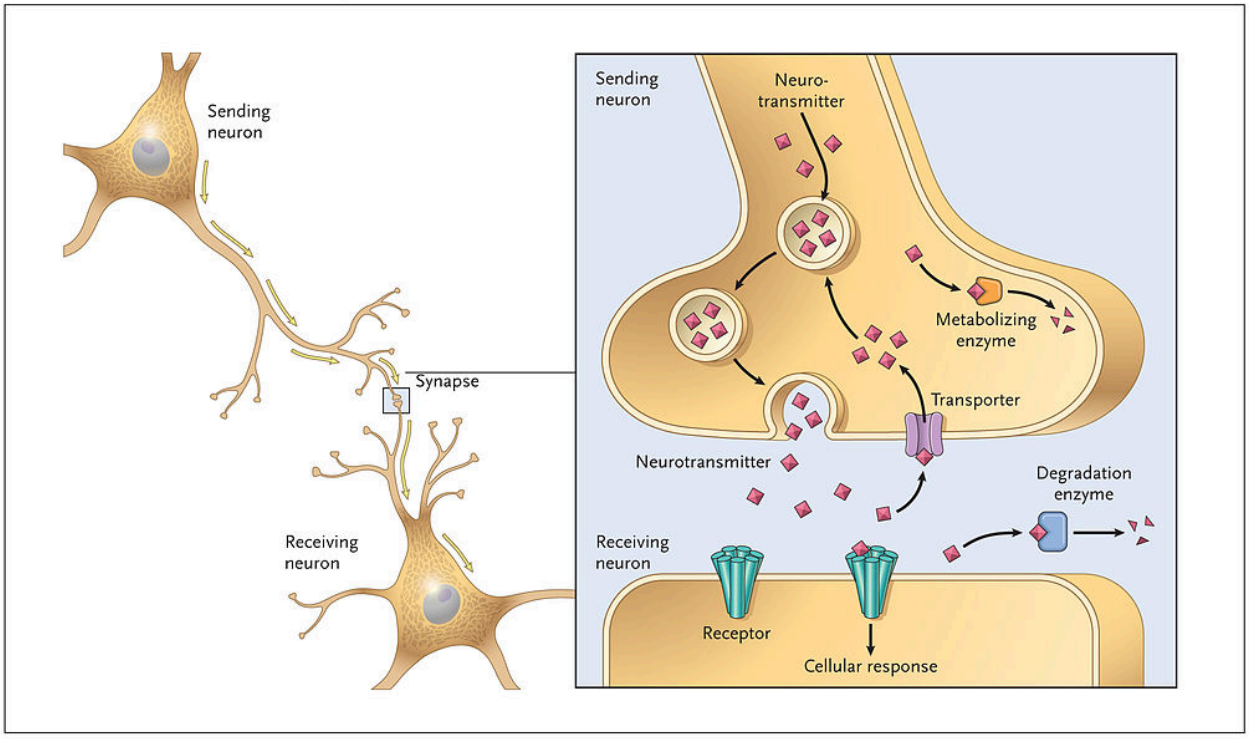
1.4

The Synapse

Up to this point we have discussed how action potentials propagate down axons but not how they move between neurons. The transition from one neuron to another neuron will be the major topic of this section. This transition requires the introduction of three separate parts of the neuron, the **dendrite**, the **soma** and the **axon terminal**. Typically, voltage changes in neurons flow from dendrites, to the soma, and finally the axon. *Dendrites* are short, branched processes that extend from the cell body. Dendrites function to receive information and do so through numerous receptors located in their membranes that bind to chemicals called *neurotransmitters*. The *cell body* is the portion of the cell that surrounds the nucleus and plays a major role in synthesizing proteins. Once an axon reaches a target, it terminates into multiple endings, called *axon terminals*. The axon terminal is designed to convert the electrical signal into a chemical signal in a process called **synaptic transmission**. This transition occurs at a structure called the synapse.

Structurally, two types of synapses are found in neurons: chemical and electrical. **Chemical synapses** occur when neural membranes are very close together but remain distinct, leaving a space. **Electrical synapses** occur when membranes are linked together (gap junctions) via specialized proteins (connexins) that allow the flow of ions quickly from one cell to another. Electrical synapses are found in heart muscle. Because electrical synapses are rare in the nervous system, the remaining discussion will address the chemical synapse.

Generic Neurotransmitter System



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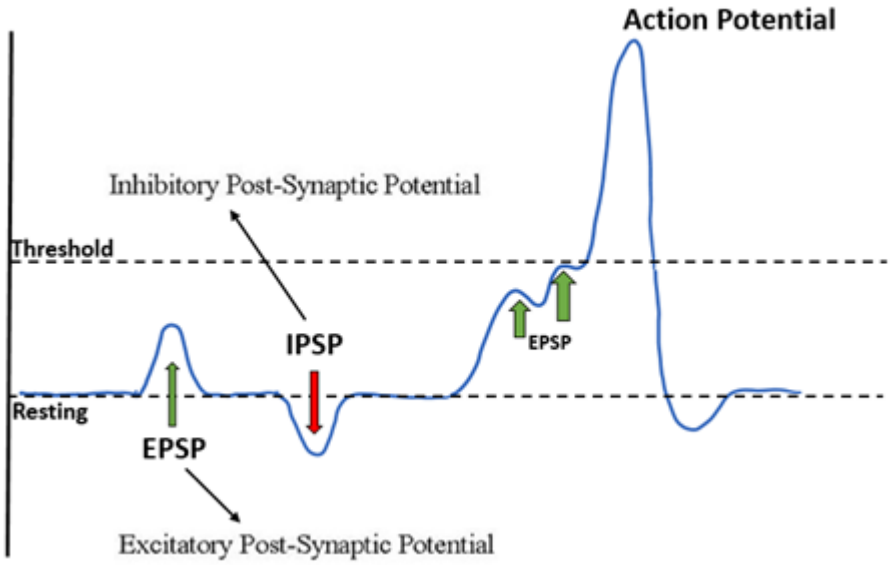
As stated chemical synapses use chemicals called *neurotransmitters* to communicate the messages between cells. The part of the synapse that releases the neurotransmitter into the synapse is called the *presynaptic terminal*, and the part of the synapse that receives the neurotransmitter is called the *postsynaptic terminal*. The narrow space between the two regions is called the *synaptic cleft*. Both the presynaptic and postsynaptic terminals contain the molecular machinery needed to carry out the signaling process.

The presynaptic terminal contains large numbers of vesicles that are packed with neurotransmitter molecules. When an action potential arrives at the presynaptic terminal, due to the actions of voltage-gated Na+ channels, voltage-gated Ca2+ channels open, which allow for the influx of Ca2+ which then activates an array of molecules in the neuronal membrane and the vesicular membranes called SNARE proteins. These newly activated protein molecules then induce exocytosis of the vesicles, which results in the release of the neurotransmitter from the cell and into the synaptic cleft. There are a variety of different chemicals that have been shown or hypothesized to serve as neurotransmitters (ie., gases, purines, lipids, amino acids), specific examples include: norepinephrine, acetylcholine, serotonin, glutamate, gamma-aminobutyric acid (GABA), glycine and numerous small peptides, even ATP.

The neurotransmitter then binds to receptors located in the postsynaptic membrane and induces a conformational change. Depending on the receptor, the conformation change will induce a G-protein coupling cascade (**metabotropic**) or open an ion channel (**ionotropic**). The type of channel will ultimately determine the type of response that the cell experiences in response to the neurotransmitter. For ionotropic receptors, the conformation change will cause the receptor to act as a pore in the membrane for ions to move through. Metabotropic receptor activation will result in a G-protein cascade that activates or inhibits other intracellular proteins. Depending on the type of ion, the effect on the postsynaptic cell may be depolarizing (excitatory) or hyperpolarizing (inhibitory). Depolarizing signals are called **excitatory postsynaptic potentials** (EPSP) while inhibitory signals are called **inhibitory postsynaptic potentials** (IPSP).

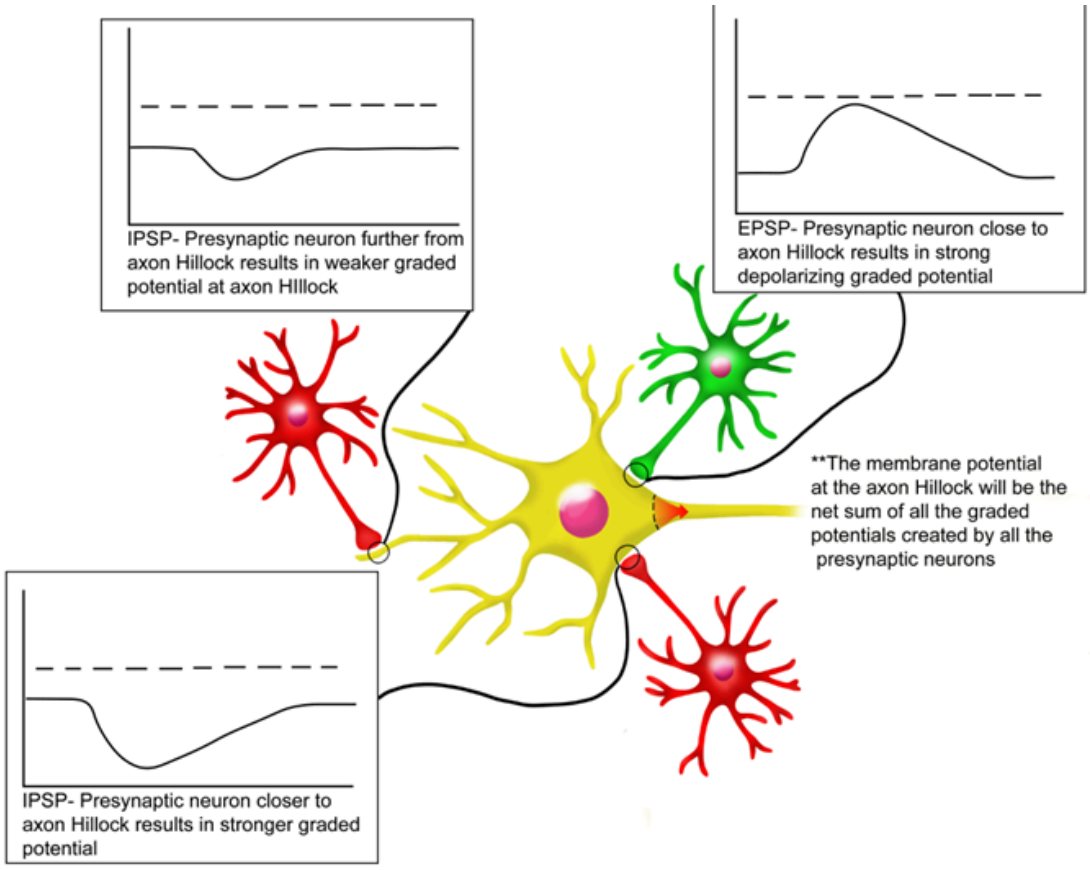
To turn off the signal there are enzymes that reside in the synaptic cleft that breakdown and inactivate the neurotransmitters. The components of the neurotransmitter are then taken back up by the presynaptic terminal to be

recycled to make more of the neurotransmitter. An example of one of the enzymes is acetylcholinesterase that breaks down the neurotransmitter acetylcholine.



An IPSP drives the membrane potential to a more negative value and an EPSP drives the membrane potential to a more positive value possibly hitting threshold to initiate an action potential.

Image by BYU-I student 2017



IPSPs and EPSPs working at a cell soma

Image by BYU-I Becky T 2018

The net effect of all the EPSPs and IPSPs is experienced at a specialized structure called axon hillock. If threshold is reached at the axon hillock, then an action potential will continue down the axon. The ultimate goal of an EPSP is to

cause enough change in the membrane to initiate an action potential. The goal of the IPSP is to cause a change in the membrane to prevent an action potential. Each EPSP or IPSP lasts a few milliseconds, and then, the membrane returns to the original resting membrane potential. Since the dendrite is non-myelinated, is very small in diameter, and has few if any voltage-gated Na+ channels, the R_m is low and the R_i is high, meaning that in many cases, a single EPSP is not sufficient to cause an action potential. Because of this, dendrites vary widely in length and diameter. In addition, dendrites can contain thousands of protrusions called **dendritic spines**. These spines serve to increase the number of possible contacts between neurons. In dendrites that are long and thin the sphere of influence from the Na+ ion experiences too much R_i to have a large effect. Therefore, many EPSPs from multiple synapses combine on a dendrite which results in a much larger voltage change that helps the sphere of influence reach the soma. This phenomenon is called **spatial summation**. EPSPs from the same synapse can also combine if they arrive in rapid succession; this phenomenon is called **temporal summation.** Requiring multiple EPSPs to fire an action potential is a way that neurons increase sensitivity and accuracy.

Although the soma is also unmyelinated and does not contain many voltage-gated Na+ channels, the large diameter of the soma makes R_i very small and the resultant length constant very large (equation 4). Thus, if a depolarizing stimulus arrives at the soma above threshold, it will continue through the soma without diminishing until it arrives at a special junction where the axon joins the soma called the **axon hillock**. The axon hillock has a large concentration of voltage-gated Na+ channels, the activation of which will start the action potential propagating down the axon. Some synapses are made directly on the soma itself, ensuring a suprathreshold depolarization when they are activated. In the brain, a synapse on the soma can result in very strong memories or emotions.

Excitatory Synapses

Most excitatory synapses in the brain use glutamate or aspartate as the neurotransmitter. These neurotransmitters bind to non-selective cationic channels that allow for Na^+ and K^+ to pass. Since the driving force for Na+ to move into the cell exceeds the driving force of K+ to leave the cell, these non-selective cationic channels are depolarizing in nature. As mentioned earlier, it takes many EPSPs from these kinds of synapses to depolarize a postsynaptic neuron enough to reach threshold and trigger an action potential.

A very important subset of synapses in the brain includes a group capable of forming memories by increasing the activity and the strength of the synapse. This process is called **long-term potentiation.** Long-term potentiation operates at the synapse, using the neurotransmitter glutamate and two different classes of receptors, the **AMPA** and **NMDA** receptors. The receptor names are derived from their activation by pharmacological agonists. Most glutamate receptors have two temporal components that can be divided into a fast phase and a slow phase. The fast phase is mediated by the AMPA receptor and the slow phase by the NMDA receptor. Upon activation both receptors are permeable to Na+ and K+, but differ in their permeabilities to Ca2+ . The AMPA receptors are activated rapidly and allow very little Ca2+ into the cell. The NMDA receptor is activated much slower but has an increased permeability to Ca2+ . The Ca2+ ion can increase a plethora of cellular functions, thus controlling the intracellular concentration of Ca2+ is very important. The NMDA receptor is unique in that it is both ligand and voltage regulated. When activated by ligands (glutamate), it becomes permeable to Na^+ and K^+, but if the charge difference is sufficient, the channel becomes permeable to Ca2+ as well. At resting conditions (-70 mV) the channel pore is clogged by the ion Mg++ and this ion only “pops” out when voltage changes rise to -60 mV. NMDA and AMPA receptors are co-localized together in many synapses. It is possible to stimulate AMPA receptors without stimulating NMDA receptors. However, if enough glutamate is released in the synapse the resultant larger depolarization allows the activation of the NMDA receptor. With the addition of intracellular Ca2+ a second messenger cascade results that can increase the number of glutamate receptors, thereby increasing the strength of the synapse. The change in strength can last for weeks, months, or even years depending on whether or not the synapse is continually used.

Inhibitory Synapses

It may seem somewhat of a paradox to have inhibitory synapses, but the excitability of neurons is essentially governed by a balance between excitation and inhibition. The main inhibitory neurotransmitters are GABA and glycine. Both neurotransmitters bind to receptors that result in an increase conductance of Cl^-. Because of the negative charge of Cl^-

and the fact that it usually moves into the cell, the effect is to oppose depolarization and cause the membrane to move away from threshold.

Modulatory Synapses

Modulatory synapses are those that regulate the excitability of other neurons. Axons associated with modulatory synapses are widespread and diverge throughout the regions of the brain. The function of these modulatory networks is not well understood but it has been demonstrated that some synapses can be "primed" by neuromodulators, so they are able to respond more powerfully to other inputs. An example of a priming neuromodulator is norepinephrine. By itself, norepinephrine has little effect on synaptic transmission, but when a cell is exposed to norepinephrine first, it will react more powerfully to glutamate. In addition, neuromodulatory synapses all involve metabotropic receptors.