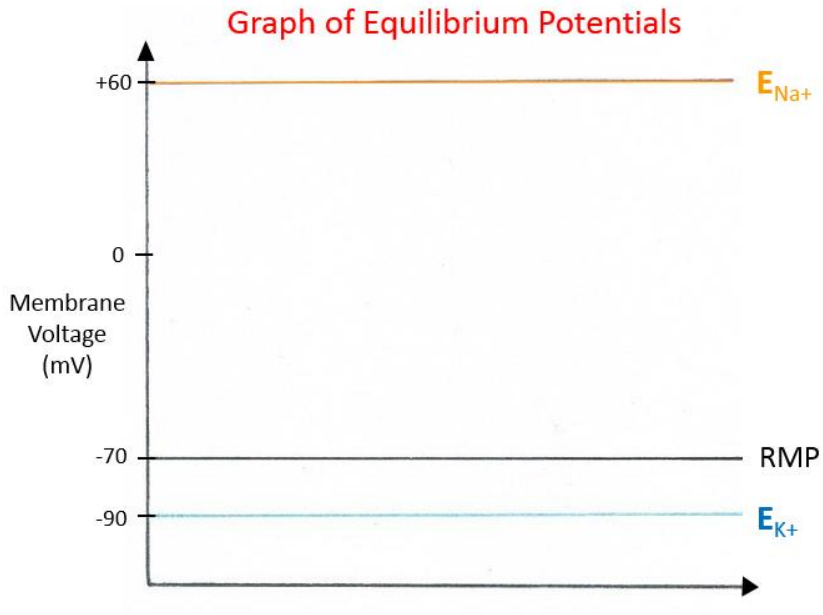
If it is assumed that Na^+ ions are freely permeable, with no restrictions to its movement, then Na^+ ions will move back and forth across the membrane until the electrochemical gradient has equilibrated. ***This would entail Na^+ moving into the cell down its concentration gradient, and also moving into the cell due to the electrical charge being the opposite (negative inside)***. The value of the voltage across the membrane for the Equilibrium Potential of Na^+ = +60 mV (E_{Na+} = +60 mV)



2) The movement of K^+ ions alone:

If it is assumed that K^+ ions are freely permeable, with no restrictions to its movement, then K^+ ions will move back and forth across the membrane until the electrochemical gradient has equilibrated. ***This would entail K^+ moving out of the cell down its concentration gradient, but it would also be pulled back into the cell due to the electrical charge being the opposite (negative inside)***. The value of the voltage across the membrane for the Equilibrium Potential of K^+ = -90 mV (E_{K+} = -90 mV)





The equilibrium potentials must balance all forces that effect the ions movement (see graph in **Figure 7.8** to the left). If Na^+ and K^+ were both equally permeable, then the RMP would be somewhere in between these two equilibrium values (in between -90 and +60 mV). However, K^+ ions are 50 to 75 times more permeable than Na^+ and therefore the RMP is much closer to the E_{K+} than the E_{Na+}. This is why the value of the RMP of -70 mV is much closer to -90 mV (the equilibrium potential for K^+), than it is to +60 mV (the equilibrium potential for Na^+).

Figure 7.8 This is a graph of membrane voltage (mV) showing the relative positions of the resting membrane potential (RMP) for a neuron and the equilibrium potentials for Na^+ and K^+. When examined carefully it gives a lot of valuable information. Note how close the equilibrium potential for K^+ is to RMP, and how very far away the equilibrium potential for Na^+ is from RMP. This alone indicates that, at rest, K^+ is more permeable to the cell membrane. Another way to look at it is that K^+ almost at equilibrium (like in the hypothetical cell) as seen by the equilibrium potential for K^+ being so close to the RMP.

3) The Na^+/K^+ Pump (also called the Na^+/K^+ ATPase):
This is a transport (membrane spanning) protein embedded in the plasma membrane that 'pumps' Na^+ and K^+ ions across the membrane against their concentration gradients. To do this, **it requires ATP directly**, and so it is a primary active transport mechanism. It pumps out or ejects 3 Na^+ ions from the inside of the cell and pumps in or imports $2K^+$ into the cell from the outside at the cost of 1 ATP for one cycle of the Na^+/K^+ pump. The pump is a protein that has catalytic ability (thus it is an enzyme as well) and it hydrolyzes **ATP** to make **ADP** + **P_i** + **Energy** and **Heat**.

As covered in a previous chapter, both Na^+ and K^+ ions continuously "leak" across the cell membrane down their concentration gradients through pores which are open protein channels or 'leaky' channels in the membrane. Because of this, the Na^+/K^+ pump must be active all the time in order to constantly 'bailout the leaky ship' and maintain the RMP. In summary, it is the three issues mentioned above that contribute to the maintenance of the RMP: **1)** the equilibrium potential for Na^+; **2)** the equilibrium potential for K^+; and **3)** the Na^+/K^+ Pump.

There are four types of Primary Tissues in the Human Body

In the human body there are four types of primary tissue: Epithelial tissue: Connective tissue: Muscle tissue; and Nervous tissue. Below are succinct descriptions of these four tissues and their major roles in the body.

1. **Epithelium** - Protective coverings, senses environment, controls movement of materials across surface.
2. **Connective** - Integrates and connects various body structures and provides support and protection.
3. **Muscle*** - Allows movement of a body part or entire body movement.
4. **Nervous*** - Relays, stores and communicates information throughout body.
   **Called 'excitable tissue' because it sends and responds to electrical signals.*

In anatomy the tissues are examined in great detail and usually in this order. In physiology however, the first type of tissue we examine is **nervous tissue** and the first type of cell is the nerve cell or the **neuron**. Both Muscle and Nervous tissue are 'excitable tissues' because they are capable of producing and responding to electrical signals when excited (stimulated). In other words, they can have action potentials, a topic which we are just about to delve into.

Excitable tissue cells have various RMP's, for example most neurons have a RMP of **-70 mV**, whereas most cardiac muscle cells have a RMP of **-90 mV**. As we may already know, the flow of charged particles is an electrical current, and the flow of these currents across cell membranes are used in the body to send signals or do work. We will see how **voltage gated protein channels** respond to changes in the voltage of the plasma membrane and how these channels can impact the voltage of the cell in a way that communicates information.

Graded Potentials and Action Potentials

There are two ways that a neuron can undergo rapid changes in RMP and this really means that there are two ways that neurons can electrically communicate. The two ways neurons can electrically communicate are by: Graded Potentials and Action Potentials.

What is a Graded Potential?

A **Graded Potential** is a local change in membrane potential with varying degrees of magnitude; this means the size of the graded potential can vary. This type of communication is for short distances. The stronger the triggering event, the stronger the graded potential is.

What is a trigger for a graded potential?

Here are some examples of what can trigger a graded potential:

1. A Specific stimulus energy - a change in temperature, pH, light intensity, etc.
2. A surface Receptor on the plasma membrane - binding of the receptor by a ligand.
3. Spontaneous changes in membrane potential - may be caused by 'leaky' channels, etc.

Visualizing Changes in Membrane Voltage on a Graph

When we speak of cells having a graded potential, it is about the voltage of the resting cell membrane changing. The best way to understand this is to visualize these changes in membrane potential on a graph that displays the cell's voltage. Imagine the neuron is being monitored by the Volt-O-meter and this changing membrane is displayed on a graph. This is how we will view graded and action potentials.

Graded potential occur on the cell body or soma. The spread of a **graded potential** is **decremental**, that is, it ***diminishes*** over distance. Looking at the graph below in **Figure 7.9**, there are seven different graded potentials, all of them varying in magnitude (size) and direction (positive or negative), but none of them hit **threshold**, which is **-55mV** in a neuron. This is because threshold triggers an action potential to occur (examined next). Therefore, in a recording of voltage changes, all graded potentials must be below threshold.

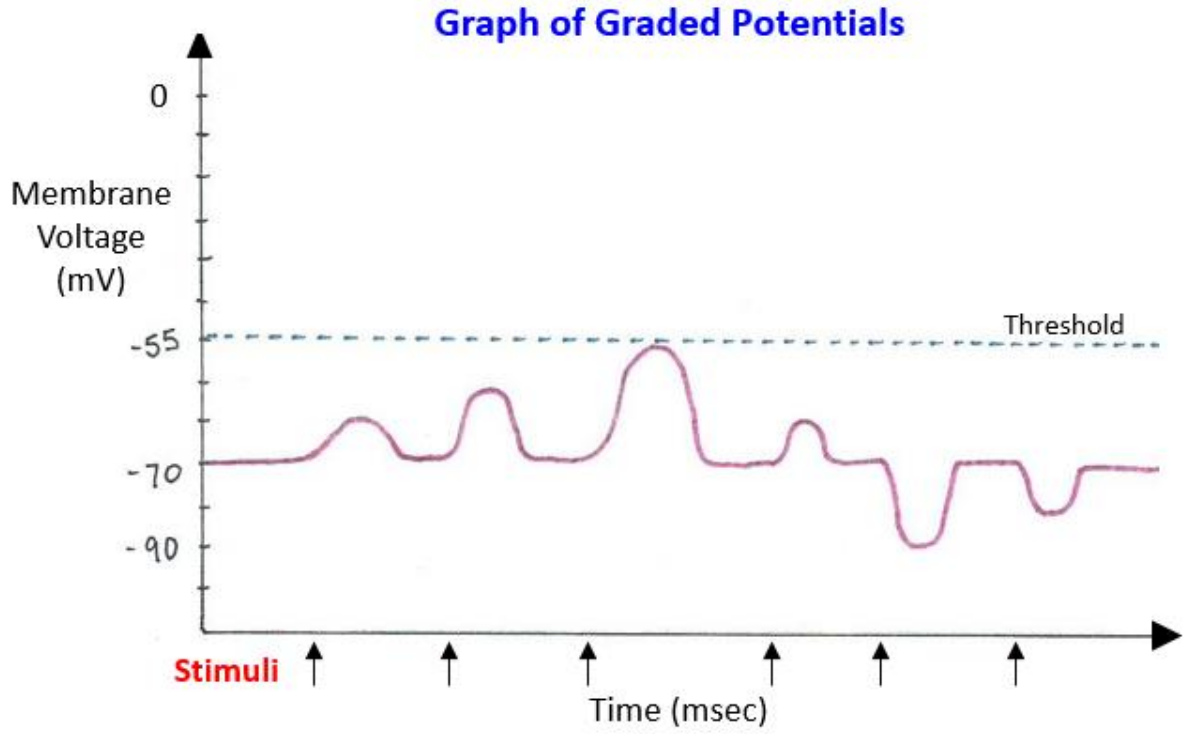


Figure 7.9 Here are examples of what graded potentials look like on a graph measuring the membrane voltage of a neuron receiving various input (stimuli). What they all have in common is that none of the stimuli is strong enough to reach threshold, the dashed line (-55mV). Their magnitude (size) and direction (up or down) can vary. Graded potentials are not action potentials but they can trigger an action potential if they reach threshold.

What is an Action Potential?

An **Action Potential** is a brief reversal of resting membrane potential by a rapid change in plasma membrane permeability. 'Reversal' means going from -70 mV (RMP) to +30 mV back to -90 mV and finally returning to RMP. These signals are for long distance information transmission.

The spread of an action potential is **non-decremental**, that is, the strength of the signal ***does not diminish over distance***, and it is maintained from the site of origin to destination. An action potential can be described as an **All or None** event. During an action potential, significant changes occur in membrane permeability for Na^+ and K^+. This causes rapid fluxes of these ions across the plasma membrane down their electrochemical gradients. The typical graph of an action potential is shown below in **Figure 7.10**.

There are 4 Phases of an Action Potential

① **Threshold**

② **Depolarization phase**

③ **Repolarization phase**

④ **Hyperpolarization phase**

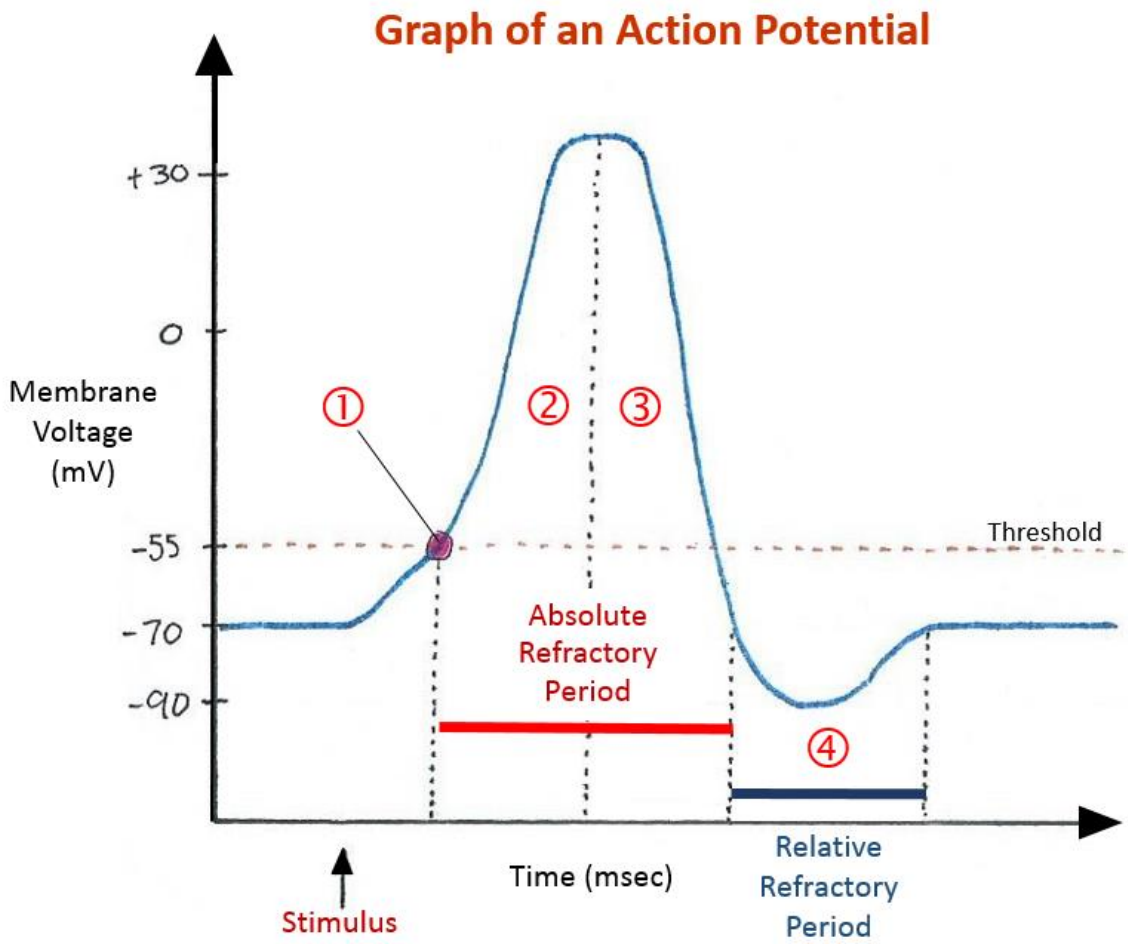


Figure 7.10 This is what an action potential looks like on a graph that is measuring the membrane voltage of a neuron receiving input (stimuli) that reaches threshold and triggers the sequence of events that is always the same. Action potential for neurons always have the same magnitude and phases, which are: Threshold; Depolarization; Repolarization; and Hyperpolarization. The step by step details are described in the text.

Step by Step Sequence of Events of an Action Potential

① Threshold

If we were measuring Neuron **X** in the drawing below in **Figure 7.11**, and the stimulus coming from Neuron **A** was strong enough to reach **Threshold** (-55 mV) in Neuron **X**, this would then result in the opening of **voltage gated ions channels for both Na^+ and K^+** in the soma of Neuron **X**.

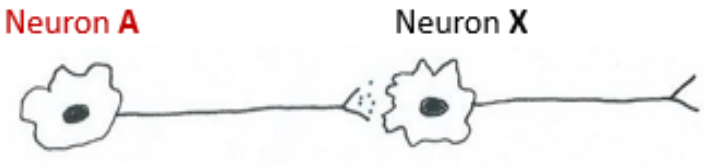


Figure 7.11 When looking at an action potential we are seeing the change in voltage of Neuron X as a consequence of it receiving a signal from Neuron A.

Note: In some research and textbooks, it is suggested that the K^+ channels open later, and that is OK, nothing in science is ever settled. Currently, most sources suggest that both Na^+ and K^+ channels open at the same time - in response to threshold being met - and that the K^+ channels are 'slow to open/slow to close' and therefore there is a delay in the effects of K^+ efflux (exit from cell). Either way, it works out the same. For this text, we go with both the Na^+ and K^+ channels open at the same time.

② Depolarization phase

Once the voltage gated Na^+ channels open there is a rapid influx (entry) of Na^+ making the inside of the cell become more positive very quickly, going from -55 mV (RMP) to a positive value of +30 mV. This is called the **Depolarization Phase** of the action potential. The change in membrane voltage is very rapid due to the nature of the positive feedback of the voltage gated Na^+ channels (see p 119 below).

At the 'Peak' of the action potential (+30 mV), the Na^+ channels close and are **deactivated**. This means they remain closed and cannot open to allow Na^+ influx, and they are inactive until RMP is restored.

③ Repolarization phase

Meanwhile, the *slow to open* K^+ channels can now fully open at the peak of the action potential, and there is an efflux (exit) of K^+, down its concentration gradient. This net outward movement of positive charges (K^+) brings the membrane potential back down toward RMP, since the positively charged K^+ is leaving the cell and no Na^+ can enter. This is the **Repolarization Phase**.

④ Hyperpolarization phase

These K^+ channels are also *slow to close* and they remain open after the membrane comes back down to RMP and continue to allow the positively charged K^+ to leave the cell. This makes the cell become more negative inside and leads to the **Hyperpolarization Phase**. As the slow K^+ channels finally close (at -90mV), the RMP is restored and the action potential is over.

In Summary

For an action potential to occur, ***threshold must be reached***. The threshold value in neurons is -55 mV. When the RMP is altered and it reaches threshold, this change in the voltage of the membrane causes voltage gated channels to open, triggering the onset of an action potential that will always be the same in magnitude and direction.

Re-examine the action potential graph in **Figure 7.10** and apply the four detailed phases outlined above to that graph. Take a piece of paper and draw this graph of an action potential with the complete details of which ion is going in or out of the cell. In fact, before you go on any further, draw it 10 times. You will be surprised how much more clear an action potential will become after doing that.

An Action Potentials has 2 Refractory Periods

There are two 2 refractory periods in the action potential for neurons. They both occur in specific phases and have definitive purposes in terms of the control of the frequency of actions potentials and as a safeguard for the information that may become a signal.

1. Absolute Refractory Period

- This refractory period occurs during the **Depolarization** and **Repolarization Phases** of the action potential. During the absolute refractory period, the cell is unresponsive to any further stimuli and no other action potentials can be fired at this point, regardless of the strength of the stimuli.

- Recall the peak voltage of the neuron action potential is +30 mV, and this is the voltage that causes the voltage gated Na^+ channels to close and deactivate. If no Na^+ can enter the cell, then there cannot be another action potential. Thus, the deactivation of the Na^+ channels is key to the absolute refractory period.

- The role of the absolute refractory period is to prevent further action potentials from occurring during those phases and help to ensure one-way propagation of action potentials in the body.

2. Relative Refractory Period

- This refractory period occurs during the **Hyperpolarization Phase** of the action potential. During the relative refractory period, another action potential can be triggered but the strength of the stimuli must be greater than normal to trigger an action potential.

- During the Hyperpolarization Phase the membrane dips below RMP, this means that the formerly deactivate voltage gated Na^+ channels can now open. Since the membrane is now lower than RMP, the stimulus must be stronger (of greater magnitude and positive) than it would normally be at -70 mV (RMP).

- The role of the relative refractory period is to help limit the frequency of action potentials, such that cells only send action potentials if the stimulus is stronger than usual during this period.

There are three types of Gated Ion Channels

As we have seen, in the previous section regarding cell membrane transport, ion channels are an important mechanism of cell transport. Now we can expound upon that information and examine how ion channels, and in particular gated ion channels play a critical role in cell signaling.

The three types of gated ion channels have already been described in chapter 5, however, here we will discuss them again building on that information and the magnitude of their importance will become more evident at the end of this section when we fully explore the **synapse**. The three types of gated ion channels are:

1. <u>Voltage Gated</u> - channel opens and closes in response to changes in membrane potential or the voltage across the plasma membrane.

2. <u>Ligand (chemically) Gated</u> - channels open and close in response to binding of a specific chemical messenger with a membrane receptor in close association with a channel. Conformational changes occur due to ligand-receptor complex.

3. <u>Mechanically Gated</u> - activation of channels from mechanical distention of the cell membrane, there is a stretch or deformation of the plasma membrane causing the channel to open.

We will be examining voltage and ligand gated channels in more detail below as they relate to graded and actions potentials in neurons.

The Positive Feedback Loop of Voltage Gated Na^+ ion Channels.

There is something special about the voltage gated Na^+ channel in neurons plasma membrane that is worth detailing at this point, as it relates to homeostatic mechanisms and the employment of the much less common but vitally important **Positive Feedback Loop**.

As shown in **Figure 7.12** below, the voltage gated Na^+ channel is just sitting in the membrane minding its own business (①) when the voltage across the cell membrane changes. Specifically, the cell becomes more positive inside (②), moving from the RMP to become more positive (from -70 mV up to -55 mV), which as we have seen in the descriptions for action potentials above is 'threshold' for neurons. This triggers the gate to open and the Na^+ that has been kept out of the cell is finally allowed to rush in, down both its electrical and chemical gradients. At the peak of the action potential (+30mV) the voltage gated Na^+ channels are deactivated (③) - they close and are unable to open again until RMP has been restored (-70 mV). Once RMP has been restored, they revert to their closed (able to open) configuration (①).

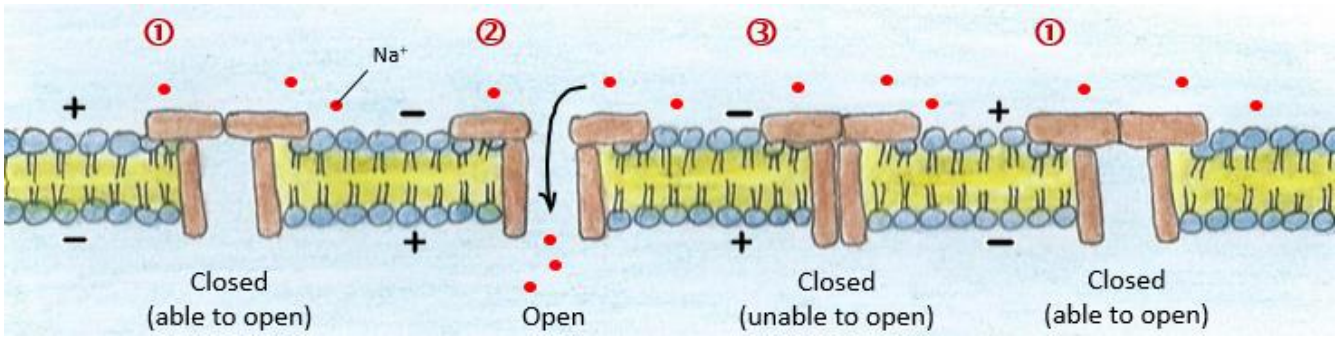


Figure 7.12 The voltage gated Na^+ channel is shown in its conformational states: ① Closed but able to open; ② Open and allowing Na^+ influx to occur; and ③ Closed and unable to open again until resting membrane potential is restored. Note that the trigger for this gated channel to be in the open configuration is a change in membrane potential wherein the inside of the cell becomes more positive. At the peak of the action potential ③ the channel is closed and deactivated so it cannot open again until the membrane is back at RMP.

The aspect of the **positive feedback loop** of this channel is as follows:
The triggering event of reaching threshold opens the channels and allows Na^+ influx, this brings into the cell its positive charge. As a consequence, this increases the membrane voltage further, making it become more positive, <u>which</u> <u>opens more voltage gated Na^+ channels</u>, causing the influx of more Na^+. This influx further increases the membrane voltage, leading to the opening of more voltage gated Na^+ channels,

causing greater influx of Na^+, further increasing the voltage . . . and on and on, in the manner a positive feedback loop. The response intensifies the original stimulus. The loop is broken when the membrane voltage reaches +30 mV, at this point the voltage gated Na^+ channels close and are unable to open again (they become **deactivated**). These channels typically cannot open again until RMP has been restored (-70 mV). The nature of this voltage gated Na^+ channel is important in creating the absolute refractory period.

Summation of Graded Potentials

Summation is when the magnitude of graded potentials can be added together; literally we can summate them to see their combined effect on the postsynaptic membrane. Summation of graded potentials can occur in two ways: **1)** Temporal Summation; and **2)** Spatial Summation.

1) Temporal Summation occurs from the summation of graded potentials overlapping in time. In other words (using the example in class), as the frequency of a signal (action potential) from neuron A to another neuron (neuron X) increases, the graded potentials (from A) can summate.

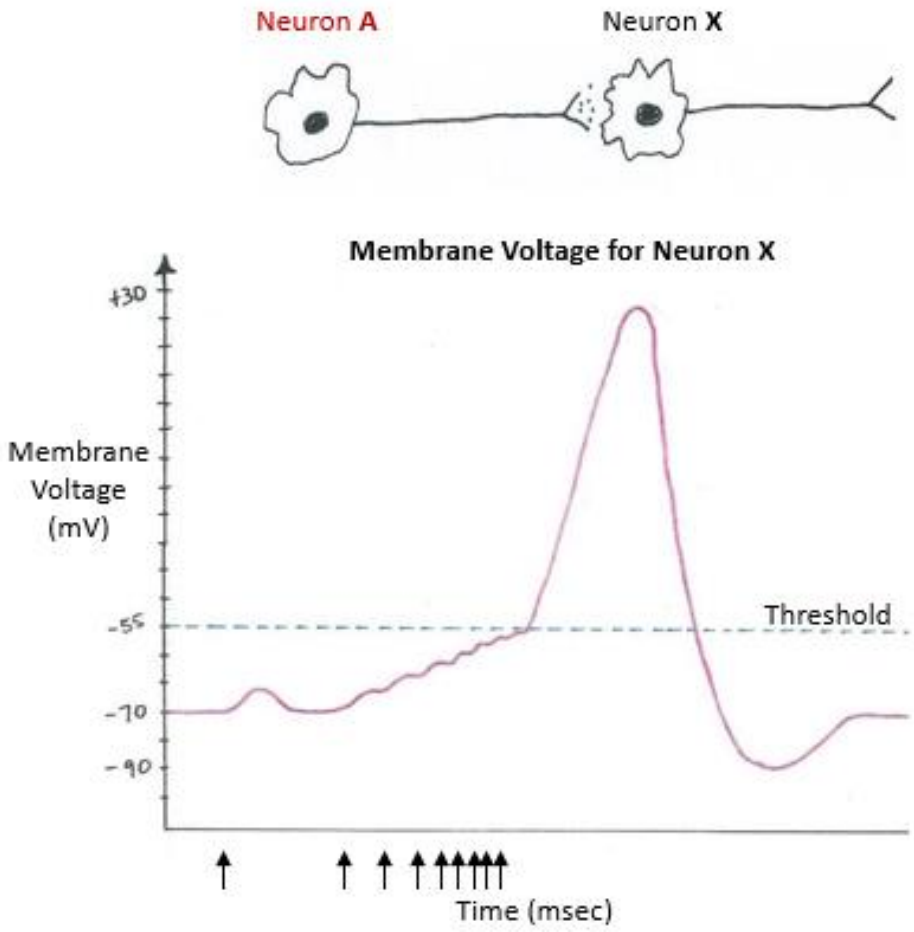


Figure 7.13 Here is an example of temporal summation of graded potentials that stimulate neuron X more and more frequently, such that the membrane voltage does not have time to recover and go back down to RMP (-70mV0) and continues to increase (go up) until it reaches threshold, the dashed line (-55mV) and becomes an action potential.

Temporal Summation: As its name implies is about time. As the time in between each stimuli gets smaller and smaller the frequency of stimulation gets higher and higher. The measurements of the membrane potential of neuron X on the graph in **Figure 7.13** show that as neuron X sits at 'rest', it has a membrane potential of -70 mV, or it is at RMP.

As neuron A stimulates neuron X once there is a small depolarization (an excitation) of the membrane, seen at the first arrow. If the frequency of stimulation from neuron A to neuron X increases (indicated by arrows), there is less time for the membrane of neuron X to return to RMP before the next stimulation by neuron A, and as a consequence the membrane of X continues to become more and more depolarized as the frequency of stimulation from A increases. If the increased frequency of stimulation causes the membrane of neuron X to reach threshold (-55 mV), an action potential will occur (as seen on the graph).

2) Spatial Summation occurs from the summation of several graded potentials from **several converging neurons simultaneously**. This can occur when several different neurons in space (e.g., A, B and C) send signals simultaneously to one neuron (neuron X). These graded potentials that are sent at the same time are summated by neuron X to determine the overall response.

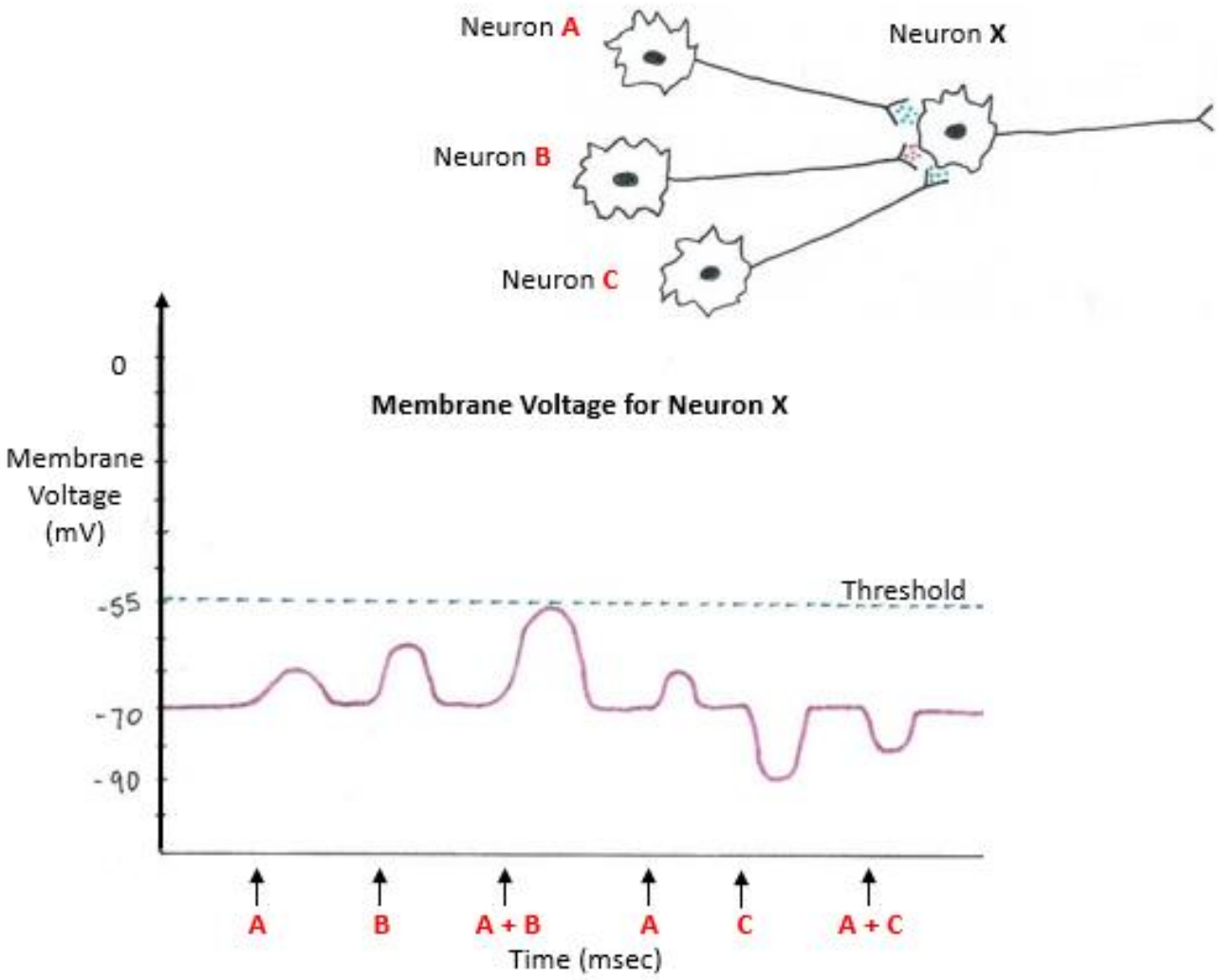


Figure 7.14 Above shows an example of spatial summation, where neurons **A**, **B** and **C** could stimulate the post-synaptic neuron X at the same time. Looking at the graph of the membrane voltage for neuron X, we can see that the other neurons sending it signals have various effects on the RMP of neuron X. Neurons **A** and B push the membrane up, causing depolarizations of the membrane or EPSPs. Neuron **C** causes the membrane to go down, or hyperpolarize, causing an IPSP. If any of the neurons signal simultaneously, their effects will be summated.

Spatial Summation: As its name implies, this is about multiple neurons in 'space' all stimulating neuron X simultaneously – all at the same time! As seen in **Figure 7.14** above, as neuron X sits at -70 mV (RMP) it is stimulated by neuron A only and its membrane depolarizes (goes up) 5 mV. It is then stimulated by neuron

B only and depolarizes 9 mV. At the 3rd arrow neuron X is stimulated by A and B at the same time and its membrane depolarizes 14 mV (the sum of +5 and +9). As neuron X is stimulated by neuron C only and its membrane hyperpolarizes (goes down) 10 mV. At the last stimulus arrow neuron X is stimulated by A and C at the same time and its membrane depolarizes -5 mV (the sum of +5 and -10).

Summary Comparison of Graded and Action Potentials

Examine **Fig. 7.15** and consider how the samples in the graph might best be described. Below is a side-by-side comparison of graded and action potentials.

Graded Potentials	Action Potentials
1) Magnitude varies	**1)** No variation - All or None
2) Decremental (passive spread)	**2)** Non-decremental (self-regenerating)
3) No Refractory Periods	**3)** Two Refractory Periods (absolute and relative)
4) Summation is possible	**4)** No Summation possible
5) Trigger: NT's, hormones, etc.	**5)** Trigger: Threshold reached
6) Occurs at cell body (direction can vary)	**6)** Occurs at axon hillock (one way direction)

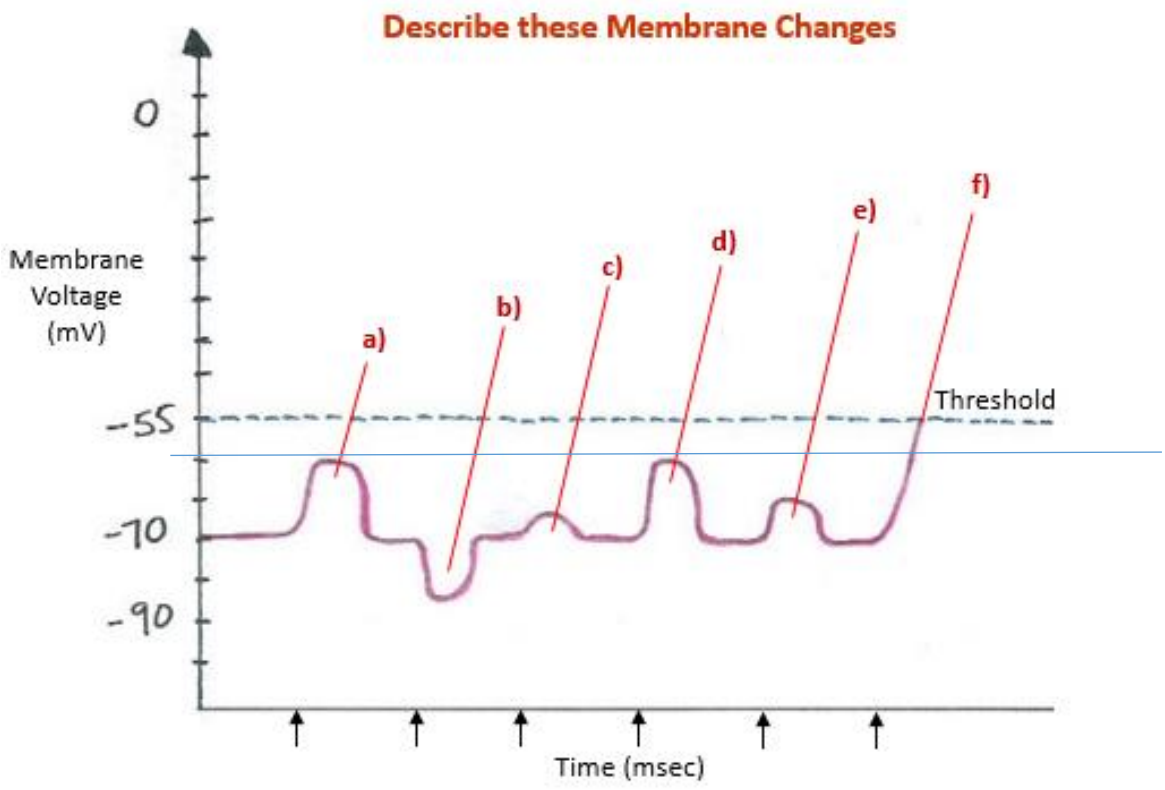


Figure 7.15 Above shows the changes in membrane potential (mV) caused by various stimuli (shown with arrows on the x-axis). For the membrane changes, **a)**, **b)**, **c)**, etc., use the space on the next page to estimate and describe the magnitude and directions of the stimulations this neuron is experiencing.

As an exercise, examine the graph above and estimate the direction and magnitude of the various stimulations (a through b) on the post-synaptic neuron X as indicated by the scale on the graph.

a) **c)** **e)**
b) **d)** **f)**

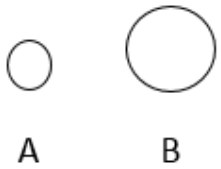
Answers provided in Appendix B.

Speed of the Conduction of the Signal

Although the magnitude of an action potential is always the same, the speed that it travels (is propagated) down an axon can vary. The 3 ways the speed of an action potential can vary are discussed below.

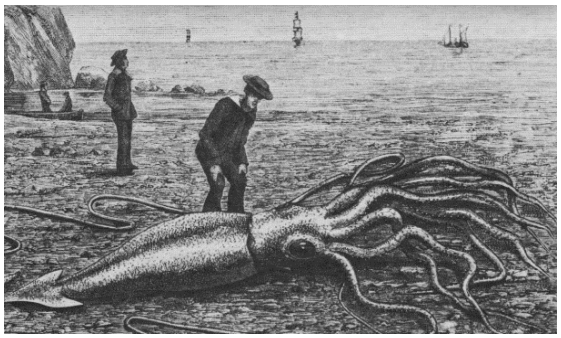
1. Diameter of Axon

Compare the cross sectional diameter of axons A and B below (imagine the axon is coming toward you and it is cut in cross section to show its thickness. Which of these axons will conduct a signal faster and why?



Answer: The larger axon will conduct a signal faster than the smaller axon. This is because there is less friction between the moving charged particles (predominantly Na^+ and K^+) and the sides of the axon in the larger axon, providing greater and faster flow. Larger diameter axons are said to have **higher conduction velocity**, which is directly related to the ions meeting less resistance to flow.

Axons in the human body do vary in their diameter, as seen in **Figure 7.16** to the tight. However, there is a limit to how large the diameter of an axon can be within the confines of the entire human body. The giant squid axons (below) can be as large as 1mm in diameter, which is **50 times** larger than the largest human axons!



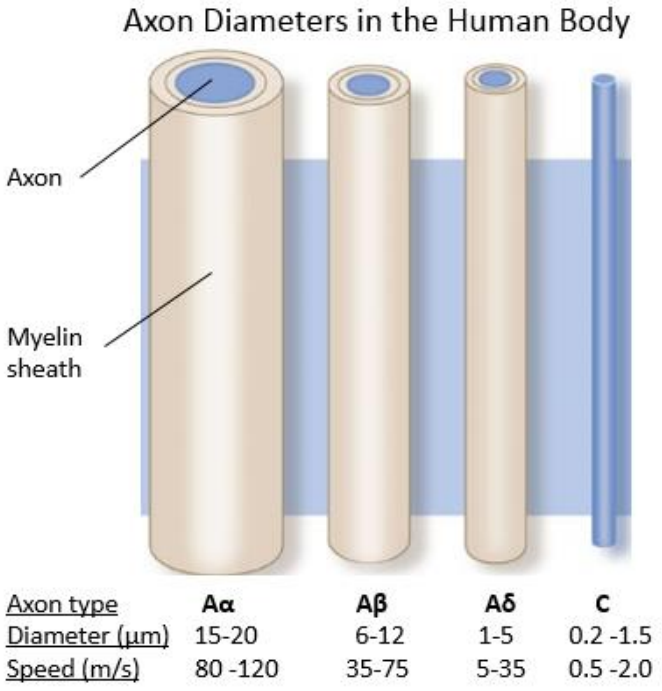


Figure 7.16 We may not have amazingly large axons like the giant squid (left) but there are a number of different sizes of axon diameters in the human body (right). They are **Aα** (muscle spindle, Golgi tendon organ), **Aβ** (stretch receptors of muscle spindle), **Aδ** (free nerve endings of touch and pressure, cold thermoreceptors), and **C** (nociceptors, warmth receptors).

It makes sense that nerves involved in muscle reflexes are large, thus very fast conductors of signals and responses. Interestingly the pain from some nociceptors and warmth detected with axon C diameters are a little slow and there is often a slight delay between painful stimulus and the perception of pain.

2. Temperature

The temperature of the body and its environment can have a big impact on physiology and the speed of nerve conduction. When the surrounding temperature in the body **increases**, chemical reactions **speed up**. Thus, if axon temperatures increase, the rate of conduction of the impulse (action potential) along the axon will **increase**. Conversely, if body temperatures decrease, the rate of conduction of the impulse down the axon will **decrease**. Normally, body temperature remains very constant but can change dramatically in some situations. A dramatic drop in T_b will significantly slow down neuronal transmission. For example, if a person falls into the very cold water of a frozen over lake, all of their nervous responses will be significantly slowed as a consequence of the massively slower conduction of action potentials.

3. Myelination of Axons

The **myelin sheath** that covers many axons is made from the cytoplasm of glial cells, either **Schwann cells** in the PNS (**Fig. 7.17**) or **oligodendrocytes** in the CNS. The myelin sheath is mostly composed of **lipids** and therefore is an excellent **insulator**, which is the same as saying it is a poor conductor of electrical charge. In this way, it reduces the electrical 'leakiness' along the axon and helps to conduct the signal more quickly within and along the axon.

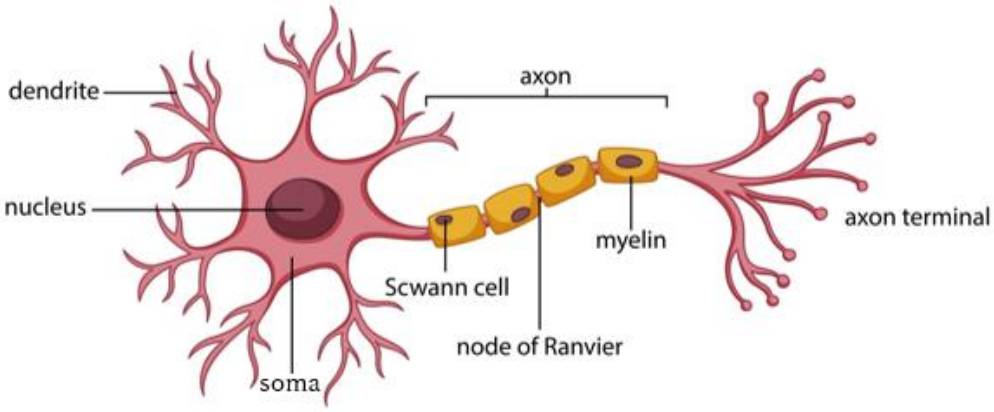


Figure 7.17 This show a typical motor neuron that has a myelinated axon made of Schwann cells. The action potential is said to 'jump' from one node of Ranvier to another, making the signal travel along the axon much faster than it would without the myelin sheath insulator.

The little gaps in the myelin sheath, called **'Nodes of Ranvier'** (see **Fig. 7.17**), allow the action potential to move faster along the axon. The electrical signal is said to jump from node to node, thus it is called ***Saltatory Conduction*** (*saltare* means 'to jump' in Latin). This is not what actually happens at the nodes of Ranvier, but at this stage it is convenient to think of the signal as 'jumping' down the myelinated axon significantly faster than a non-myelinated axon.

Of these three factors that can affect the speed of an action potential traveling down an axon, (diameter, temperature and axon myelination), it is **axon myelination** that is the most significant. This is mainly because axon diameters and body temperature are normally kept fairly constant in the body.

The degenerative disease **multiple sclerosis** is due to the destruction of the myelin sheath on somatic motor neurons that control skeletal muscle movement. Initially it causes a slowing of the signal and eventually it can stop motor signals to skeletal muscle all together. The sensory neurons that are bringing

in sensory information are not affected by multiple sclerosis, thus for example, a person can feel their legs normally but would have problems sending signals outward for muscle movement and control of them.

Synaptic Transmission - The way Neurons Communicate

Finally, we have arrived at the **synapse**. Synapses are thought to be the sites of communication between nerve cells. It is a specialized cell junction where neurons communicate with other neurons. At a synapse, a neuron releases a signal molecule (a **neurotransmitter**) that diffuses across a small gap between the cells (called the **synaptic cleft**), binds to and activates special **receptors** on the target cell.

The synapse consists of a **presynaptic** neuron sending the message and a **postsynaptic** neuron receiving it, there is a conversion of **electrical signals** from the action potentials coming down the axon of the presynaptic neuron, into a **chemical signal** when the neurotransmitter is released into the synaptic cleft.

Neurons also communicate with other tissue, such as muscle tissue where it is called a **neuromuscular junction** (NMJ), or with glands where it is called a **neuroglandular junction**. It is helpful to be able to draw and label a synapse (like the one below). As practice, draw the diagram shown in **Figure 7.18** shown below, on a blank page, several times! The specific details of the sequence of events are presented below.

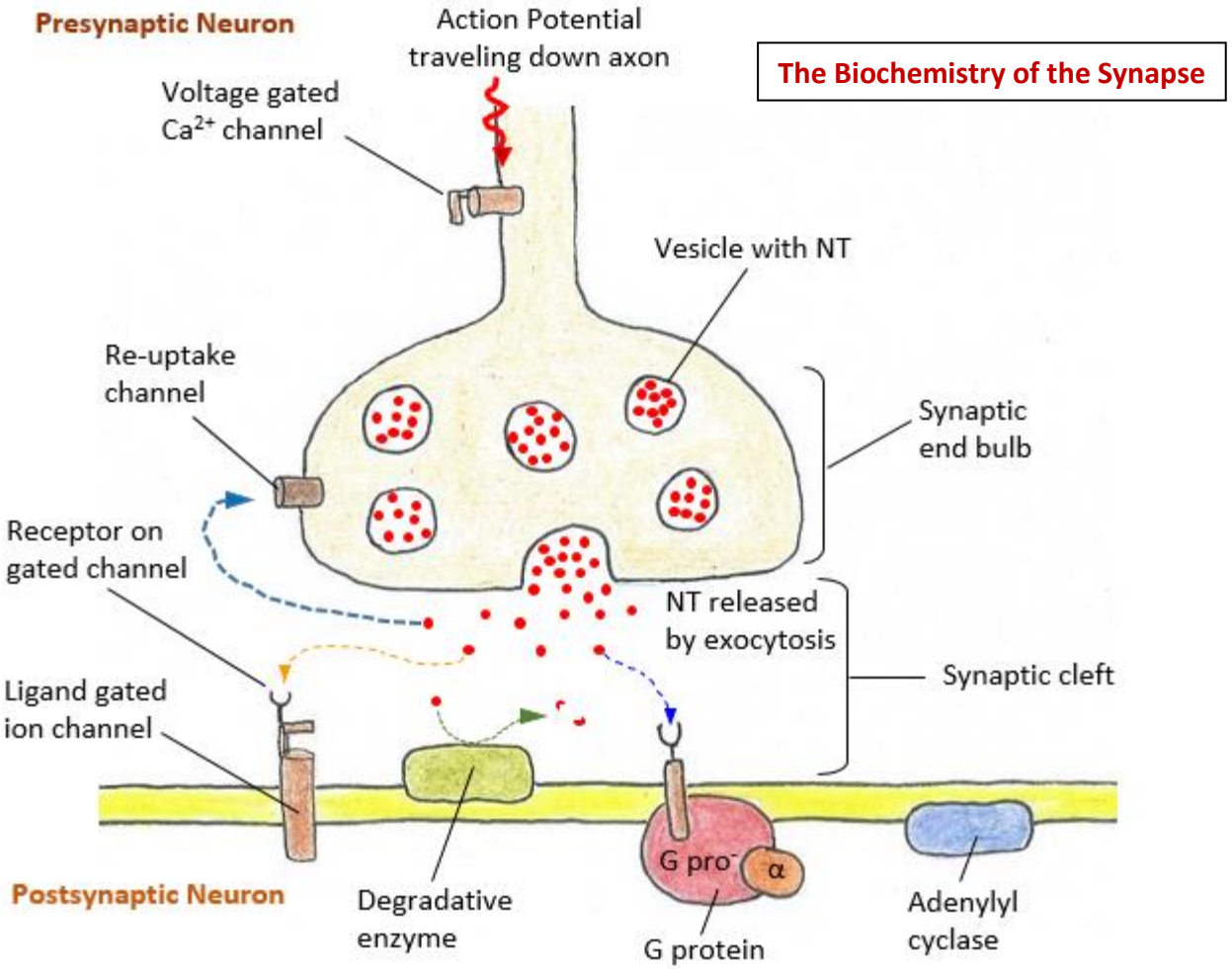


Figure 7.18 This is a diagrammatic representation of a synapse, which is the site of communication between two neurons. There is a pre-synaptic neuron that is sending the signal and a post-synaptic neuron that is receiving the signal. The neurotransmitter is the signal molecule released that binds to receptors on the post-synaptic neuron.

Synaptic Transmission - The Sequence of Events

Synaptic transmission or neurotransmission is the process of communication between the **pre-synaptic neuron**, that is, the cell sending the signal, and the **post-synaptic neuron**, the one receiving the signal.

Reading carefully through the events for each neuron below, the fundamentals will become more distinct and clear. For example, it is the pre-synaptic neuron releases the neurotransmitter and this binds with various receptors on the dendrites of the post-synaptic neuron where it can elicit various responses.

Ultimately both the presynaptic and postsynaptic events are all one flowing episode, however, for the sake of understanding each neuron of the synapse separately at first, we will describe the events first in terms of what occurs at the pre-synaptic neuron, then what occurs at the post-synaptic neuron. As we shall see, the pre-synaptic has a set process, really only varying in the type of neurotransmitter it releases, whereas the postsynaptic neuron has several different ways it can respond to a neurotransmitter.

Events in the Pre-Synaptic Neuron

1. A nerve impulse or **action potential** (AP) moves from the axon hillock down the axon and arrives at the synaptic terminal.

2. **Voltage gated Ca^{2+} ion channels** located at the at the end of the axon open in response to the change in membrane potential from the AP traveling along the plasma membrane.

3. The opening of the voltage gated Ca^{2+} ion channels allows an **influx of Ca^{2+}** ions from the extracellular fluid into the cell, since the concentration gradient favors this direction of movement.

4. The increase in intracellular Ca^{2+} ions ($[Ca^{2+}]_i$) triggers **vesicular fusion** with the plasma membrane and **exocytosis** of the synaptic vesicles that 'docked' on the membrane.

5. Vesicles release large quantities of neurotransmitter by **exocytosis** into the **synaptic cleft**. After the neurotransmitter (NT) is released, the empty vesicles drop back into synaptic end bulb and may reload with more NT. The increase in $[Ca^{2+}]_i$ also causes more vesicles to detach from cytoskeleton and dock with membrane in preparation for the next release of NT.

6. Once released from the pre-synaptic neuron, the NT moves across the synaptic cleft by **simple diffusion** to reach and bind to receptors that are located on the post-synaptic membrane.

Events in the Post-Synaptic Neuron

It is important to know that there are two main ways that the post-synaptic neuron can respond to a neurotransmitter, either: **1)** The **Ionotropic** Effect; or **2)** The **Metabotropic** Effects.

1) Ionotropic Effects – This mechanism is when the neurotransmitter binds to a membrane receptor and **directly opens an ion channel**. This then leads to a rapid change in membrane potential of the postsynaptic cell, whether **Excitatory** or **Inhibitory**. This type of effect is very common for Nervous system transmissions, which are rapid and brief.

2) Metabotropic Effects – This mechanism is mediated by a **second messenger system**, like cyclic adenosine monophosphate (cAMP). It takes longer but is very powerful in its effect in the body; it can open ligand gated channels indirectly, change the activity of enzymes, or trigger transcription.

1) Events in the Post-Synaptic Neuron: Ionotropic Effects

1. The NT released from pre-synaptic neurons binds to **receptors** on the postsynaptic membrane.

2. The post-synaptic membrane receptors are linked to **ligand gated ion channels**, that is, they directly open in response to being bound by the NT.

3. Since most ligand gated ion channels are specific in terms of which ions they allow to pass through them, let's methodically explore the possibilities that are most common.

    a. What if the ligand gated channels allowed **Na^+** to go through it? When the NT binds to the receptor, the ligand gated Na^+ channel opens and there is an **influx of Na^+** in the post-synaptic neuron. This influx of Na^+ **depolarizes** the membrane (makes it become more positive). Because the membrane is brought closer to threshold (see graph), we can also call this 'excitatory'. This is also called an **Excitatory Post Synaptic Potential (EPSP).** This is not an action potential, the membrane is becoming more positive and it may make an action potential more likely to occur (see **Fig. 7.19** right below).

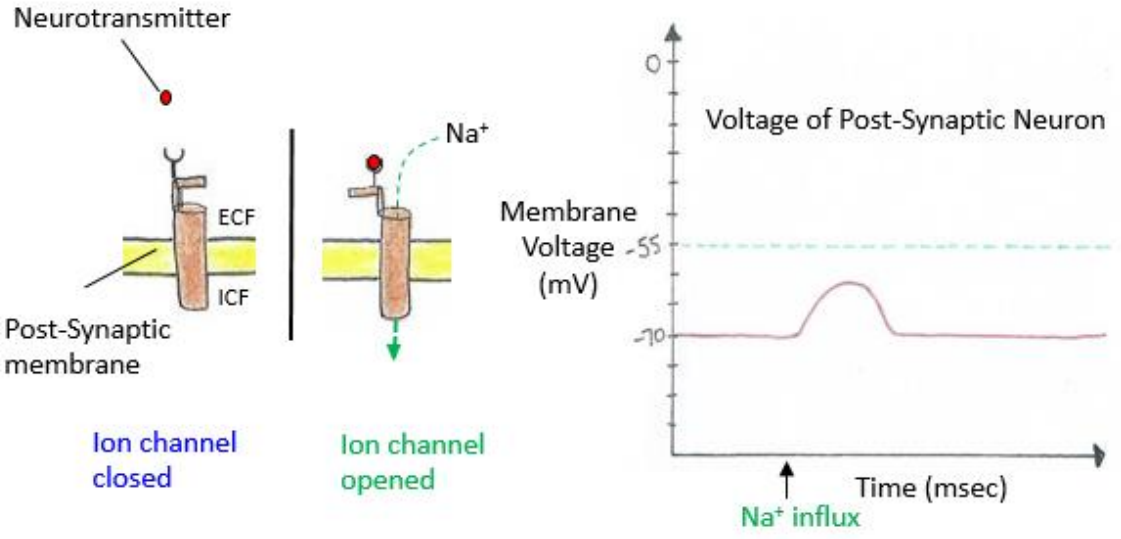


Figure 7.19 Shown at left is the opening of a Na^+ channel when the neurotransmitter binds. At right is how the cell membrane voltage changes as a consequence of the opening of that channel.

b. What if the ligand gated channels allowed **K^+** to go through it? When the NT binds to the receptor, the ligand gated K^+ channel opens and there is an **efflux of K^+** in the post-synaptic neuron. This efflux of K^+ **hyperpolarizes** the membrane (makes it become more negative). Because the membrane is pulled down further from threshold (see graph), we can also call this 'inhibitory'. This is also called an **Inhibitory Post Synaptic Potential (IPSP).** This is not an action potential either, the membrane is becoming more negative and it may make an action potential less likely to occur (see **Fig. 7.20** right below).

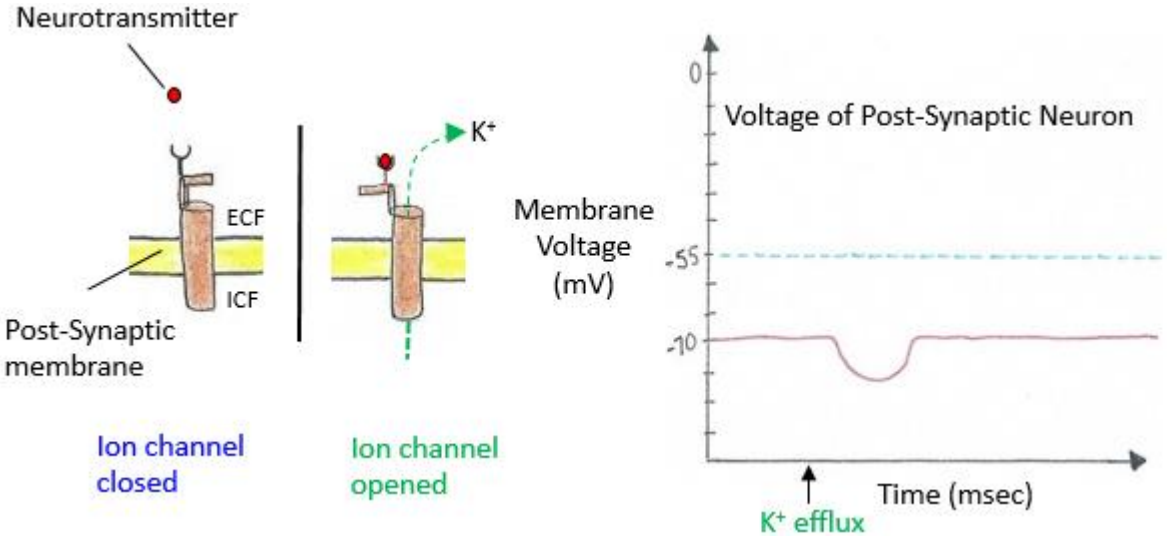


Figure 7.20 Shown at left is the opening of a K^+ channel when the neurotransmitter binds. At right is how the cell membrane voltage changes as a consequence of the opening of that channel.

c. What if the ligand gated channels allowed **Cl^-** to go through it? When the NT binds to the receptor, the ligand gated Cl^- channel opens and there is an **influx of Cl^-** in the post-synaptic neuron. This efflux of Cl^- **hyperpolarizes** the membrane (makes it become more negative). Because the membrane is pulled down further from threshold, we can also call this 'inhibitory'. This is also called an **Inhibitory Post Synaptic Potential (IPSP).** This is not an action potential either, the membrane is becoming more negative and it may make an action potential less likely to occur (see **Fig. 7.21** right below).

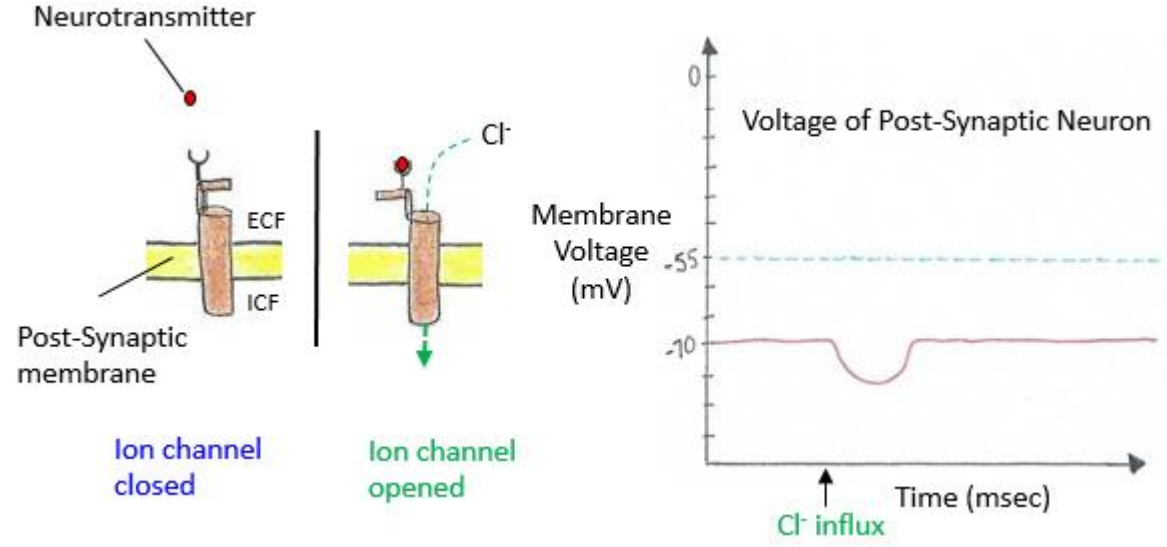


Figure 7.21 Shown at left is the opening of a Cl^- channel when the neurotransmitter binds. At right is how the cell membrane voltage changes as a consequence of the opening of that channel.

Summary of the Ionotropic Effect

This mechanism involves the direct opening of ligand gated ions channels of the post-synaptic neuron. The binding of the neurotransmitter to the membrane receptor directly opens an ion channel. It will cause an immediate change in the membrane voltage, by either elevating it or lowering it. This type of effect is very common for Nervous system transmissions, which are rapid and brief.

What does Depolarization mean?

The word depolarization, comes from 'polarized' which means a divide or difference between two sides or opposing groups, or in this case a difference in electrical charge across a membrane. The de- prefix means un-polarized, so when the membrane is depolarized it is becoming less different on opposite sides, or moving towards 0 mV. At zero mV there is no electrical polarization of the membrane.

What does Hyperpolarization mean?

The prefix hyper- means above, higher than normal, so if the membrane hyperpolarized it means the two sides of the membrane are more different. In neurons this occurs when the membrane is going downward or more negative.

If the postsynaptic membrane is *depolarized* and brought closer or to threshold, then it is called an Excitatory Post Synaptic Potential (**EPSP**). For example, if Na^+ ions enter the cell, the inside of the cell becomes more positive, and the RMP of -70 mV gets moved closer to threshold (-55 mV).

If the membrane potential is *hyperpolarized* and moved further away from threshold, then it is called an Inhibitory Post Synaptic Potential (**IPSP**). For example, if K^+ ions leave or Cl^- ions enter the cell, the inside of the cell becomes more negative, and the RMP of -70 mV gets moved further away from threshold, making the cell less likely to reach threshold.

Hypokalemia and Hyperkalemia

As we know, K^+ ions are the most important ion that determines the RMP, and therefore significant changes in K^+ levels in the blood will have an impact on the resting excitability (voltage) of not only neurons, but all excitable tissue, including cardiac and other muscle.

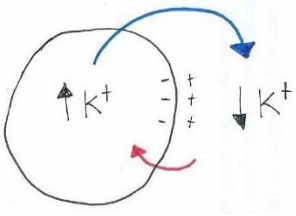
- **Hypokalemia** is the medical term for having lower than normal potassium (K^+) levels in the blood. Factors associated with a low plasma potassium levels include severe medications that hamper kidney function (diuretics), having heart failure, hypertension, a low body mass index (BMI), eating disorder, alcoholism, diarrhea, or Cushing's syndrome. All of these and more could lead to depressed K^+ levels in the blood and other body fluids. Normal levels of potassium range from **3.5** to **5.1** mmol/L in adults. Reference ranges vary from lab to lab). Usually, levels **under 2.5 mmol/L** are considered to be very serious.

- **Hyperkalemia** is the medical term describing higher than normal potassium (K^+) levels in the blood. The leading causes of hyperkalemia is chronic kidney disease, highlighting the vital role of the kidneys K^+ in maintenance. It can also be caused by uncontrolled diabetes, dehydration, having had severe bleeding, consuming excessive dietary potassium, and various drugs and medications. Blood K^+ level is normally **3.6** to **5.2** millimoles per liter (mmol/L). Hyperkalemia is typically when levels of potassium are **above 5.5 mmol/L** (or between **5.0** to **5.5 mmol/L**.

The RMP is effected by Hypokalemia and Hyperkalemia

The blood levels of K^+ are normally highly regulated by the **kidneys** where K^+ can be retained when it is needed, and eliminated if there is any excess of it. It is clear that both hypokalemia and hyperkalemia are deleterious states for the human body to be in for any length of time.

An important aspect of understanding physiology is to know exactly how (if possible) a state away from homeostasis (balance) causes dysfunction. The imbalance of K^+ is a good example of how valuable details are known about how a K^+ imbalance effects neurons, and in fact any excitable tissue, including the heart. Recall that normally the a K^+ inside the cell is much higher than the K^+ outside the cell (see left), and that the equilibrium potential for K^+ (E_{K+}) in neurons is -90 mV, which is extremely close to the -70 mV of resting membrane potential (RMP).



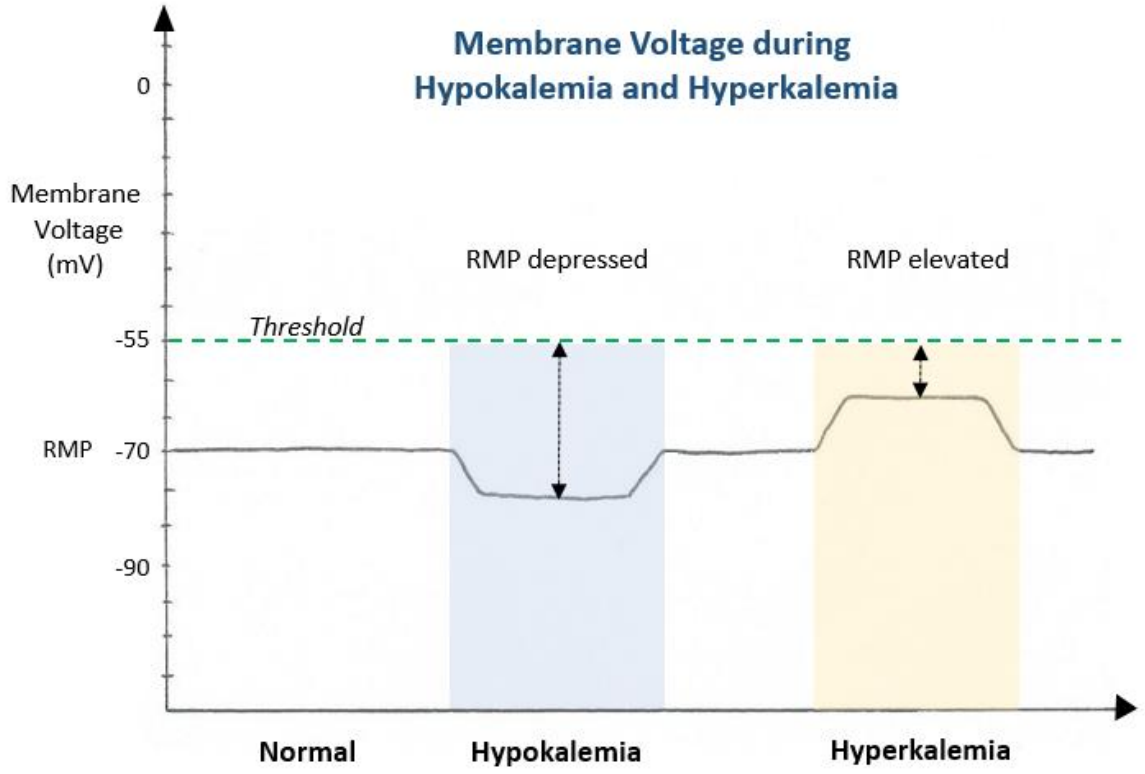


Figure 7.22 This graph shows the membrane voltage (mV) of a neuron that is initially under normal conditions. Then in **a)** there is a period of hypokalemia and the resting membrane potential (RMP) is depressed, taking is further away from the normal threshold of -55 mV, thus reducing the excitability of the cell membrane. In **b)** there is a period of hyperkalemia and the RMP is elevated closer to threshold, making the cell membrane more excitable than normal.

Let's consider **a)** <u>hypokalemia</u>: If less K^+ is in the blood, then less K^+ will be in the interstitium surrounding neurons. Since there is still high K^+ inside the cell, the difference between the inside and the outside of the cell in terms of K^+ is **larger**. The measure of the RMP is the ***difference*** between the inside and the outside of the cell, therefore this state makes the membrane become <u>more different</u> or ***hyperpolarized***. This depresses the RMP, taking it lower which makes it harder to reach threshold (see the graph in **Figure 7.22** above). Neurons and myocardiocytes in this state are **less excitable** thus **less responsive** to stimuli.

Now let's consider **b)** hyperkalemia: If more K^+ is in the blood, then more K^+ will be in the interstitium surrounding neurons. Since there is high K^+ inside the cell, the difference between the inside and the outside of the cell in terms of K^+ is **smaller**. Therefore, the RMP becomes less different or ***depolarized***. This elevates the RMP, taking it higher which makes it easier to reach threshold (see the graph in **Figure 7.22** above). Neurons and myocardiocytes in this state are **more excitable** thus **over responsive** to stimuli.

As we can see, neither of these states is manageable for too long, it is not feasible to have such critical tissues in the body be under- or over-responsive. In fact, information to underscore the important of keeping K^+ in balance, is that solutions of **saturated KCl** given in an I.V. can be lethal very quickly, this is the major component of 'lethal injections'. If the K^+ gradients in our cells were eliminated or reversed and this was not rectified, it would ultimately lead to death.

2) Events in the Post-Synaptic Neuron: Metabotropic Effects

The mechanisms of the metabotropic effect are mediated by a **second messenger system**, like cyclic adenosine monophosphate (cAMP). The metabotropic effects are summarized below and in **Fig. 7.23**:

1. As is the same for the ionotropic effect, the Presynaptic neuron releases a neurotransmitter (**first messenger**) via exocytosis into the synaptic cleft.

2. Also like the ionotropic effect, the neurotransmitter (NT) diffuses across the synaptic cleft and binds **receptors** on postsynaptic membrane of the neuron.

3. The receptor here is linked to a **G protein** and when the NT binds to this receptor it activates the G protein which hydrolyses GTP to GDP. This allows for the **α subunit** that is bound to the G protein to migrate (move) along plasma membrane to the inactive **adenylyl cyclase** enzyme that is on the intracellular aspect of the plasma membrane.

4. The detached α subunit of the G protein activates the **adenylyl cyclase**, which is an enzyme that uses **ATP** as its substrate to make cyclic AMP (**cAMP**), the postsynaptic cell's **second messenger**.

5. The enzyme adenylyl cyclase acts to remove 2 phosphate (**P**) groups from ATP to make **cAMP** and this is called the **second messenger** because this molecule inside the cell acts to relay the original signal received by the cell from the **first messenger** (the neurotransmitter) which started at the receptors on the outer surface of the cell. This form of cell communication is called "the second messenger system".

6. The increase in cAMP inside the cell that occurs activates **Protein kinase** (e.g., PKA) enzymes.

7. Enzymes which are protein kinase act to phosphorylate (add phosphates to) other proteins (including enzymes, protein channels or regulatory proteins) in the cytosol of the postsynaptic cell and can increase or decrease various cellular activities as a consequence.

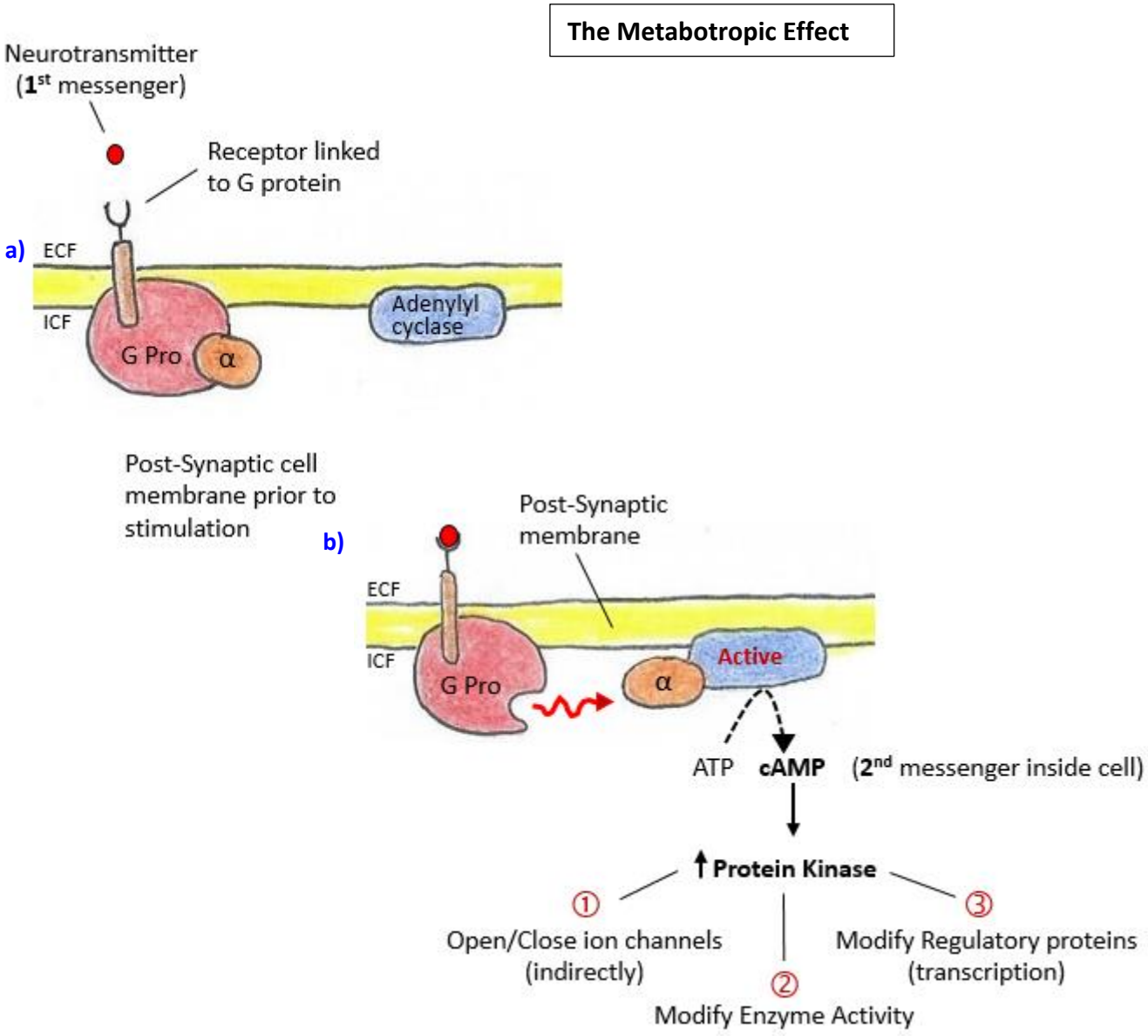


Figure 7.23 In this diagram the metabotropic effect on the post-synaptic neuron is shown. In **a)**, the neurotransmitter is the first messenger that binds to a receptor on the post-synaptic membrane that is linked to a G protein inside the cell. In **b)**, the binding of the receptor activates the G protein, which liberates the alpha subunit that shuttles across and activates the enzyme adenylyl cyclase. Using ATP as the substrate, it makes cyclic AMP (cAMP), which acts as the second messenger within the cell. The cAMP then activates protein kinase, which phosphorylates proteins. These proteins may be: ① ion channels (making them open or close); ② enzymes (making them increase or decrease activity); ③ regulatory proteins controlling gene transcription (turning on or off genes).

Summary of the Metabotropic Effect

The metabotropic effects, shown and discussed above, can have several effects that fall into **3** categories. The key concept involved in this effect is that it is a step-wise fashion (that takes more time than that ionotropic effects) that protein kinases are activated.

What is a **kinase**? Its -ase ending tells us it is an enzyme, and a kinase is a type of enzyme that sticks phosphates on things. Additionally, a **protein kinase** sticks phosphates onto proteins. Notice that in all 3 consequences the change or modification occurs to **proteins**, as that is the substrate upon which the kinase acts.

Summary of the 3 Categories of Responses to the Metabotropic Effect:

1. Ligand gated ***protein*** channels in the plasma membrane are phosphorylated. Depending on the type of ion channel, this may open or close the channel. This will then change cell permeability and membrane voltage. Since this occurred through the second messenger cAMP and then protein kinase, this is not a direct opening of an ion channel like the inotropic mechanism.

2. Enzymes (which are ***proteins***) can be phosphorylated, and as we have learned, this modulates enzyme activity, either increasing or decreasing it. This may turn on or off other metabolic pathways.

3. Regulatory ***proteins*** (that control transcription of genes in the nucleus) can be phosphorylated, and this can change their activity. This can trigger genetic transcriptions and synthesis of new proteins.

All of these actions of protein kinase can cause significant activity within a that postsynaptic cell. The metabotropic effect takes a longer time period to occur because of the many steps involved, however, it usually has very powerful effects. This is because each step is often an order of magnitude greater than the previous, which is why it is often called an **amplification cascade**. For example, for every one molecule of the neurotransmitter, 10 molecules of cAMP may be activated, and for every molecule of cAMP, 10 molecules of Protein Kinase may be activated, creating a comprehensive and expansive response in the post-synaptic neuron.

The When and Where of Ionotropic and Metabotropic Effects

Most neurons engage the **ionotropic effect**, which is characteristic of a **fast** and **brief** response. The direct opening of ion channels is a very effective means of rapid communication.

There are some very important neuronal circuits that use the **metabotropic effect**, for example the **adrenergic neurons** that transmit epinephrine engage in this type of cell signaling. This mechanisms has a much broader effect across tissues and again, although they take a little longer to transmit, they are very powerful when they act. This is why this type of cellular response is prominently seen in the endocrine system, as the metabotropic effect is characterized by its slower but more powerful responses.

Stopping Signal Transmission

Now that all the fuss has been made and the important signal was sent and received, it is just as important to stop the signal and clean up the synaptic cleft.

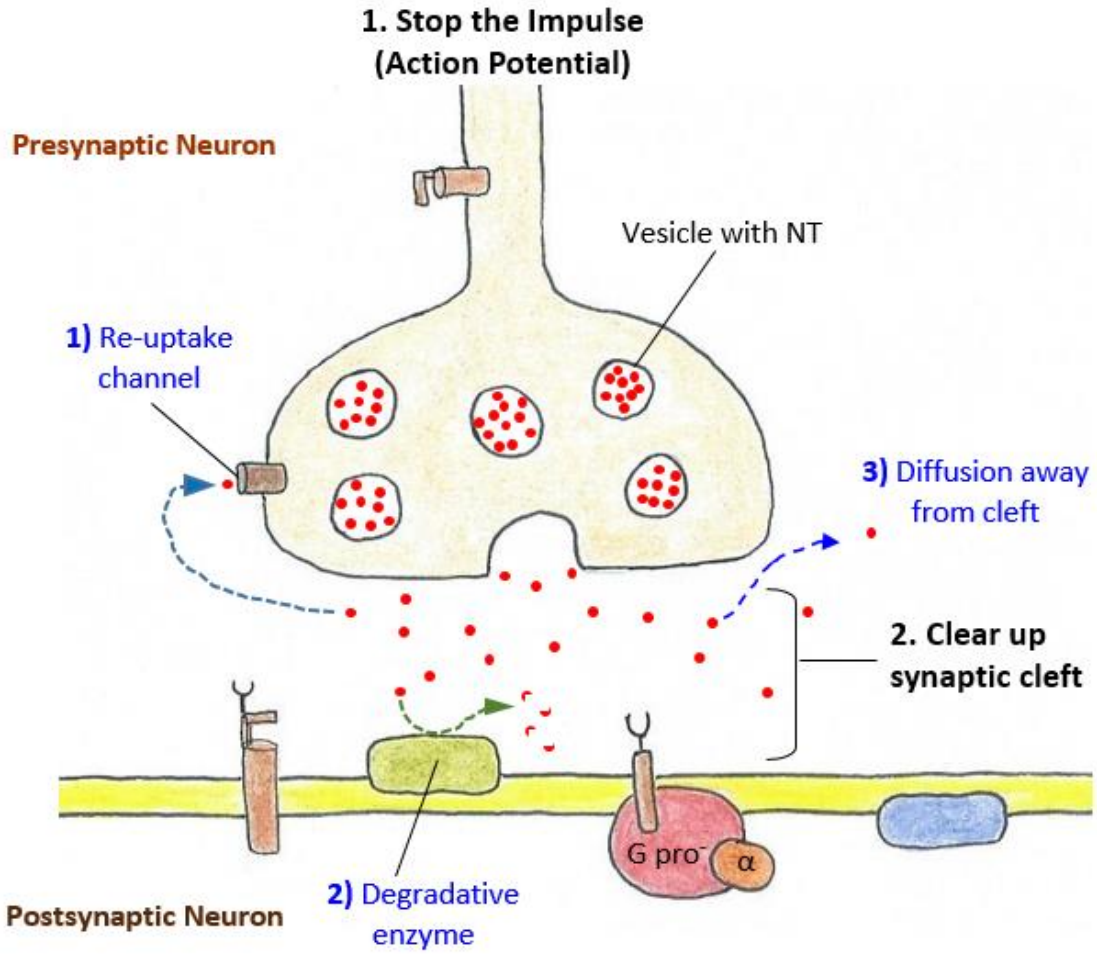


Figure 7.24 Signal transmission needs to stop in order to start again. To stop, the first thing that needs to happen is **1.** For the pre-synaptic neuron to stop sending action potentials. Then **2.** The synaptic cleft needs to be cleared away of the neurotransmitter. This is achieved in three ways: **1)** The reuptake channels of the presynaptic neuron recover some of the neurotransmitter it just released; **2)** Degradative enzymes break down the neurotransmitter into non-stimulating fragments; and **3)** the neurotransmitter moves by diffusion to where it is less, away from the synaptic cleft.

As seen in **Figure 7.24** above and listed below, a number of things must occur to stop the postsynaptic cell from responding and begin the process to restore the cell to its resting state so that it can receive and possibly transmit a signal again. These Important things must happen:

1. Stop the Impulse (Action Potential): The impulses (signal or action potential) from presynaptic nerve fiber stops. The action potential ends, no more Ca^{2+} influx, no vesicle fusion and exocytosis, thus no further release of neurotransmitter into the synaptic cleft occurs.

2. Clear up the Synaptic Cleft: The synaptic cleft must be cleared of residual neurotransmitter in preparation of another signal arriving. This can be achieved in 3 ways:

1) The neurotransmitter reuptake channels on the presynaptic neuron help to remove neurotransmitter from the cleft. This can entail the recycling of the entire neurotransmitter or just fragments of it.

2) Degradation of the neurotransmitter enzymatically hastens the return of the membrane to resting membrane potential (RMP). Sometimes these enzymes are embedded in the postsynaptic membrane or they may me enzymes that reside in the synaptic cleft.

3) Diffusion of the neurotransmitter away from receptors in the synaptic cleft is also a contributor to the clearing away of the synaptic cleft and the cessation of postsynaptic stimulation.

Degradative Enzymes for Neurotransmitters

Enzymatic degradation of the neurotransmitters is an important component of stopping the signal. For the various categories of neurotransmitters there are different degradative enzymes. For example, when ACh comes in contact with **Acetylcholinesterase** (**AChE**) it is degraded and produces Acetate + Choline, both of which are non-stimulating fragments of the neurotransmitter ACh.

For the category of neurotransmitter that are termed biogenic amines (e.g., NE, E, Dopamine, Serotonin) when they come in contact with the degradative enzyme **Monoamine Oxidase** (**MAO**) produces non-stimulating fragments of these NT. The only glutamate-degrading enzyme that requires glutamate as its sole substrate is **glutamate decarboxylase (GAD)**.The main degradative enzyme for GABA is **GABA-transaminase (GABA-T)**, though the steady state of GABA levels are normally controlled by GAD.

Poison and Drugs are not good for Human Health

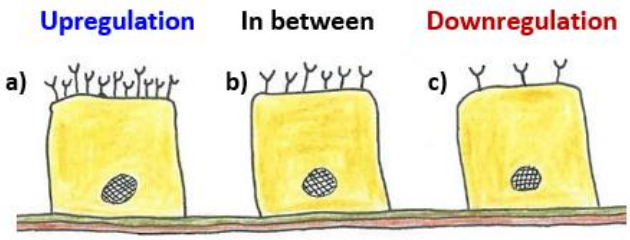
The use of **blockers** or **inhibitors** for both **1)** the reuptake channels for neurotransmitters, and for **2)** the enzymes that degrade and deactivate the neurotransmitter have long been a very popular drug method for 'treating' depression or anxiety. For example, **serotonin selective reuptake inhibitors** or **SSRI's** was the mechanism of Prozac. And "**MAO inhibitors**" were the original miracle "Anti-depressant" medication before more selective and targeted inhibitors were created.

Whether **blocking re-uptake** or **blocking degradative enzymes**, this will result in more neurotransmitter lingering in the synaptic cleft. This will therefore continue to stimulate the post-synaptic membrane even though the body has turned off that signal. For neurotransmitters like **serotonin**, **dopamine** and **norepinephrine**, this excess over stimulation may result in feelings of euphoria and elation, just like taking heroin or cocaine would.

Up and Down Regulation of Receptors

Both of the mechanisms described above regarding the use of reuptake blockers or degrative enzyme inhibitors to deactivate various neurotransmitters, have long been a very popular drug method for 'treating' depression or anxiety.

HOWEVER, the receptors will **downregulate** in response to being overstimulated (see image at right) and thus the cells will require greater and greater stimulation in order to maintain the "happy" feeling, just as any other drug addict always needs more of the drug to maintain its effects.



Changes in Cell Receptor Density (Sensitivity)

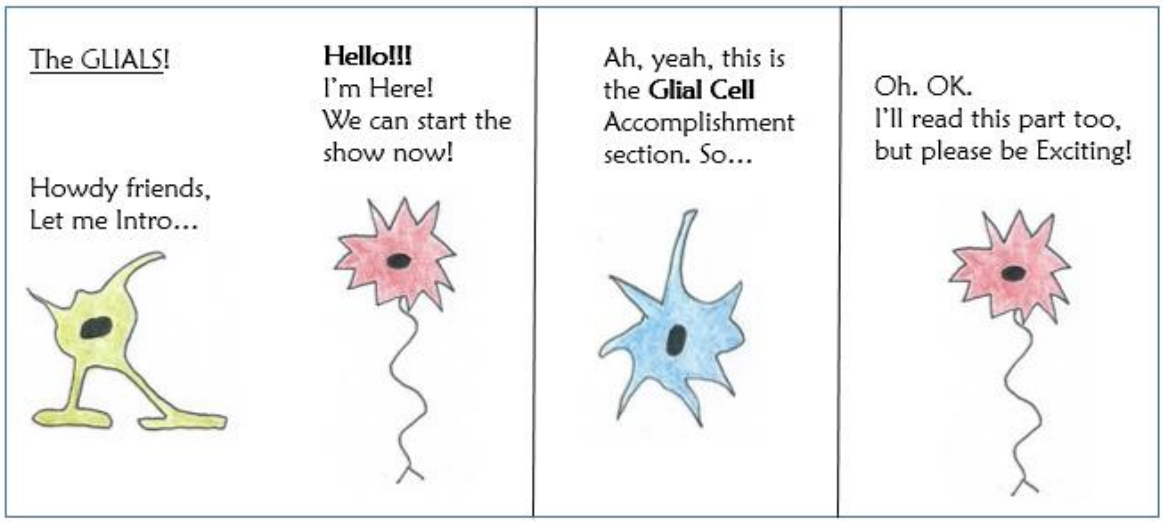
This is a physiological fact that is covered in more detail in the next chapter, but here is a basic overview. The various types of receptors on the surface and inside of cells are dynamic, and this means that their number (density) changes in response to what your body is experiencing.

The **upregulation of receptors** involves the increase in the number (density) on a cell's surface or within it (cell on the left in image above), causing an increase in sensitivity, which leads to a heightened response to a specific signal. The **downregulation of receptors** involves the decrease in the number (density) of receptors on a cell's surface or within it (cell on the right in image above), causing a reduced response or sensitivity to a signal (see image above).

The harmful side effects and degradation of neuronal circuitry caused by toxic drugs can be devastating to health, and these effects certainly will not make people happy in the long term. There are so many other positive and healthy ways to improve mood that have nothing to do with taking a pill etc. For example, the simple act of being in nature improves mood. Those ideas are explored further in the next section.

Neuroglial (Glial) Cells in the Nervous System

There are **two general types** of cells in the nervous system: **Neurons** and **Glial** cells. As we have seen, neurons are the cells of communication within the nervous system and throughout the body. The glial cells, in general, are cells that support the neurons.



The name glia comes from Latin meaning 'glue'. This is because it was initially thought that the glial cells were the *glue* that held the brain together. For the most part this holds true. A typical brain has at **least 8 times more glial cells than neurons**. That would be about **800 billion** glial cells! Glial cells do not conduct nerve impulses, and therefore are not thought to be involved directly in communication. However, unlike neurons, glial cells are capable of **mitosis**, thus can divide and multiply.

While glia cells (or **neuroglial**) are correctly thought of in a supporting role of the neurons in the nervous system, researchers have discovered that they play a role in responding to nerve activity and modulating communication between nerve cells. When glial cell function is disrupted, the result can be devastating, as most brain tumors are caused by mutations in glial cells, they are called **gliomas** (-oma = cancer). It is entirely accurate to say that neurons would be unable to function without the vital roles that are fulfilled by these glial cells.

There are 6 Types of Glial Cells

In the body there are six (6) types of glial cells, and broadly speaking, similar general roles can be ascribed to all of them. However, **each type has a specific and unique role in the nervous system** that makes them distinct and easy to remember! Their primary function is often also linked to their name, as we shall see in a moment. First we'll describe what all glial cells have in common, then look at how each one is different.

All Glial Cells Perform These Functions

Glial have many pivotal roles, including guiding developing neurons to their destinations, shielding neurons from harm by chemicals or trauma.

The three main functions of all Glial cells are to:

1. **Create the 3-D network of nervous tissue**. The immense number of glial cells enables them to physically be the framework of support which surrounds neurons and holds them in place.

2. **Facilitate Exchange**. Glial cells facilitate the supply of nutrients and O_2, and the removal of wastes and CO_2 for neurons.

3. **Insulate, Protect and Repair neurons**. Neurons are shielded and insulated in different ways by all of the glial cells, and are routinely repaired by nearby glial cells.

Of the 6 Glial Cells - 2 are in the PNS and 4 are in the CNS

All glial cells share some common functions and at the same time, each of the six (6) glial cells has a unique role. There are 2 types of glial cells in the PNS, they are: Schwann cells and satellite cells. There are 4 types of glial cells in the CNS: Oligodendrocytes, astrocytes, ependymal, and microglia. The unique attributes and functions of the glial cell are described for each in detail below.

Glial Cells of the PNS

Schwann cell. This is the cell that creates the insulative myelin sheath around axons in the peripheral nervous system (outside of the brain and spinal cord). This lipid rich cell insulates the electrical signal along the axon and allows axons to transmit nerve impulses much faster and much more efficiently than unmyelinated axons. The Schwann cell is one of two cells that provide the myelin sheath for axons, the other is the oligodendrocyte in the CNS. Schwann cells are different from oligodendrocytes, in that a single Schwann cell wraps around only a portion of one axon segment and no others (see model in **Figure 7.25** below).

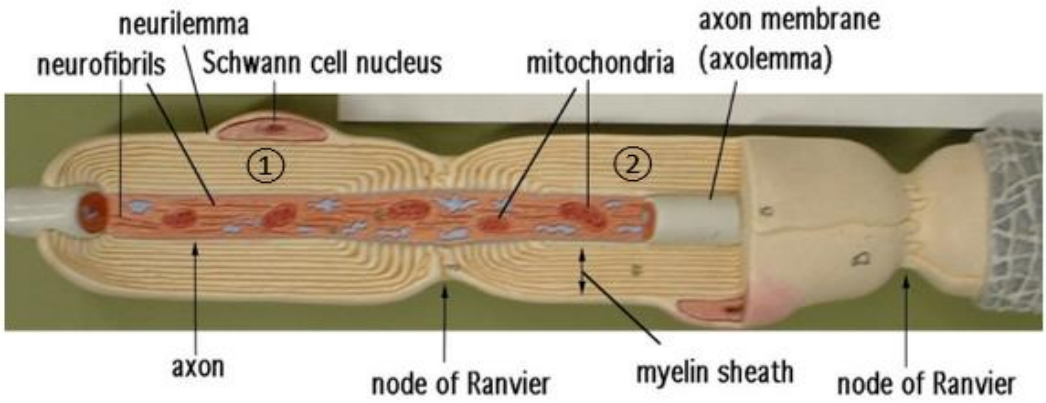
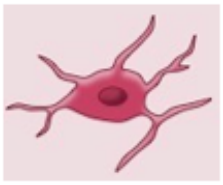


Figure 7.25 Shown above is a model of a myelin sheath covering an axon created by Schwann cells. The ① and ② in the photo denotes the separate Schwann cells that line up along an axon, leaving only the node of Ranvier gap in between them.

The Schwann cell wraps around the axon like a cinnamon roll, creating quite a thick cushion of protection for nerves that can be somewhat exposed in the periphery, and the lipids provide an excellent electrical insulation. The nucleus and cytoplasm of the Schwann cell are on the edge of the myelin sheath. Many neurodegenerative diseases, such as multiple sclerosis, involve damage to the myelin sheaths

Satellite cell. The other of the two types of glial cells found in the peripheral nervous system is the satellite cell. Satellite cells are the glial cells that cover the surface of nerve cell bodies in sensory and autonomic **ganglia**, where they surround and cushion the soma or cell body of neurons. They were formerly called amphicytes. Since they are out in the peripheral ganglion (see **Figure 7.26** below right) and based on their appearance under the microscope, the term satellite cell was established. These cells provide support to the neurons at ganglion, performing similar functions in the periphery as astrocytes do in the central nervous system (CNS). Like all other glial cells they supply nutrients to the surrounding neurons, play an important structural role and add a protective, cushioning these neurons. Their special feature is represented mostly by their location in the peripheral ganglion.



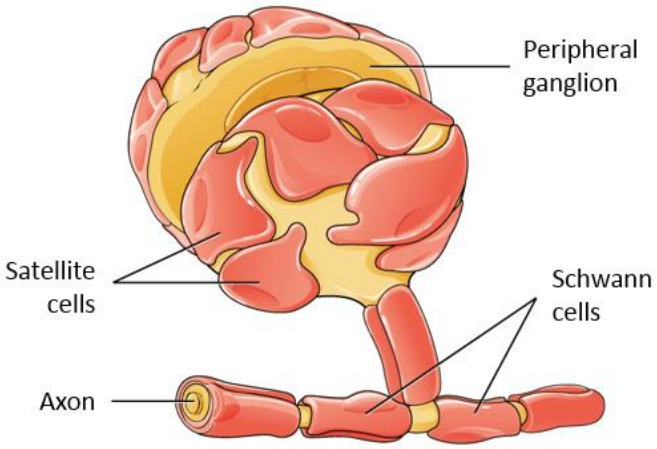
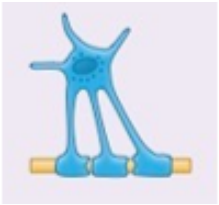


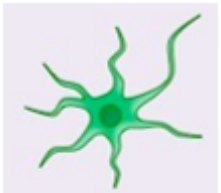
Figure 7.26 Underneath all the satellite cells is the cell body of a sensory neuron in the PNS. Also notice the Schwann cells wrapping around the axon.

Glial Cells of the CNS

Oligodendrocyte. This is the glial cell that insulates, **myelinates axons in the CNS**, so it is the counter part to the Schwann cell in the PNS. The name oligodendrocytes means "cell of a few branches" (oligo "few"; dendro "branch"; cyte "cell"). Oligodendrocytes have processes that reach out to multiple axon segments, such that one of these cells can participate in myelination of many different axons. There are a few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. One oligodendrocyte will provide the myelin for multiple axon segments, either for the same axon or for separate axons. This is in contrast to the Schwann cell, in which the entire surrounds just one axon segment.



Astrocyte. The most common glial cell in the brain are the astrocytes. Astrocytes have many processes extending from their main cell body (not axons or dendrites like neurons, just cell extensions), and appears to be star-shaped under the microscope so named astro- "star" cyte. Astrocytes form the **blood-brain barrier** (BBB). This is a restrictive barrier that prevents many substances that circulate in the rest of the body from getting into the central nervous system to protect the CNS. Molecules such as glucose (the primary energy source for the brain), amino acids, water and gases can pass through the BBB, but other molecules cannot. Like other glial cells, they act to clean up brain debris, facilitate exchange with neurons, digest damaged tissue, remove excess signaling molecules and regulate the extracellular environment. Astrocytes have been shown to become active in response to nearby nerve activity, transmitting Ca^{2+} waves between astrocytes, and modulate the activity of surrounding synapses.



Microglia. These are smaller than most of the other glial cells, as indicated by their name. Microglia are responsible for clearing damage after injury and can be thought of as the **immune system** of the brain. They are like **small macrophages** in that they phagocytose material and errant cells. In fact, it is theorized they are derived from the white blood cell (WBC) monocytes during early development.

Since the BBB restricts cells from entering the CNS, there are no WBCs in the CNS, so the microglia act as the resident defense cells. When microglia encounter damaged cells in the CNS they ingest and digest them or pathogens. Like astrocytes, microglia digest parts of dead neurons.

Ependymal cell. These cells are very much like epithelial cells in that they line surfaces in the CNS. Ependymal cells line the fluid-filled ventricles of the brain and the central canal of the spinal cord. They are involved in the production of **cerebrospinal fluid** (CSF), which serves as a cushion for the brain, moves the fluid between the spinal cord and the brain, and is a component for the choroid plexus. Because of the BBB, the extracellular space in nervous tissue does not easily exchange components with the blood.

The vascular **choroid plexus** is a specialized structure in the ventricles where ependymal cells come in contact with blood vessels and filter and absorb components of the blood to produce CSF. Because of this, ependymal cells can be considered a component of the BBB, or a place where the BBB breaks down. They also have cilia on their apical surface to help move the CSF through the ventricular spaces.

Review Questions for Chapter 7: Neurophysiology

1. A cell releasing a signal molecule that binds to receptors on adjacent cells is called _____, whereas a signal molecule released into the bloodstream to effect distant tissue is a form of _____ control.

a) paracrine, autocrine
b) autocrine, paracrine
c) paracrine, long distance
d) long distance, local
e) endocrine, nervous

2. In terms of just one neuron, the **dendrites** represent which part of the information feedback loop?

a) Receiving the incoming information.
b) The processing and integration of information.
c) Sending the signal out.
d) Releasing the signal molecule.

3. All of these characteristics belong to action potentials, except:

a) refractory periods
b) constant magnitude
c) passive spread
d) no summation
e) non-decremental

4. The **relative refractory period** of a neuron during an action potential

a) is due to the positive polarity of the inside of the neuron
b) is due to opening of Na^+ ion channels
c) occurs only during the repolarization phase
d) occurs only during the depolarization phase
e) occurs only during the hyperpolarization phase

5. If an EPSP from neuron **A** causes a 5mV change and an IPSP from neuron **B** causes a 6mV change, then what would be **true** for the postsynaptic neuron **X** that is receiving input from neurons A and B?

a) summation of B and A would be an action potential
b) stimulation by A would depolarize the cell
c) stimulation by B would repolarize the cell
d) stimulation by B would depolarize cell
e) b and c

6. With regard to axon diameter, the **Aα** axons fibers found in muscle spindles and Golgi tendon organs are _____ than the **Aδ** axons for pressure and touch, and therefore the **Aα** axons are _____.

a) Longer, faster
b) Larger, slower
c) Larger, faster
d) Smaller, slower
e) Smaller, faster

7. The glial cells that produce the myelin sheath in the central nervous system are _____; and the glial cells that create the blood brain barrier in the central nervous system are _____.

a) Schwann cells oligodendrocytes
b) Astrocytes; Schwann cells
c) Microglia; satellite cells
d) Oligodendrocytes; astrocytes
e) Pitocytes; microglia

8. Which statement is **not true** regarding the role of cAMP in post-synaptic neurons?

a) It acts as a neurotransmitter inside the cell.
b) ATP is used as the substrate to make cAMP.
c) Adenylyl cyclase is the enzyme that is activated to make cAMP.
d) The production of cAMP activated protein kinase in the cell.
e) It acts as a second messenger.

9. If a post-synaptic membrane responds to a neurotransmitter by directly opening a Cl^- channel, then

a) This is an example of an ionotropic effect
b) This is an example of an metabotropic effect
c) The influx of Cl^- will cause the cell to hyperpolarize
d) The influx of Cl^- will cause the cell to depolarize
e) a and c

10. How would **hypokalemia** alter neuronal excitability?

a) It would cause the RMP to be elevated, making neurons less excitable.
b) There would be no net change in excitability of neurons.
c) It would cause the RMP to be lowered, making neurons more excitable.
d) The RMP would be depressed, making neurons less excitable.
e) It would cause the RMP to be elevated, making neurons more excitable.

Answers in Appendix B