Psychopharmacology

R.H. Ettinger

Chapter 1: Organization and Function of the Nervous System

Our behaviors, including our thoughts, sensations, emotions, remembering, and even our states of consciousness, are all a result of complex interactions between neurons distributed throughout our brain. These neurons form elaborate systems that communicate their activity by releasing small amounts of transmitter substances which act both on receiving neurons as well as on the neuron sending the message. In order for us to understand just how drugs act to treat certain psychological conditions, we must first understand the intricate and sometimes subtle ways in which neurons function to regulate our behaviors. We must also appreciate the complex systems of neurons within the brain that specialize in different functions including movement, emotions, learning and memory, and our motivational states.

The average human brain weighs approximately 1400 grams (or roughly three pounds) and contains nearly 200 billion neurons. Each of these neurons may in turn communicate with just a few or as many as tens of thousands of other neurons. How the structure and organization of neurons and their surrounding environment allows for such communication will be the topic of the first part of this chapter. We then describe the structures and functions of systems within the brain that allow humans and other organisms to function in, and adapt to, their continuously changing environments. This

background will be necessary for us to understand how psychological disorders may arise and just how drugs might help to alleviate them.

The Structure and Function of Neurons

As mentioned above, the brain contains approximately 200 billion individual nerve cells or neurons. These neurons are the basic units of the brain as well as the rest of the nervous system. Neurons vary in shape, size, and other characteristics according to their location and their specific function.

There are three major classes of neurons; sensory neurons, motor neurons, and interneurons. Sensory or afferent neurons carry ascending messages to the CNS from receptors in the skin, ears, nose, eyes, as well as some organs, muscles, and joints. The brain and sometimes the spinal cord interpret these messages and send appropriate responses through descending motor or efferent neurons, which lead to sensory organs, muscles, glands, and other peripheral tissues to control movement and the functioning of glands, sensory organs, and other tissues. **Interneurons**, reside only within the central nervous system and function to bridge communication between sensory and motor neurons. Without these connecting neurons, sensory messages would never result in the appropriate bodily response. Interneurons also communicate with each other throughout the nervous system. Although neurons vary in size, shape, and function, they share four common structures: the cell body, the dendrites, the axon, and the terminal buttons.

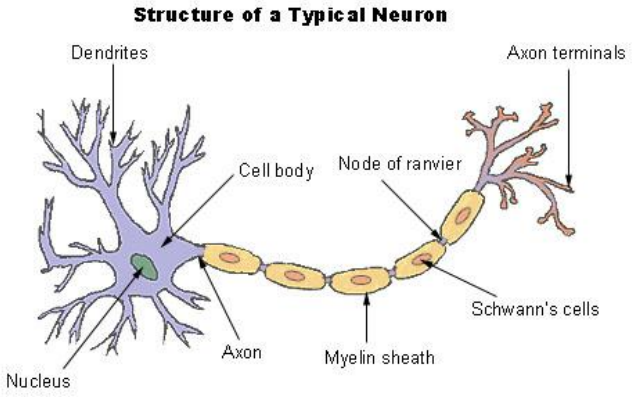

Figure 1*: Neuron Structure*

Cell Body or Soma The cell body or soma is the largest part of the neuron. It contains structures that control the cell's metabolic functions (cell respiration and metabolism), it also contains the nucleus which contains the cell's genetic information encoded in DNA. The membrane of the cell body can have receptors and receive messages from other neurons, although the cell body is not typically the cell's primary receiving target.

Dendrite Neurons typically receive messages from other cells at a collection of extensions from the cell body called dendrites, which branch out from the cell body like roots of a tree. (The word *dendrite* comes from the Greek word for tree.) Dendrites may receive information from a few to thousands of surrounding neurons. The more extensive the neuron's network of dendrites, the more connections can be made with other neurons. Interneurons in the brain typically contain far more dendritic branches than neurons in the spinal cord or the peripheral nervous system. Signals received by dendrites are passed on

to the membrane of the cell body where excitatory and inhibitory signals are integrated and a *decision* is made whether to transmit the signal along its axon.

Axon The axon is typically an extended branch of the cell that functions to transmit the electrical signal from the surface of the cell body towards receiving cells. The point on the cell body where both the axon and the electrical signal originate is called the **axon hillock**. The electrical signal is transmitted along the entire length of the axon, which may range from several feet in length in spinal cord and PNS neurons to fractions of millimeters in neurons within the brain. The axon may divide into two or more major branches called collaterals, thereby increasing its capacity to communicate with other neurons. Axons may be myelinated or unmyelinated. Myelin is a type of glial cell that wraps around the axon providing it with insulation. Most peripheral axons are myelinated, and most (but not all) of the axons in the brain are unmyelinated. Myelin serves both to insulate the axon, much like insulation on a wire, and to increase the speed of conduction along the axon. It is myelin that gives brain tissue, which is normally grayish brown, a white color (white vs. gray matter).

Terminal Button The transmitting end of the axon consists of small bulblike structures known as terminal buttons**.** The terminal buttons store and release neurotransmitters which either excite or inhibit adjacent neurons. Terminal buttons are also where neurotransmitter substances are taken back into the cell after their release. The structure that allows for neurotransmitter reuptake is a protein called a reuptake transporter. These transporter proteins will be given considerable attention throughout this text as they are

the site where many psychotropic drugs are designed to work.

Once the recycled neurotransmitters, or their precursor chemicals, have been taken back into the terminal button it is further transported back into synaptic vesicles where it is stored for subsequent release. The amount of neurotransmitter available in synaptic vesicles for release depends on the availability of its metabolic precursors and on the frequency of cell firing.

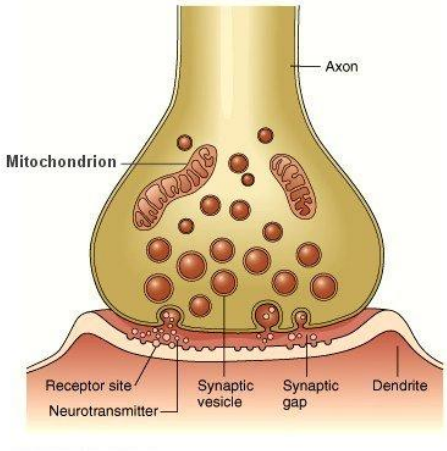

Figure 2*: Terminal Button of Axon*

Neural Transmission

In order for a message to travel from neuron to neuron, it must move from the terminal button at the end of one neuron's axon to the dendrites or cell body of an adjacent neuron. The process by which impulses are transmitted in the CNS is called neural transmission and it involves both electrical and chemical processes.

Within the peripheral nervous system, messages are transmitted along the extended axonal fibers of both motor and sensory neurons that are contained within bundles of neural fibers called nerves. The multitudes of neural circuits or pathways within the central nervous system are made up of perhaps hundreds of thousands of individual neurons. These fibers extend as continuous structures from sensory receptors or muscles to the CNS. For example, a sensory message from a pain receptor in the skin of your finger is transmitted along a single axonal fiber that extends the length of your arm to a point at which it enters the spinal cord and transfers its message to an interneuron.

Neuron Electrical Activity

All cells, including neurons, are enclosed in a lipid membrane composed of two layers of lipid molecules called a lipid bilayer. This membrane acts as a kind of skin that permits the cell to maintain an internal environment different from the fluid outside of the membrane. The membrane communicates with its external environment through specialized integrated proteins that are distributed throughout the lipid structure. These proteins function to carry glucose to internal cell structures and to carry metabolic waste back out. They also serve to carry chemical ions back and forth across the membrane. These ions carry either a positive or a negative electrical charge and therefore change the membrane's electrical potential. Ions that are particularly important in neural transmission are negatively charged organic ions (An^-), chlorine ions (Cl^-), positively charged sodium ions (Na^+), and potassium ions (K^+). If the cell membrane did not act as a barrier, these ions would be equally distributed both inside and outside of the neuron.

However, the negative organic ions do not pass through the cell membrane to the surrounding fluid and the membrane is only semi permeable to other ions. For instance, sodium and chlorine ions pass through only when gates are open for them. These gates called **ion channels** are actually proteins embedded in the cell's membrane and they become activated by changes in the membrane potential or by the presence of specific chemicals on their surface.

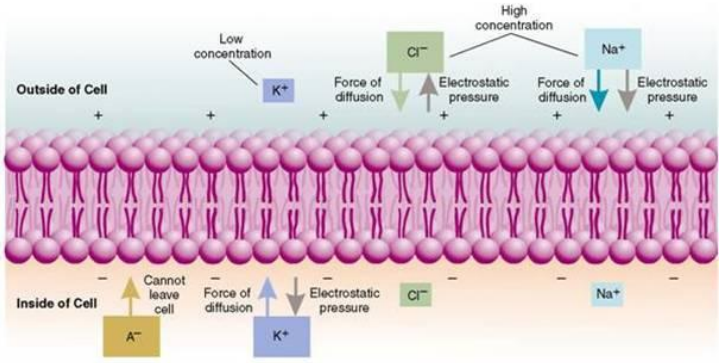

Figure 3: *Electrostatic and diffusion pressures act on charged ions. At rest the membrane is impermeable to Na+ so it is not at equilibrium. The concentration of Na+ is greater on the outside and it is attracted towards the negative inside charge. Although K^+ is relatively free to pass through the membrane the positive electrical charge outside keeps it from escaping. K^+ ions are at equilibrium as these forces are balanced at rest.*

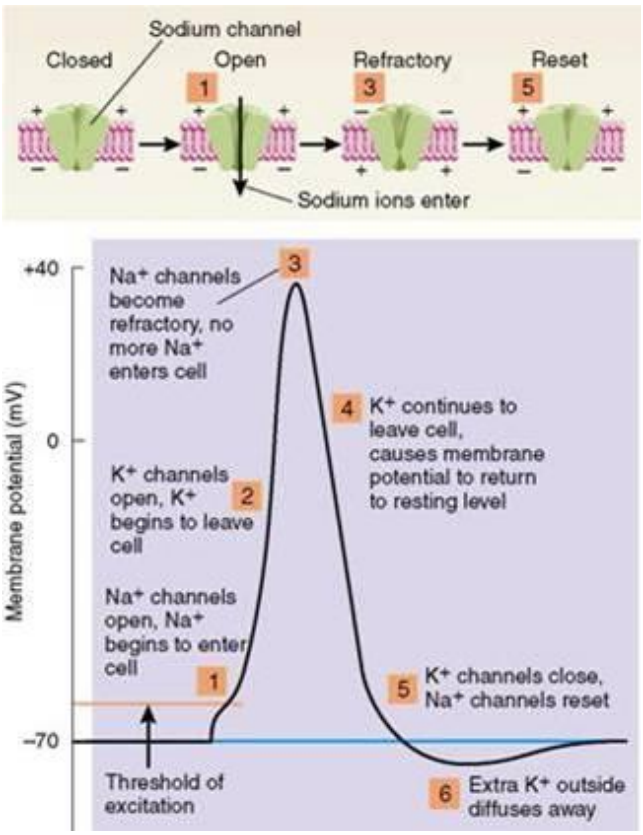

Figure 4*: The Action Potential. Once the membrane reaches its threshold voltage of about -55mV, Na^+ channels open and begin to depolarize the membrane further. Because K^+ is no longer at equilibrium, after Na^+ influx, it begins to leave the cell. Na^+ channels close and the membrane returns to its resting potential. Na^+- K^+ transporters reinstate the resting concentrations of these charged ions.*

Resting Potentials

There are essentially two forces acting on these charged ions. The first force is diffusion which is the pressure on ions to distribute themselves equally in a medium. That is, to move from high to lower concentrations. Perfume diffuses from an open bottle throughout a room. The second force is electrostatic. Ions of similar charge repel each other as do similarly charged sides of a magnet. This electrostatic force acts to move ions towards the opposite charge and away from a similar charge. When these two forces are at equilibrium the neuron is said to be in its resting state. The distribution of negatively

and positively charged ions on either side of the membrane determines the cell's electrical potential during this resting state. This **resting potential** is therefore mostly determined by the concentrations of charged ions in the fluids on both sides of the cell membrane. The ion transport proteins that are embedded in the cell membrane can also contribute to the resting potential to some extent because they also carry an electric charge.

The negative and positive charges are unequal on either side of the membrane when the two forces are at equilibrium, so its interior has a negative electrical potential with respect to its exterior. This phenomenon is due primarily to the negatively charged organic ions on the inside and a high concentration of positively charged sodium ions outside the membrane. Most neurons at rest (that is, when their membrane potential is not changing) have a net negative charge of about –70 millivolts (70/1,000 of a volt) relative to their outside environment. The membrane is said to be in a polarized state when the neuron is at rest.

This differential charge gives the resting neuron a state of potential energy known as the resting potential. In other words, it is in a state of readiness to be activated by an impulse from an adjacent neuron. Maintaining this resting potential allows the neuron to store the energy that it utilizes when it transmits an impulse. The resting potential is maintained because the membrane is relatively impermeable to the positively charged sodium (Na^+) ions concentrated on the outside of the neuron and to the negatively charged organic ions on the inside. Potassium ions can move relatively freely until the two forces operating on it are at equilibrium. That is, the diffusion force trying to expel it from the neuron is counteracted by the higher positive charge outside. Chlorine is also

essentially at equilibrium and cannot enter the more negatively charged inside of the cell.

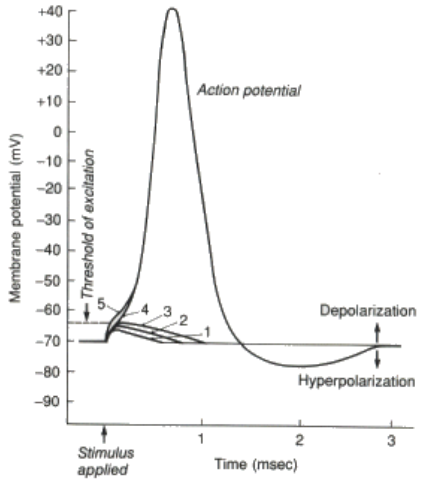

Figure 5: *Graded potentials (1-2) are not sufficient to open Na+ channels and initiate an action potential. At position 3 the graded potential reaches threshold.*

Graded Potentials The resting potential is disturbed when an impulse is received from another neuron. This disturbance is referred to as a **graded potential**, and its strength varies with the intensity and frequency of stimulation. If we were to measure the charge on the axon during a graded potential we would observe a change from –70 millivolts to perhaps –60 millivolts, depending on the amount of excitatory stimulation the cell receives. A graded potential by itself is of little consequence. However, when several graded potentials occur simultaneously or in rapid succession, together they may be sufficient enough to depolarize the neuron to a threshold value (the minimum voltage change sufficient to allow Na^+ ions to enter the cell) of about –55 millivolts.

The determination of whether or not a graded potential is sufficient to bring the axon

to its threshold level is made at the axon hillock, a specialized region of the cell body near the base of the axon. The axon hillock integrates all of the graded potentials that reach it. If the sum of these graded potentials reaches a sufficient magnitude or threshold, a sudden depolarization begins at the axon hillock. This depolarization is referred to as an action potential.

Action Potentials An **action potential** is initiated when the axon is depolarized to its threshold level (approximately –55 millivolts). When the membrane reaches this threshold level, a sudden complete depolarization results—that is, the axon goes from about –55 millivolts to approximately + 30 millivolts. This rapid depolarization is the result of the membrane changing its permeability to sodium (Na^+) ions. When the membrane is no longer impermeable to Na^+, it enters the cell, bringing the charge on the inside of the membrane to a positive value (about +30 millivolts). Some potassium ions begin to leave the axon at this time because the electrostatic gradient inside the axon becomes weakened as sodium ions enter. However, the number of potassium ions that leave the inside of the axon is far outweighed by the number of sodium ions that enter.

The change in permeability to Na^+ is extremely brief, and the resting potential is quickly restored by the closing of the Na^+ gates and the rapid expulsion of K^+ from within the axon. Potassium ions are repelled because of the positive charge now inside the membrane. As potassium ions leave, the charge across the membrane returns to its resting state. In fact, an excess of potassium outflow briefly hyperpolarizes the membrane. This complete process for an action potential takes about 1 millisecond (1/1,000 of a second). Some drugs disrupt this process and prevent the propagation of

action potentials by blocking Na^+ channels. Local anesthetics such as lidocaine block pain messages this way.

Once an action potential occurs at the axon hillock it causes sufficient depolarization further down the axon to reach threshold and initiate another. This process is rapidly repeated as the action potential flows (or propagates) along the entire surface of the axon to the terminal button. Once the action potential reaches the terminal button it initiates processes that lead to the release of neurotransmitter substances which carry the message to adjacent neurons. We will discuss this process in some detail later on.

Unlike the graded potential, the strength of an action potential does not vary according to the degree of stimulation. Once an action potential is triggered it is transmitted the entire length of the axon with no loss of intensity. Partial action potentials or nerve impulses do not occur; thus, an axon is said to conduct without decrement. Because of this, the action potential is said to follow the all-or-none law: If the sum of the graded potentials reaches a threshold, there will be an action potential; if the threshold is not reached, however, no action potential will occur.

According to the all-or-none law, a neuron fires at only one level of intensity. The fact that, even though a single neuron's impulse level is always the same, two important variables may still change: the number of neurons affected by stimulation and the frequency with which neurons fire. Very weak stimuli may trigger graded potentials in only a few neurons, whereas very strong stimuli may cause thousands of neurons to fire. The frequency in which neurons fire can also vary greatly, from fewer than 100 times per second for weak stimuli to as often as 1,000 times per second for strong stimuli. Thus, the combination of how many neurons fire and how often they fire allows us to distinguish

different intensities of stimuli.

The speed with which an impulse travels through a neuron varies with the properties of the axon, ranging from less than one meter per second to as fast as 100 meters per second (roughly 224 miles per hour). At least two important factors affect speed. One is the resistance to current along the axon—there is an inverse relationship between resistance and conduction speed, so that speed is reduced as resistance increases. Resistance is most effectively decreased by an increase in axon size, which helps explain why large axons such as those in PNS neurons tend to conduct impulses at a faster rate than do small axons.

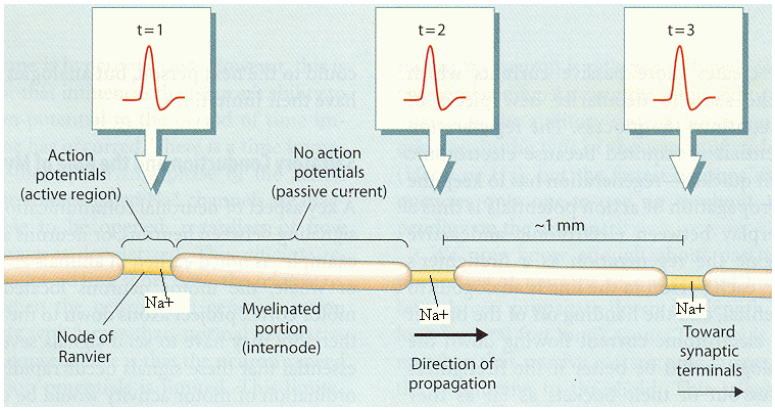

***Figure 6**: Myelinated Axon. The passive current beneath the myelin remains above threshold so sodium channels at times t=1-3 open almost simultaneously and depolarize the membrane quickly. A myelinated axon can transmit signals about 200 times faster than an unmyelinated neuron.*

However, if the nervous system had to depend only on axon size to transmit impulses quickly, there would not be enough room in our bodies for all the large axons we would need. Fortunately, a second property also helps to increase the speed of

transmission of nerve impulses. Specialized cells, called glial cells**,** wrap around some axons, forming an insulating cover called a myelin sheath. (One type of glia cell, the oligodendrocyte, forms the myelin within the CNS. In the PNS the insulating sheaths are built from another type of glia cell known as the Schwann cell.) Between each glia cell the axon membrane is exposed by a small gap called a **node of Ranvier.** It is at these small gaps in the myelin where Na^+ influx occurs. So, an action potential at one node of Ranvier can sufficiently depolarize the neuron further down the axon than can an unmyelinated axon.

In these myelinated neurons, nerve impulses do not propagate smoothly down the axon. Instead, they jump from node to node, in a process called *saltatory conduction* (from the Latin *saltare,* meaning to leap). Saltatory conduction is so efficient that a small myelinated axon can conduct a nerve impulse just as quickly as an unmyelinated axon 30 times larger. Because myelin plays such a critical role in the nervous system, it follows that the effects of certain diseases (such as multiple sclerosis [MS]) that involve progressive breakdown in these insulating sheaths can be devastating. In MS, the loss of myelination may short-circuit or delay the transmission of signals from the brain to the muscles of the arms and legs. As a consequence, a person with MS experiences a weakness or loss of control over the limbs. As the disease progresses more and more neurons become disrupted by demyelination.

Glial cells appear to play numerous other significant roles in the development and function of the nervous system. For instance, astrocytes (named after their star-like structure) form long processes that guide developing neurons to their final destinations. Once these neurons develop and form connections these glial processes disappear. Other

astrocytes are involved in the formation of synaptic connections between neurons. They essentially form the "glue" that holds synapses together. These astrocytes do not merely assist in the formation and structure of synapses, however, they may also be involved in other essential neuronal functions such as the synthesis of neurotransmitter substances and neurotransmitter removal after it has been released. Astrocytes are also involved in subtitle neuronal communication in what are termed **tripartite synapses** that may function to regulate neuronal activity. They are mentioned here because drugs of the future may actually target glial functioning and some forms of depression appear to be associated with glial cell loss (Allen et al., 2009).

The transmission of an electrical impulse from one neuron to another (or to other types of cells) involves a series of events beginning with the arrival of the action potential at the terminal button. Neurons communicate primarily through the release of neurotransmitters. Far less common is the electrical synapse, in which an electrical potential is conducted from one neuron to the next because of a tight junction between them. These rare electrical synapses will not be discussed here. Because there are several steps in synaptic transmission, and pharmacologists can take advantage of each of them in designing drugs, we will discuss these processes in some detail.

Synaptic Transmission

Neurotransmitter Release When the axon fires, the action potential travels along the axon to the terminal button. When it arrives at the terminal button, the membrane there changes its permeability to another ion, calcium (Ca^{++}). Calcium then enters the terminal button and allows the synaptic vesicles to migrate to the presynaptic membrane, where

they fuse with the membrane and release their contents into the synapse. The total amount of neurotransmitter released depends on how much Ca^{++} enters the terminal button. More intense stimulation produces a greater frequency of action potentials, which in turn allows more Ca^{++} to enter, thus increasing the amount of neurotransmitter released. The Ca^{++} channel proteins control how much calcium enters the terminal button, but these proteins themselves can be regulated by other proteins that can be activated by both endogenous substances as well as by specific drugs which target them. For example, THC in marijuana attaches to a specific cannabinoid receptor (CB2) which controls Ca^{++} channel protein activity.

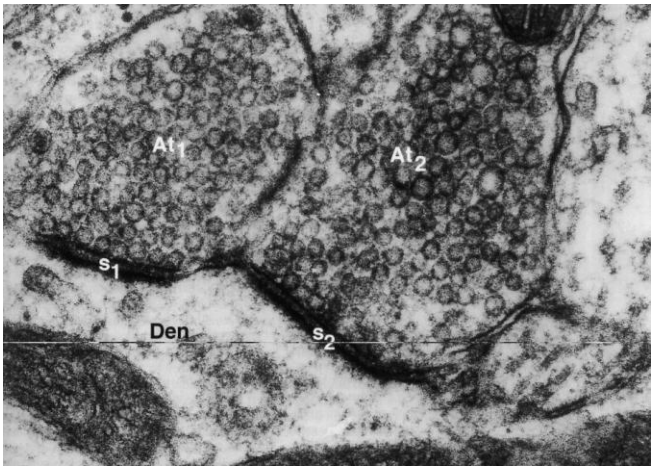

Figure 7*: Electron micrograph of active synapse. At1 and At2 refer to axon terminals with synaptic vesicles, S1 and S2 are active synapses on a cell dendrite (Den).*

Receptors Once neurotransmitter is released into the synaptic gap it diffuses towards the postsynaptic membrane of a receiving cell. The postsynaptic membrane contains sites on specific proteins or chains of amino acids called receptors. These receptors are composed of highly specific molecular structures on the end of an amino acid string exposed in the

synaptic gap. The specific molecular configuration of the receptor determines which substances can bind temporarily with it. When a neurotransmitter binds with the receptor complex the postsynaptic membrane's permeability to ions changes briefly allowing them to flow either in or out depending on the synapse. Drugs may also be designed to bind with receptors and their effects can either be to mimic the neurotransmitter or they may be to block or prevent the neurotransmitter from binding. These drug effects will be discussed throughout the remaining chapters of this text.

Not only do synapses vary in which ions flow either in or out of the cell, they also vary in how their receptors are configured and how they ultimately control an ion channel. When a receptor directly controls an ion channel, often because it is part of the same protein, it is called an **ionotropic receptor**. When the receptor is not part of the ion channel and other proteins are involved in controlling an ion channel it is classified as a **metabotropic receptor**.

Ionotropic Receptors Ionotrpoic receptors contain both a binding site for their specific neurotransmitter and they control an ion channel that opens when the neurotransmitter is bound to it. Upon binding with the neurotransmitter the receptor protein undergoes a change in configuration opening the ion channel. The passage of ions either in or out of the cell membrane results in a graded membrane potential. Ionotropic receptors operate quickly to depolarize the postsynaptic membrane. The ion channels controlled by them remain open for only a few milliseconds as the neurotransmitter is quickly released from the binding site and degraded by a breakdown enzyme.

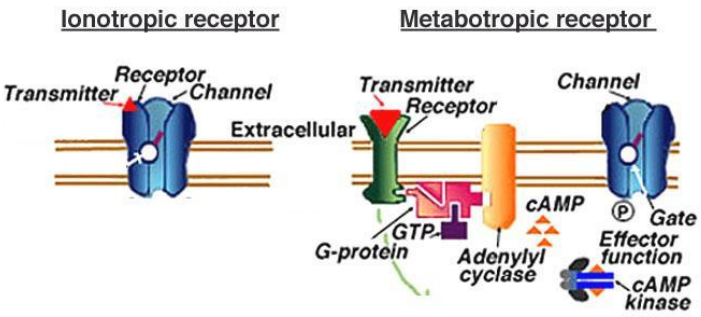

Figure 8: *Comparison of ionotropic and metabotropic receptors. Ionotropic receptors control an ion channel allowing the rapid influx of either Na^+ (excitatory or Cl^- (inhibitory) or the outflow of K^+ (also inhibitory). Metabotropic receptors activate G-proteins. When the receptor is activated by neurotransmitter the G protein undergoes a change in conformation and a subunit of the protein dissociates. The dissociated units then activate an enzyme that facilitates the formation of cyclic AMP from ATP. Cyclic AMP acts as a second messenger by activating a third protein which controls an ion channel. Metabotropic receptors can be either excitatory or inhibitory depending on the ion channel they control.*

Metabotropic Receptors Unlike ionotropic receptors that are relatively simple and quite fast, metabotropic receptors do not directly control ion channels. Rather, when neurotransmitter is bound to the receptor site a series of events requiring cellular energy are initiated—thus the term metabotropic. Metabotropic receptors are located in close proximity to another membrane protein called a G protein, short for guanine nucleotide binding protein. When the receptor is activated by neurotransmitter the G protein undergoes a change in conformation and a subunit of the protein dissociates or breaks away. The detached subunit of the G protein is called an ά subunit. The ά subunit then activates an enzyme that facilitates the formation of cyclic AMP (cAMP) from ATP. Cyclic AMP acts as a **second messenger** by activating a third protein which controls an ion channel. Metabotropic receptors can both open and close ion channels for all three of

the polarizing ions (Cl^-, K^+, and Na^+). Because these receptors require several steps involving enzyme action, the formation of a second messenger, and the activation of an ion channel protein these receptors are relatively slow when compared to ionotropic receptors. In addition, the ion channels controlled by metabotropic receptors remain in their open or closed state for much longer. In fact, they may remain in their altered state for as long as several minutes. Finally, metabolic receptors may be located on the neuron releasing the neurotransmitter and thereby control the amount of neurotransmitter released. We have more to say about these receptors later on. Many of the drugs discussed in later chapters alter the functioning of metabolic receptors. Because there are numerous steps and these receptors control the functioning of several cell processes they provide pharmacologists more options for altering receptor functioning with drugs.

Neurotransmitter Reuptake

Some neurotransmitters are broken down by enzyme action once they have accomplished their function. The enzymes that function to breakdown neurotransmitter substances are manufactured and released by the same neuron releasing the neurotransmitter. One such enzyme, acetylcholinesterase, breaks down the neurotransmitter acetylcholine into acetate and choline molecules. These breakdown products then reenter the terminal buttons to be recycled for further use. In some cases the neurotransmitter substance is retrieved into the terminal button intact without enzyme degradation. The reuptake processes is controlled by specialized membrane proteins called transporters. The density and availability of these transporter proteins determines how quickly neurotransmitter is cleared from the synapse.

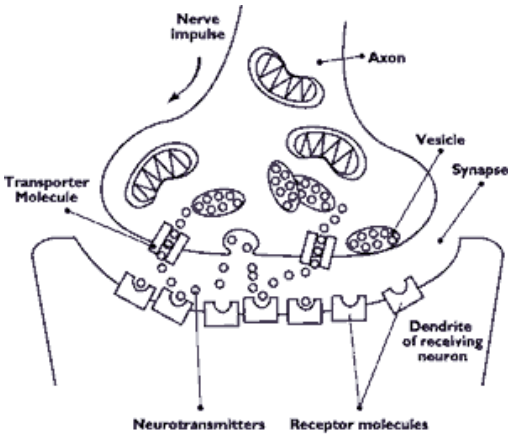

Figure 9*: Reuptake Transporter. Reuptake transporters transport neurotransmitter in the synaptic cleft back into the terminal button. Once in the terminal button it is transported again into the synaptic vesicles by vesicular transport.*

These breakdown and reuptake processes, which are essential for normal neuronal functioning, can be influenced by a number of drugs. For example, drugs such as amphetamine and cocaine inhibit the reuptake of several neurotransmitters, resulting in heightened alertness and activity. Other drugs may block the breakdown process resulting in prolonged neurotransmitter action. Some of the antidepressants we discuss later on work in this manner.

Excitatory and Inhibitory Synapses The postsynaptic membrane of the receiving neuron contains specialized receptor sites that respond to a variety of neurotransmitters. Neurotransmitters act on these receptor sites to produce a change in the permeability of the postsynaptic membrane. Depending on the receptor site and the type of neurotransmitter, this change in permeability can either excite or inhibit action potentials in the receiving neuron.

As stated earlier, neurotransmitters exert their effects by opening ion channels in the postsynaptic membrane, letting either positively or negatively charged ions pass through. If positively charged sodium ions enter, the membrane is excited or depolarized. Neurotransmitters that cause these changes are called excitatory neurotransmitters, and their effects are referred to as **excitatory postsynaptic potentials**, or **EPSPs**. Conversely, if positively charged potassium ions pass to the outside of the postsynaptic membrane, or negatively charged chloride ions enter, the membrane inhibited and the graded potential results in making the membrane more negative--a process called hyperpolarization. Neurotransmitters that act in this way are called inhibitory neurotransmitters, and their effects are called **inhibitory postsynaptic potentials**, or **IPSPs**.

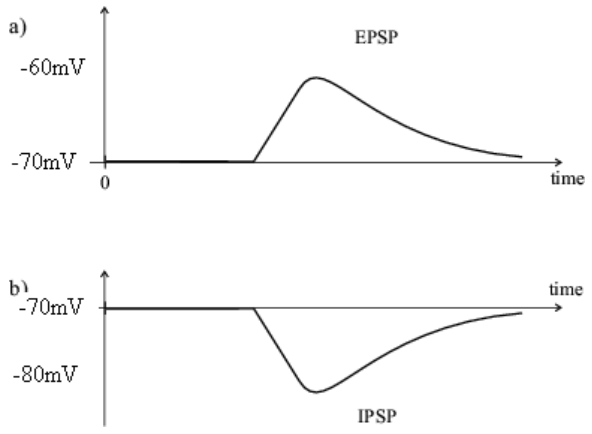

Figure 10: *Comparison of EPSPs and IPSPs. An EPSP depolarizes the membrane while an IPSP hyperpolarizes it moving it further from its threshold.*

Since hundreds or even thousands of axon terminals may form synapses with any one neuron, EPSPs and IPSPs may be present at the same time. The combination of all these excitatory and inhibitory signals determines whether or not the receiving neuron will fire. For an action potential to occur EPSPs must not only predominate, they must do so to the

extent of reaching the neuron's threshold. To prevent this from happening, there needs to be a sufficient number of IPSPs present to prevent the summation of EPSPs and IPSPs from reaching the threshold of depolarization.

Some neurotransmitters seem to be exclusively excitatory or inhibitory; others seem capable of producing either effect depending on which ion channel it opens in a specific pathway or neural structure. When transmitters have both excitatory and inhibitory capabilities, the postsynaptic receptor protein determines what the effect will be. Thus, these neurotransmitters may have an inhibitory effect at one synapse and an excitatory effect at another.

Neurotransmitters interact with receptors on the postsynaptic cell membrane to change its electrical potential. If the change is sufficient to depolarize the cell membrane, a graded potential is initiated, thus beginning the cycle outlined earlier.

Autoreceptors As mentioned briefly above, some receptors for neurotransmitters are located on the sending cell itself. These receptors are called autoreceptors and they function to regulate the activity of the sending neuron. Autoreceptors can either excite or inhibit the neuron’s activity and thus the amount of neurotransmitter it produces and releases, but it does not do this by controlling ion channels. Instead, autoreceptors regulate internal process of the cell through the activity of second messenger systems. Most often autoreceptors are proteins of a distinct subset of metabotropic receptors for a specific neurotransmitter. That is, for each known neurotransmitter there are several subtypes of receptor proteins that it binds with. These receptor subtypes have unique functions, such as the autoreceptor, and are located on different regions of the cell or

even different neural pathways or structures. Interestingly, drugs designed to alter the function of a particular neurotransmitter system may actually only be targeting a specific subtype of receptor. This approach can often result in drugs that alter behavior appropriately without producing undesirable side effects.

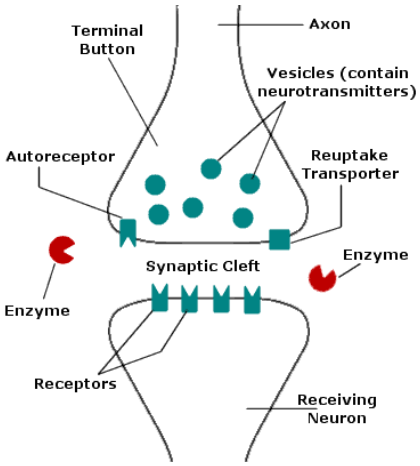

Figure 11: *Neurotransmitter binds to an autoreceptor which regulates the amount of neurotransmitter synthesized and released.*

Heteroreceptors Heteroreceptors function nearly the same as autoreceptors with the exception that these receptors receive neurotransmitter released by another neuron. These receptors may either excite or inhibit internal processes that control the synthesis and release of a neurotransmitter. As with autoreceptors, heteroreceptors are metabotropic and it is the activity of a second messenger, not the control of ion channels that determine its effects.

Presynaptic Effects So far our discussion has focused on synapses between terminal buttons and receptor sites located on either dendrites or cell bodies of receiving neurons. Synapses between axon terminal buttons and the axons of receiving neurons (axoaxonal synapses) are also common. These synapses differ in one significant way, however. Recall from our discussion of neural transmission above that a receiving cell integrates the excitatory and inhibitory influences it is receiving at any given moment. If the neuron is receiving sufficient excitatory input to reach threshold an action potential will occur. With axoaxonic synapses there is no contribution to neural integration but an effect that contributes to the amount of neurotransmitter released. If the axoaxonal synapse is facilitatory it is called **presynaptic facilitation** and when it is inhibitory it is called presynaptic inhibition. Some analgesics reduce pain by presynaptic inhibition of pain signaling neurotransmitters. The pain signaling neuron is still producing action potentials, but the amount of neurotransmitter released is significantly reduced.

NEUROTRANSMITTER SUBSTANCES Since the discovery of the first neurotransmitter by Otto Loewi in the 1920s, about 50 additional substances have been identified as neurotransmitters. A large number of other neuroactive substances called **neuromodulators** have also been described that modulate the effects of neurotransmitters, but do themselves meet all of the identifying criteria. For a substance to be considered a neurotransmitter it must: (a) be synthesized and stored in the presynaptic neuron, (b) be released into the synapse when the neuron fires, (c) cause a post-synaptic effect after it interacts with a receptor, and (d) there must be some

mechanism for degradation or reuptake. Table 1 presents a list of several important substances known to be neurotransmitters, as well as the functions they are thought to perform.

TABLE 1

Chemicals Known to Be Major Neurotransmitters or Neuromodulators

Neurotransmitter-Neuromodulator Effects	**Location**	**Functions**
Acetylcholine (ACh) Excitatory	Cortex, spinal cord, target organs activated by the parasympathetic nervous system	Excitation in brain. Either excitation or inhibition in target organs of PNS. Involved in learning, movement, and memory.
Norepinephrine (NE) Excitatory, Inhibitory	Spinal cord, limbic system, cortex, target organs of the sympathetic nervous system	Arousal of reticular system. Involved in eating, emotional behavior, learning, and memory.
Dopamine (DA) Inhibitory	Limbic system, basal ganglia, cerebellum	Involved in movement, emotional behavior, attention, learning, memory, and reward.
Serotonin (SE) Inhibitory	Brain stem, most of brain	Involved in emotional behavior, arousal, and sleep.
Gama-amino-butyric acid (GABA) Inhibitory	Most of brain and spinal cord	Involved in regulating arousal and anxiety. It is the major inhibitory neurotransmitter in brain.
Endorphins	Spinal cord, most of brain	Functions as a natural

Inhibitory		analgesic for pain reduction. It is also involved in emotional behavior, eating, and learning.
Glutamate Excitatory	Brain and spinal cord	Major excitatory neuro-transmitter in brain. Most neurons in the brain receive excitatory input from glutamate
Glycine Inhibitory	Brain and spinal cord	Co located on Glutamate receptors, widespread inhibitory effects throughout the brain.
Substance P Excitatory	Spinal cord	Released by pain transmitting neurons in the dorsal horn of the spinal cord.
Anandamide Inhibitory	Brain, spinal cord, and peripheral nervous system.	Neuromodulator that acts on heteroreceptors to regulate neurotransmitter release.
Adenosine Inhibitory	Brain and peripheral nervous system	Neuromodulator released by neurons and glia. Plays significant roles in sleep and wakefulness, controls vasodilatation.

NEUROTRANSMITTER SUBSTANCES

Although the list of substances so far identified as neurotransmitters is quite large, we will discuss a few that are well understood and play important roles in the psychological disorders that will be discussed in later chapters.

Acetylcholine (ACh) Acetylcholine was the first neurotransmitter discovered. Its discovery by Otto Loewi in 1921 was a bit serendipitous and through its many retellings may only slightly resemble the real occasion. However, prior to Loewi's discovery it was not known whether neuron signaling was electrical or chemical. There was considerable speculation about possible chemical agents that might be neurotransmitters, but no one had yet discovered them. Loewi apparently awoke from a dream about an experiment that would demonstrate chemical signaling. He quickly scribbled it down and went back to sleep. The next morning he found, to his dismay, that he could not read his scribbles, although he could recall that he had dreamt something important. The next night the dream returned and Loewi rushed to his laboratory to complete it. His experiment involved removing the hearts from two frogs. One heart was dissected with the vagus nerve, which controls heart rate, intact. The other was removed without the vagus nerve. Next he placed the hearts in separate dishes filled with saline solution and he then stimulated the vagus nerve of his first frog. After demonstrating a reduction in heart rate he removed some of the saline solution and applied it to the heart of his second frog. Heart rate decreased in this frog as well demonstrating that a chemical released from the vagus nerve controlled heart rate. Loewi was the co recipient of the Nobel Prize in

Physiology or Medicine in 1936 for this work.

In addition to controlling heart rate, acetylcholine plays an important role in motor movement, as it is the neurotransmitter released from motor neurons onto muscle fibers to make them contract. Several toxins such as botulism, nerve gas, and black widow spider venom interfere with acetylcholine transmission and produce paralysis in their victims. This form of paralysis is a consequence of sustained muscle contraction which can also disrupt respiratory muscles and result in suffocation. A common disorder that involves acetylcholine is Alzheimer's disease, which involves a degeneration of acetylcholine neurons in the basal forebrain. Although the causes of Alzheimer's disease are not well understood, and at the present there is no treatment, drugs that increase the availability of acetylcholine are being used to treat the symptoms of this debilitating disease (Tabet, 2006).

There are two subtypes of acetylcholine receptors, named after substances that are known to bind to them. Muscarinic receptors are metabotropic receptors named after an alkaloid found in the mushroom *Amanita muscaria*. These receptors are distributed throughout the brain but particularly in the cortex, thalamus, hippocampus, mesolimbic system, and the basal ganglia. They play important roles in cognitive and motor functions as well as in opiate reward. Muscarinic receptors in the ventral tegmental area regulate the release of dopamine in the nucleus accumbens. It is this effect that may contribute to opiate addiction.

The other receptor subtype is called nicotinic, named after the alkaloid nicotine found in tobacco plants. Nicotinic receptors are all ionotropic and are found on all muscle cells at neuromuscular junctions. When bound with acetylcholine these receptors control

sodium channels which leads to muscle contraction. On other non muscular synapses nicotinic receptors are associated with excitatory post synaptic potentials (EPSPs). Often nicotinic receptors are located on axon terminals (axoaxonal synapses) and they contribute to neurotransmitter release by presynaptic facilitation. Nicotinic receptors also contribute to increased dopamine activity in the ventral tegmental area.

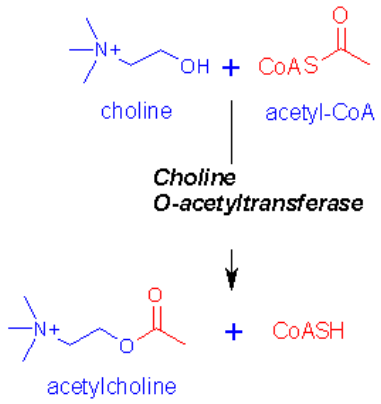

Figure 12*: Synthesis of ACh from choline and acetyl coenzyme A.*

Acetylcholine synthesis and breakdown Acetylcholine is synthesized in cholinergic neurons from two precursor compounds; choline and acetyl coenzyme A (acetyl-CoA) . Choline is made available from dietary fat and acetyl coenzyme A results from glucose metabolism in most cells. Acetylcholine neurons themselves produce choline acetyltransferase (CoASH), the enzyme required to synthesize acetylcholine from these precursors. How much acetylcholine is produced depends both on the availability of its precursors (not typically a problem) and how active these neurons are. Adjusting diet to increase acetylcholine production or ingesting choline has little or no effect.

Once acetylcholine has been released into the synapse it is quickly broken down by the enzyme acetylcholinterase (AChE). Acetylcholinesterase not only breaks down

acetylcholine that is free in the synapse, it also breaks down acetylcholine that is within the terminal buttons and not within synaptic vesicles and the acetylcholoine attached to postsynaptic receptors. The breakdown of acetylcholine into choline and acetic acid helps to regulate the amount of acetylcholine available in the neuron as well as to terminate its effects on receiving neurons quickly. Choline is taken back into the neuron by activating the choline transporter protein located on the terminal button. We will have more to say about the synthesis and breakdown of acetylcholine in later chapters when drugs that alter these processes are discussed.

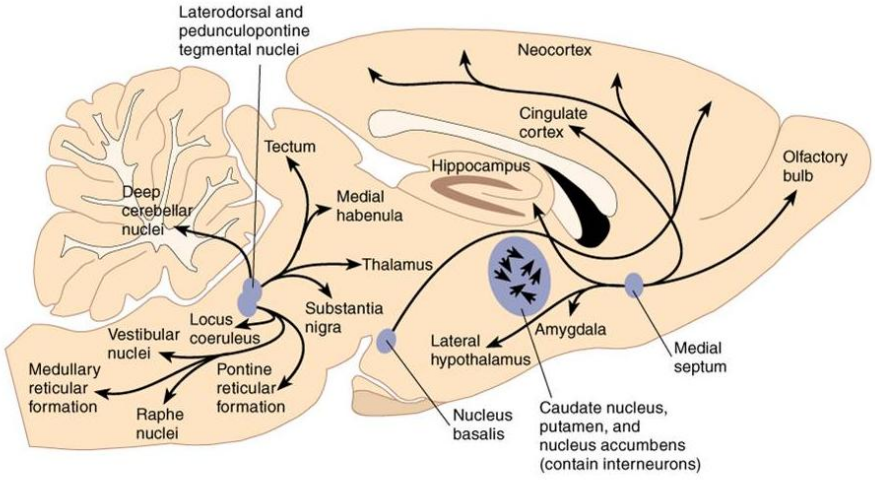

Figure 13: *Major acetylcholinergic pathways originate in several brainstem regions and the nucleus basalis. They project throughout the brainstem, the limbic system, the basal ganglia, and the cortex.*

Norepinephrine (NE) Norepinephrine is distributed throughout the central and peripheral nervous systems. The noradrenergic neurons originate in the pons of the brainstem in a region called the locus coeruleus. They form an excitatory pathway to the

cortex known as the reticular activating system (RAS). This system is primarily responsible for maintaining cortical arousal. Structures that are innervated along the way include the thalamus, the hypothalamus, and all other limbic structures where it is involved in controlling attention, emotion, and eating. Noradrenergic neurons also play important roles in the peripheral nervous system regulating organs such as the heart. Deficiencies in norepinephrine activity are linked to depression and to attention deficit disorders (Biederman, 2005).

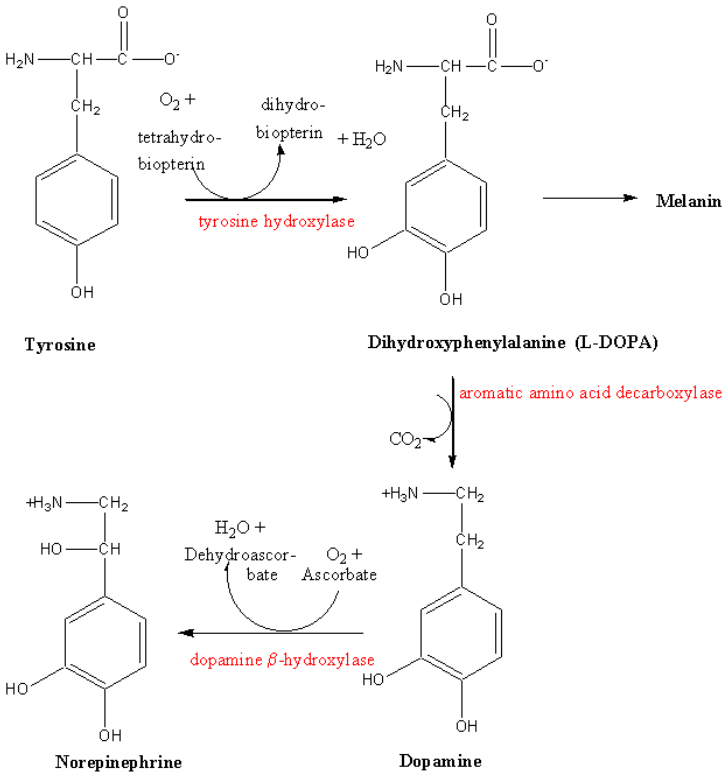

***Figure 14**: Norepinephrine and dopamine are synthesized from dietary tyrosine. Synthesis is terminated at dopamine in dopaminergic neurons.*

Norepinephrine binds to several different receptors subtypes which control widely different functions. Norepinephrine α and β subtypes are each separated into 2 further subtypes $_1$ and $_2$. All four of these receptor types are found in the brain and in the

peripheral nervous system where they control various organs. The α_2 receptor is also an autoreceptor regulating the synthesis and release of norepinephrine from sending neurons. All noradrenergic receptors are metabotropic and they activate second messenger systems in these neurons. Noradrenergic receptors can produce both excitatory and inhibitory effects depending on the specific receptor. The α1 and both β_1 & $_2$ receptors are excitatory while the α_2 receptors are inhibitory.

Norepinephrine synthesis and breakdown Norepinephrine belongs to a family of neurotransmitters and hormones called catecholamines, a name which describes their primary molecular structure. All catecholamines are synthesized from the same precursor compound, tyrosine, which is made available from dietary proteins. The synthesis of norepinephrine from tyrosine involves several enzymes produced by noradrenergic neurons. The first phase of the synthesis involves the conversion of tyrosine into DOPA by the enzyme tyrosine hydroxylase. As you might expect by its name, this enzyme facilitates the reaction that adds two hydroxyl groups to tyrosine. The second phase of synthesis from DOPA to dopamine involves the enzyme aromatic amino acid decarboxylase which cleaves a carbon and several oxygen molecules from DOPA. Finally, dopamine is converted into norepinephrine with the aid of a third enzyme dopamine β-hydroxylase, which adds another hydroxyl group to the molecule. The rate of synthesis depends both on the availability of tyrosine and tyrosine hydroxylase which is termed a rate limiting enzyme. When norepinephrine levels are high in the terminal button tyrosine hydroxylase is inhibited, thus decreasing synthesis. When noradrenergic neurons are firing at a high rate, this enzyme is facilitated. As long as there is a sufficient

source of tyrosine in one's diet there is no other way to alter norepinephrine levels without drugs. And because the pathways to NE synthesis are complex there are numerous opportunities to alter its synthesis pharmacologically.

Norepinephrine is quickly removed from the synapse by two processes; reuptake and breakdown by the enzyme momoamine oxydase (MAO). Much of the available norepinephrine in the synapse is transported back into the terminal button intact through the NE transporter protein. The remaining transmitter is broken down by MAO. We will be discussing drugs that block the NE transporter and the activity of MAO later on in our discussions of depression.

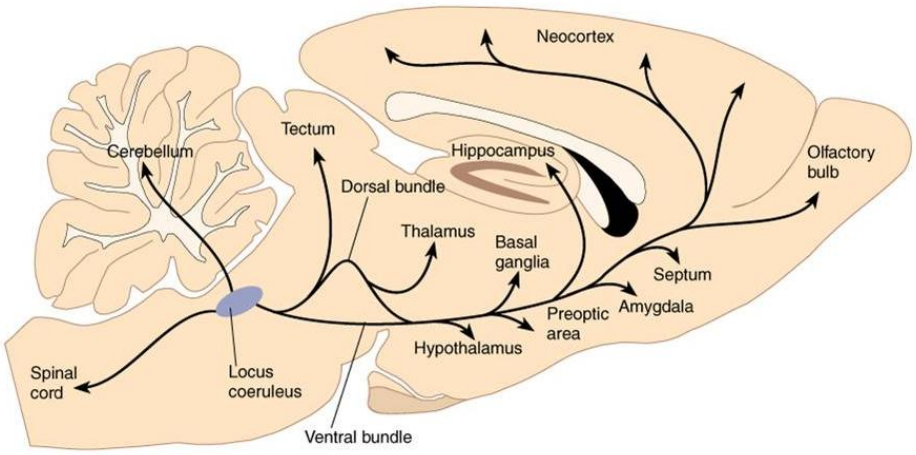

Figure 1.15 *Major noradrenergic pathways originate in the locus coeruleus of the brainstem and project throughout the limbic system and cortex.*

Dopamine (DA) Dopamine is located in three distinct pathways which all begin in the brainstem. First, the **nigrostriatal pathway** begins in the brainstem area called the substantia nigra, meaning dark substance as its color appears somewhat darker than surrounding neural tissues. Axons extending from the cell bodies of dopamine neurons in

this region terminate in all regions of the basal ganglia. The primary function of these structures involves voluntary movement, particularly the initiation of movement. Deficiencies in dopamine in the nigrostriatal pathway result in Parkinson's disease, which is a severe motor disorder resulting from progressive degeneration of these dopamine neurons. Parkinson's disease is at the present most effectively treated with a drug (l-DOPA) that is converted into dopamine in the brain (Hurley & Jenner, 2006).

The second major dopamine pathway originates in the ventral tegmental area adjacent to the pons. Axons projecting from the cell bodies of these dopamine neurons form the **mesolimbic system** and project to the nucleus accumbens, the septum, the amygdala, and the hippocampus. Other axons from the ventral tegmental area form the third pathway and project to the frontal cortex. This system is sometimes referred to as the **mesocortical system**, or the reward system. As the name implies, these neurons and their targets have been implicated in reinforcement and they are activated by all addictive drugs. We will have much more to say about this pathway in discussions of drug abuse. The dopamine pathways are also implicated in the psychotic disorder schizophrenia.

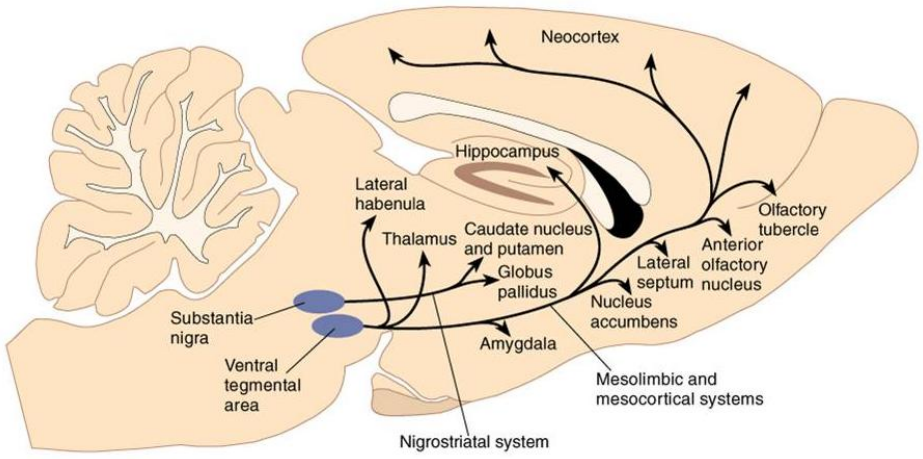

Figure 1.16 *Major dopamine pathways originate in the brainstem and midbrain. The mesolimbic system originates in the ventral tegmental area of the midbrain (VTA). The nigrostriatal system originates in the substantia nigra.*

The receptors for dopamine fall into five groups, D_1-D_5. D_1 and D_2 receptors are the most common and they are distributed throughout the basal ganglia and the mesolimbic system as described earlier in this chapter. Both of these receptors are metabotropic and regulate the activity of **second messenger systems**, but they have opposite effects. D_1 receptors activate the formation of the second messenger adenylyl cyclase while D_2 receptors inhibit it. D_2 receptors are primarily inhibitory resulting in hyperpolarization of the receiving neuron. Because dopamine receptors differ widely in their functions and their distributions they control a large number of important functions. Modern pharmacology attempts to target specific receptor subtypes to produce the desired effects while minimizing unwanted side effects that may also be mediated by dopamine receptors.

Dopamine synthesis and breakdown Dopamine, a catecholamine related to norepinephrine, is also synthesized from dietary tyrosine. The major difference between dopamine and norepinephrine synthesis is that dopamine neurons do not produce the enzyme dopamine β-hydroxylase which converted dopamine into norepinephrine. Like norepinephrine, the rate limiting enzyme for dopamine production is tyrosine hydroxylase. Dopamine is quickly removed from the synaptic gap by both reuptake and breakdown. The dopamine transporter protein (DAT), located on the presynaptic membrane, transports dopamine back into the terminal button intact where it can be integrated back into synaptic vesicles and released again. Other dopamine is metabolized

by the enzyme MAO. There are two subtypes of monoamine oxidase, MAO-A and MAO-B. Which one plays the major role in break down depends on brain location and which neurotransmitter is involved. MAO-A has greater specificity for norepinephrine and serotonin while both MAO-A and B metabolize dopamine. Drugs that block the activity of MAO are referred to as monoamine oxidase inhibitors (MAOIs) and they have been widely used to treat depression.

Serotonin (SE) Serotonin, or 5-hydroxytryptamine (5-HT), belongs to a class of compounds known as monoamines because of their single amine molecular structure. It is distributed throughout the brain and spinal cord and is involved in the control of the sleep/wake cycle, mood, aggressive behavior, and appetite. In fact, since its discovery in the 1970s, it has been implicated in numerous behavioral problems including sleep disorders, aggression, obesity, anorexia, and depression. A common myth is that simply increasing or decreasing the levels of this neurotransmitter may be the cure to any of these problems. The treatment of behavioral disorders is never this simple.

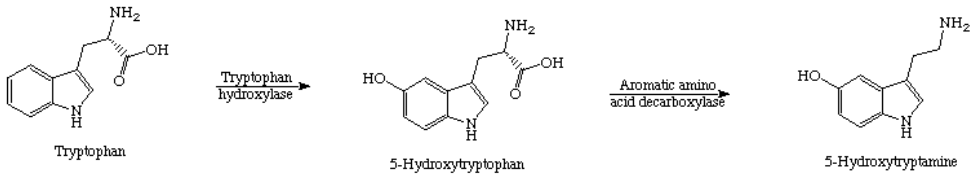

Figure 17: *Serotonin (5-hydroxytryptamine) is synthesized from dietary tryptophan.*

Serotonin neurons also originate in the brain stem in a region of cell bodies called

the raphe nuclei (the term nucleus refers to brain regions that are predominantly cell bodies of a specific neuron type). Two of the regions of greatest interest are the dorsal raphe nucleus and the median raphe nucleus. Axons from these cells travel throughout the cortex and other main brain structures including the basal ganglia, the thalamus, the hypothalamus, and the mesolimbic system. Receptors for serotonin include both ionotropic and, more predominantly, metabotropic types. They are classified into several subgroups including the 5-HT_1, 5-HT_2, 5-HT_3, etc., through 5-HT_7. These are further divided into 5-HT_{1A} and 5-HT_{1B} for this subgroup. Each of these receptor types seems to have specific functions and they are distributed in different regions of the brain. We will only discuss a few of these as they have been main targets for pharmacological research. The 5-HT_{1A} subtype function as autoreceptors on serotonin cell bodies regulating the synthesis and release of serotonin and they are mainly located in the hippocampus and amygdala. 5-HT_{1B} receptors, also autoreceptors, are found predominantly on serotonin axon terminals and 5-HT_{2A} receptors are located throughout the cortex, the basal ganglia, and the mesolimbic system. The 5-HT_{2A} receptors are metabotropic receptors that activate a second messenger system within the receiving cell.

Serotonin synthesis and breakdown Serotonin is synthesized from tryptophan, an amino acid found in a variety of foods including dairy products, meats, fish, and poultry. Tryptophan is converted into 5-hydroxytryptophan by the enzyme tryptophan hydroxylase which is produced by sertotonergic neurons. This intermediate is converted into 5-HT by amino acid decarboxylase. The amount of serotonin produced is dependent on both the availability of tryptophan and the rate limiting enzyme tryptophan hydroxylase. However, eating foods rich in tryptophan or taking the supplement may be

sufficient to increase serotonin levels only slightly. It is interesting that serotonin levels may actually be increased to a greater extent by eating carbohydrate rich food. Apparently the amount of tryptophan that can cross from the blood into serotonergic neurons depends on the ratio of carbohydrate to tryptophan-rich protein. This may be why some people are soothed by chocolate!

Sertotonin, as with norepinephrine and dopamine, is removed from activity by both reuptake and by enzymatic breakdown. Reuptake is accomplished through the serotonin transporter protein imbedded in the presynaptic membrane. Once inside the terminal button serotonin can be transported further into the synaptic vesicles for later release. The remaining serotonin is rapidly degraded by monoamine oxidase which breaks serotonin into its metabolite 5-hydroxyindolacetic acid. The amount of this metabolite is an index of serotonin activity and it can be easily measured. Both of these processes are targets for drug development and some the most popular antidepressants used today are designed to block the reuptake process. These drugs are called serotonin specific reuptake inhibitors (SSRIs).

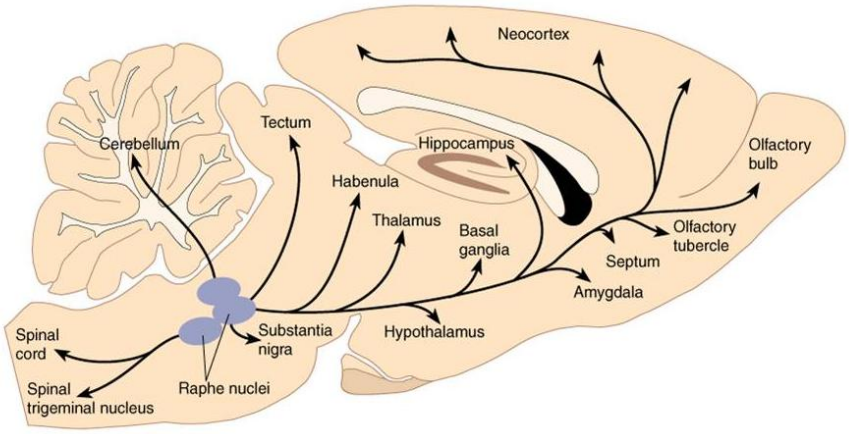

Figure 1.18 *Major serotonergic pathways in the brain originate in the raphe nuclei and project throughout the limbic system and cortex.*

Glutamate Glutamate or glutamic acid is an amino acid derived from glutamine. Not only is it used by cells for protein synthesis and other cellular functions, it is one of the most important excitatory neurotransmitters in the brain. It is known to play an important role in a process called long-term potentiation, which is a change in neuronal functioning that mediates some forms of learning and memory (Robbins et al., 2006). Because of its ubiquitous presence throughout the brain we should not be surprised to find that its activity will play a role in several of the disorders discussed in later chapters. Unlike the neurotransmitters acetylcholine, norepinephrine, dopamine, and serotonin glutamate neurons do not originate in the brainstem and form pathways through the limbic and cortical areas of the brain. Rather, glutamate neurons are found in most brain regions with large projections throughout the cerebral cortex, the hippocampus, and the cerebellum.

Glutamate receptors can be either ionotropic or metabotropic. Ionotropic receptors have been classified as either **AMPA** (α-amino 3-hydroxy 5-methyl 4-isoxazole proprionic acid), **kainate** (after kainic acid which binds to it), or **NMDA** (N-methyl D-aspartate). All of these ionotropic receptors control sodium influx which produces fast depolarization of postsynaptic membranes. In addition to controlling sodium influx, the NMDA receptor also controls calcium (Ca^{2+}) influx which contributes to both fast depolarization and it also initiates a slower and prolonged acting second messenger system. In this sense, the NMDA receptor has both ionotropic and metabotropic properties. Of these three receptor types, it is the NMDA receptor that has received the

most attention because of its role in mediating the cellular changes that underlie learning and memory. The NMDA receptor has several unique properties including functioning as both an ionotropic and a metabotropic receptor. In its resting, polarized state the glutamate receptor channel is occupied by a magnesium ion (Mg^{2+}) which prevents the Ca^{2+} membrane surrounding the glutamate receptor is completely depolarized by high frequency stimulation. Finally, this receptor requires the presence of a second neurotransmitter, glycine (an inhibitory neurotransmitter) before the ion channel for Ca^{2+} is opened. In summary, the NMDA receptor controls both Na+ and Ca^{2+} channels. The Ca^{2+} channel is only opened when both glutamate and glycine are bound to it and the postsynaptic membrane is sufficiently depolarized to eject Mg^{2+}which is blocking the Ca^{2+} channel. Once Ca^{2+} enters it initiates a second messenger system which leads to cellular changes that underlie learning and memory. This cellular change is called **long-term potentiation** referring to the fact that the postsynaptic membrane can now more readily depolarize when stimulated. Long-term potentiation is believed to be one of several important kinds of long-term synaptic changes that mediate learning. Drugs that disrupt NMDA receptors can interfere with learning and memory.

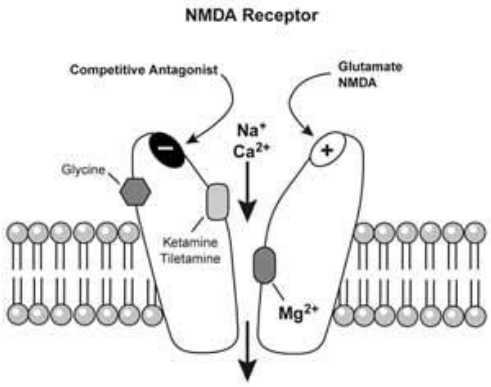

Figure 19*: Glutamate Receptor. Normally the ion channel is blocked by Mg^{2+}. Activation of the receptor displaces $Mg2^{+}$ and allows either Na^{+} or Ca^{2+} to enter. The glutamate receptor requires the presence of glycine (an inhibitory neurotransmitter) before the ion*

channel for Ca^{2+} is opened.

There are at least eight metabotropic glutamate receptors that have been identified. These metabotropic receptors mediate second messenger systems that lead to synaptic and cellular changes that contribute to a host of physiological functions including learning, motor control, and pain.

Glutamate synthesis and breakdown Glutamate is synthesized from glutamine, an abundant non essential amino acid, in all cells that is readily available from proteins in meats, fish, eggs, and dairy products. The synthesis of glutamate from glutamine is facilitated by the enzyme glutaminase. Because all cells can synthesize glutamate, cells that in addition store it in synaptic vesicles and release it when the cell is activated are called glutaminergic neurons. Glutamate can also be ingested directly. The food preservative monosodium glutamate (MSG) contains glutamate. Eating foods containing large amounts of glutamate, including the food preservative monosodium glutamate (MSG), may produce symptoms of dizziness and numbness. In large amounts glutamate is known to be neurotoxic and can lead to cell death. Excessive exposure of postsynaptic neurons to glutamate is referred to as **excitotoxicity** and we will see later that this may contribute to symptoms of schizophrenia.

Glutamate is removed from the synapse by several reuptake mechanisms. All of these are mediated by a glutamate transporter found either on the presynaptic terminal button or on surrounding glial cells. If glutamate is taken up by glial cells it is converted back to glutamine before its transport back to a glutaminercic neuron. Once inside of the terminal button glutamine is converted into glutamate and transported into synaptic vesicles for storage and later release.

Gamma-amino-butyric Acid (GABA) GABA is the major inhibitory neurotransmitter in the brain and spinal cord. Like neural excitation, neural inhibition is critical for the regulation and control of all physiological and behavior functions. Alterations in GABA functioning result from a variety of drugs, including alcohol, and they all have profound effects on behavior and mood. GABAergic neurons are distributed throughout the cortex, the hippocampus, limbic structures, the basal ganglia, and the brainstem and cerebellum. Often GABA neurons are interneurons, but GABAergic neurons may also project along pathways between brain structures. The receptors for GABA can be either ionotropic or metabotropic. The ionotropic receptor is classified as $GABA_A$ and the metabotropic receptor $GABA_B$. GABA produces neural inhibition by opening Cl^- channels so chlorine can move from the outside of the membrane to the inside. This movement of negatively charged ions to the inside hyperpolarizes the membrane from about -70 mv to an even greater negative charge making it more difficult for an action potential to occur. The $GABA_A$ receptor is composed of a membrane spanning protein that contains at least five different binding sites. The primary site is for GABA, but there are additional sites for barbiturates, benzodiazapines, steroids, Picrotoxin, and perhaps alcohol. These binding sites are named after compounds or classes of drugs which specifically bind to them. For example, the benzodiazepine drugs all appear to bind specifically to the benzodiazepine site. Each of these other compounds or classes of drugs can cause the Cl^- channel to open on is own and they can facilitate and prolong GABA binding.

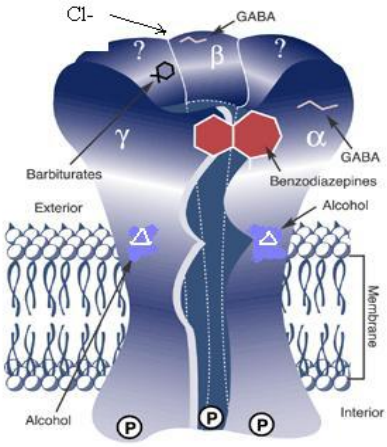

Figure 20*: GABA$_A$ Receptor Complex. Contains binding sites for GABA, barbiturate, benzodiazepine, and alcohol.*

The $GABA_B$ receptor is a metabotropic receptor that facilitates the opening of K^+ channels, also hyperpolarizing the postsynaptic membrane. The $GABA_B$ receptor is less widely distributed than the $GABA_A$ receptor and it functions both as a postsynaptic receptor and as an autoreceptor which functions to regulate the synthesis and release of GABA. Most of the GABA drugs discussed in this text primarily affect the $GABA_A$ receptor.

GABA Synthesis and breakdown Ironically GABA is synthesized from the excitatory neurotransmitter glutamate discussed above by neurons which produce the enzyme glutamic acid decarboxylase. The amount synthesized is regulated by this enzyme, not necessarily the amount of glutamate present within the cell. Drugs that block the synthesis of GABA can produce excessive neural excitation and even seizures.

GABA is removed from the synapse in a manner similar to that of glutamate. That

is, GABA is either transported intact back into the terminal button or it is taken up by glial cells and converted first into glutamate, then into glutamine. Glutamine is transported into the terminals of GABA cells for resynthesis and reintegration into synaptic vesicles for storage and release. Excess GABA within the terminal button is degraded by the enzyme GABA aminotransferase which breaks GABA into its precursor glutamate. Drugs that block the activity of this enzyme may be useful for the treatment of seizures as they can result in increased amounts of GABA available for release. Drugs that increase the activity of GABA are used to treat anxiety, insomnia, and seizures associated with epilepsy and some forms of depression.

Endorphins Endorphins are a family of peptide neurotransmitters chemically similar to opiates such as morphine. Their name is derived from endo (for endogenous) and orphin (from morphine). They are widely distributed throughout most of the brain and spinal cord. Extensive research has linked the endorphins to an array of behavioral and physiological processes including inducing analgesia, a sense of euphoria, counteracting the influence of stress, and modulating food and liquid intake. There are high concentrations of endorphin neurons distributed throughout the cortex, the thalamus, the limbic system, the spinal cord, and in the pituitary gland which controls the release of the stress hormone corticotrophin releasing factor (CRF). Receptors for the endorphins fall into three subtypes; μ (mu), κ (kappa), and δ (delta). All of the endorphine receptors are inhibitory metabotropic receptors. They control mechanisms within the postsynaptic cell that regulate either K^+ or Ca^{++} influx, or second messenger systems that inhibit cell excitability. We discuss several drugs that bind selectively to these opiate receptors

including the opiate morphine later on.

Substance P Substance P belongs to the peptide class of neurotransmitters, thus its name. Its primary function appears to be signaling messages from pain receptors called **nocioceptors** to the dorsal horn of the spinal cord. Substance P activates ascending pain neurons that comprise the spinothalamic pain pathway. Opiates and other drugs can inhibit pain signaling by decreasing the release of Substance P.

The above discussion is only a brief review of several of the most important neurotransmitters and neuromodulators that will be further discussed in later chapters. New neurotransmitters and other neuroactive substances are still being discovered and investigated. Such discoveries have been central to the development of psychopharmacology. At present, the number of substances identified and believed to be either neurotransmitters or neuromodulators exceeds 150.

The Organization and Structure of the Nervous System and Brain

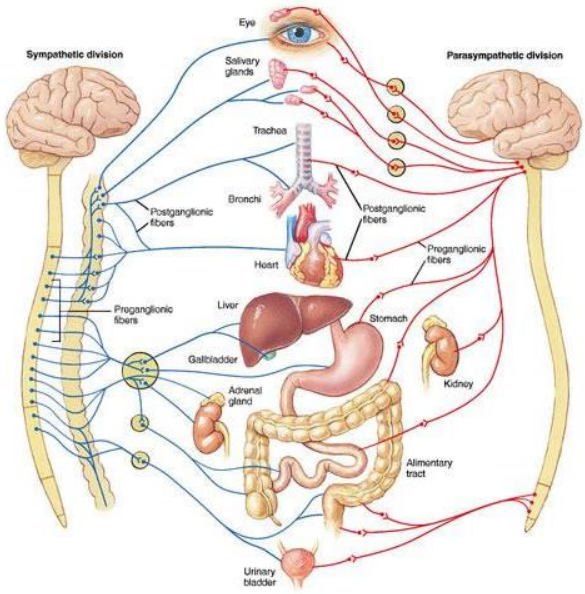

Figure 21*: Central and Peripheral Nervous Systems*

Our nervous system is separated into two distinct components; the **central nervous system** (CNS) which consists of the brain and spinal cord and the **peripheral nervous system** (PNS) which transmits and receives information to and from our muscles, our glands and internal organs, and to our skin. Both of these systems must work in synchrony for normal, adaptive behavior. For instance, information from our stomach (PNS) communicates to the CNS its state of fullness. Although peripheral signals from the stomach are only part of the complex regulation of hunger and eating, they are critical for normal eating behavior. Communication can also originate in the CNS without an eliciting stimulus. A decision to stop reading this text and go outside might originate within the CNS and direct motivational and motor systems to initiate the movement. Drugs used to treat psychological disorders may have both central and peripheral effects. While it is often the central nervous system effects that are critical for

therapy, a drug's peripheral effects (side effects) may be even more salient. Some drugs used to treat schizophrenia, for example, can produce sexual dysfunction, dry mouth, blurred vision, and high heart rate. In the following sections we will review the major components of the central nervous system and examine the structure and function of the cells that it is composed of.

Central Nervous System

As stated in the beginning, the average human brain weighs approximately 1400 grams (or roughly three pounds) and contains nearly 200 billion neurons. The brain is organized into numerous structures which interact to regulate eating and drinking, produce movement, emotion, learning and memory, and allow us to experience the world through our senses. We will examine some of these structures and their functions in this section.

If a person's skull were removed so that you could look at the surface of the brain you would be looking at the surface of the cerebral cortex. In its natural state, the human cortex looks much like a soft, wrinkled walnut, its outer surface filled with crevices and folds. The left and right sides appear to be separated by a long, deep fissure (called the longitudinal sulcus). The cortex is divided into two sides or cerebral hemispheres that, while not identical, are almost mirror images of each other. Under the cortex are many other structures. Starting from the spinal cord and working roughly upward through the base of the brain, these include the medulla, the pons, the cerebellum, the hypothalamus and other structures of the limbic system, the thalamus, and the structures of the basal ganglia including the substantia nigra, the caudate nucleus, and the putamen.

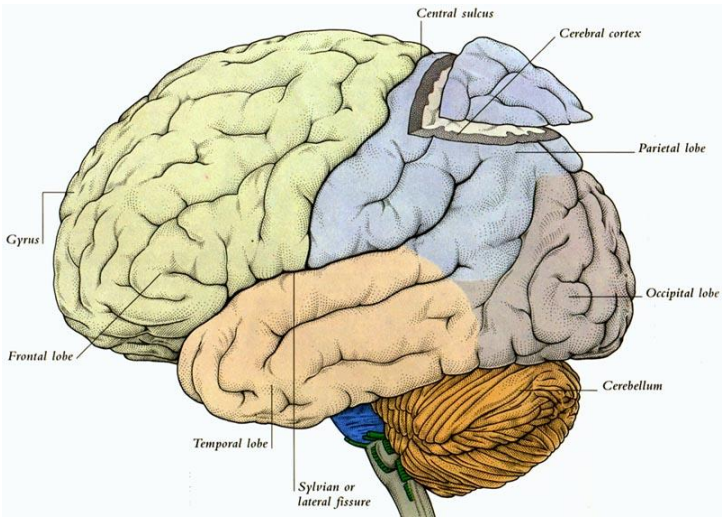

***Figure 22**: Cortex with major fissures and gyri and lobes Identified*

Cerebral Cortex

The cerebral cortex consists of the thin outer layer of the brain. Its average thickness is about 3 mm and its surface area is estimated to be about 2400 cm^2. The Latin *cortex* means bark, and the cortex covers the brain in much the same way as bark covers a tree trunk. This portion of the brain is also called the **neocortex**, or new cortex, since it was the last part of the brain to develop during evolution. A deep grove in the cortex is referred to as a fissure or sulcus and a protuberance is called a gyrus. Names for specific regions of the cortex include these terms as identifiers to distinguish and locate them. The wrinkled and convoluted appearance of the cortex is nature's solution to the problem of cramming the huge neocortical area into a relatively small space within the skull. The size of the skull is essentially fixed because increases in skull size would require commensurate increases in the size of female pelvic structures to allow for full-term child birth. As this example illustrates, evolutionary changes to one structure often require changes to others.

The cortex is divided into four lobes named after the bones of the skull that cover them. The frontal lobes includes everything in front of (rostral to) the central sulcus, the temporal lobes on either hemisphere are located below the lateral fissure, the parietal lobes are behind (caudal to) the central sulcus, and the occipital lobes are at the caudal tip of each hemisphere. These lobes are further separated into functional areas. Three of these areas receive and process sensory information: the primary auditory cortex, the primary visual cortex, and the primary somatosensory cortex. Adjacent to each of these sensory areas is an association cortex where sensory processing, perception, and memories occur. In addition to sensory processing, the cortex includes large areas for motor control and movement. The primary motor cortex is located within the frontal lobes in the gyrus immediately rostral to the central sulcus. Areas for processing emotion are located in both of the prefrontal regions of the frontal lobes and in the cingulate cortex which lies deep within the longitudinal sulcus that separates the two hemispheres. In addition to processing emotion, the prefrontal areas are involved, along with the sensory association cortices, in the processing of short term memories.

We will be discussing many of these cortical areas in later chapters as they are implicated in several psychological disorders and are sites of action for a number of psychotropic drugs.

Spinal Cord

Because the brain occupies the commanding position in the CNS, the spinal cord is often overlooked in discussions of the biological bases of behavior. However, the spinal cord fills the very important function of conveying messages to and from the brain. In addition, the spinal cord controls reflexes, which are simple circuits of sensory and motor

neurons that initiate responses to specific stimuli.

All complex behaviors require integration and coordination at the level of the brain. However, certain basic reflexive behaviors (such as a leg jerk in response to a tap on the kneecap or the quick withdrawal of a hand from a hot stove) do not require brain processing. Different parts of the spinal cord control different reflexes: Hand withdrawal is controlled by the upper spinal cord, whereas the knee jerk response is controlled by an area in the lower cord. The brain is not directly involved in controlling these simple reflexive responses, but it is clearly aware of what action has transpired.

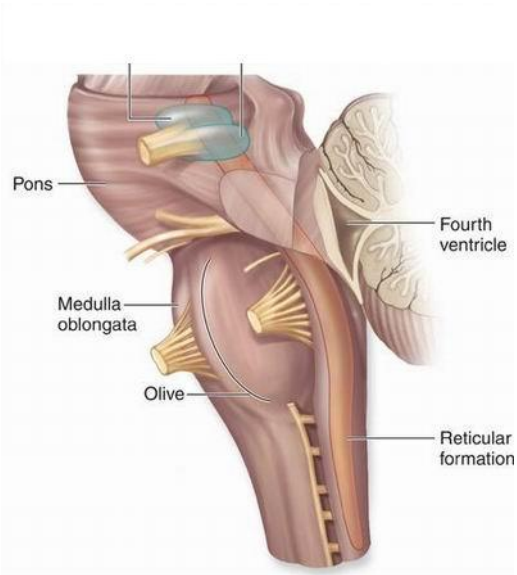

Figure 23*: Brainstem with pons, medulla, cerebellum.*

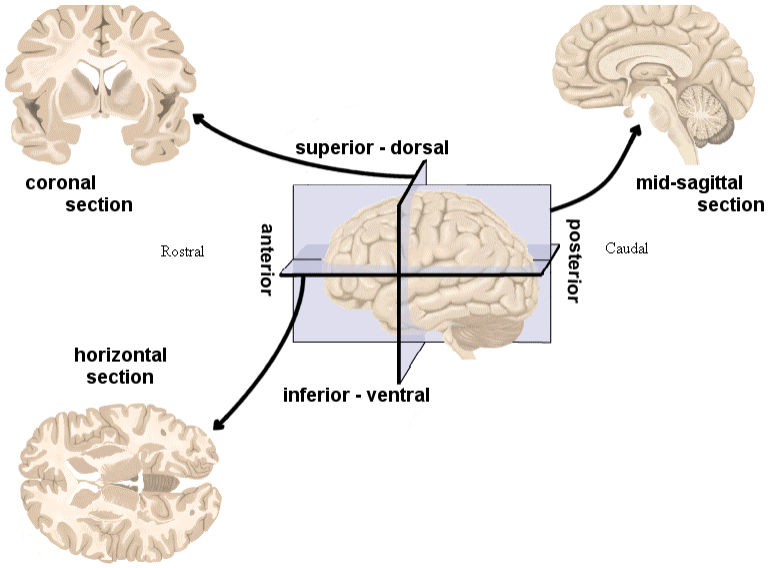

Figure 24: *Sections of the human brain from different anatomical perspectives. Each of these views reveals the relative positions of various structures within the brain.*

Before beginning our discussion of the central nervous system and its various structures and systems we need to review the terms that describe how the brain is dissected and the locations of structures relative to these dissections. Anatomists typically describe the brain from one of several transections through it. Sections along the axis from front to back are referred to as sagital sections. The most common of these sections is a mid-sagital section through the midline of the brain. Another way of observing structures within the brain that do not fall along the midline is to take a series of sections horizontally through the brain. These horizontal sections reveal the relative positions of structures that do not lie along the mid-sagital plane. Finally, sections may be taken vertically through the brain. These views of the internal structures of the brain are referred to as coronal sections. These anatomical terms will be used throughout this chapter to describe various structures and systems of the brain.

Medulla

The medulla is the lowest part of the brain, located just above (superior to) the spinal cord. This structure is in a well-protected location, deep and low within the brain. It contains centers that control many vital life-support functions such as breathing, heart rate, and blood pressure and plays an important role in consciousness and in regulating other reflexive, functions such as sneezing, coughing, and vomiting. The medulla also forms the base of the **reticular activating system** (RAS) which is discussed below.

Pons

The pons is a large bulge in the lower brain core, dorsal to the medulla. The pons plays an important role in fine-tuning motor messages as they travel from the motor area of the cerebral cortex down to the cerebellum. Species-typical behaviors (such as fear and feeding behaviors) and facial expressions are mediated by the pons, which appears to program the patterns of muscle movement required for them.

The pons also plays a role in processing some sensory information, particularly visual information. In addition, the pons contains specialized nuclei that help control respiration, and mediate pain and analgesia.

Cerebellum

The cerebellum is a distinctive structure about the size of a fist, tucked beneath the posterior part of the cerebral hemispheres. It consists of two wrinkled hemispheres covered by an outer cortex. The cerebellum's primary function is to coordinate and regulate motor movements that are broadly controlled by higher brain centers including the cortex and structures of the basal ganglia, to be discussed below. The cerebellum fine-

tunes and smoothes out movements, particularly those required for rapid changes in direction. For example, when you reach out to catch a moving ball, your cerebellum is involved in the timing of your movements. This kind of timed movement clearly involves learning. Experiments with animals have shown that the activity of specific cells in the cerebellum change during the course of learning and that blocking projections from cells within the cerebellum disrupt learned responses (Wikgren et al., 2006).

Damage to the cerebellum results in awkward, jerky, uncoordinated movements and may even affect speech. Professional boxers are especially susceptible to slight damage to the cerebellum, which results in a condition called punch-drunk syndrome. Motor impairment following alcohol intoxication may also be related to alcohol's effects on cells in the cerebellum.

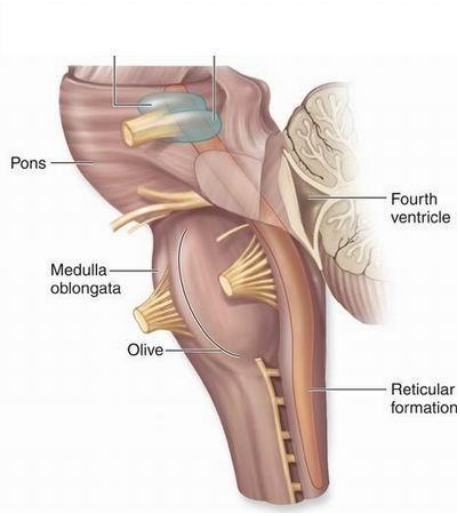

Figure 25: *The reticular formation is a complex array of neurons that ascend through the midline of the brainstem and project to the thalamus. These neurons are essential for vital functions such as respiration, heart rate, blood pressure, as well as cortical arousal.*

Reticular Formation

The reticular formation consists of a set of neural structures that extend from the medulla up to the thalamus. Research has demonstrated that the reticular formation plays a critical role in consciousness and in controlling arousal and alertness. For this reason, it has become common to refer to this collection of structures as the **reticular activating system**, or RAS. Attention-deficit hyperactivity disorder (ADHD) may result from insufficient, rather than excessive, arousal produced by the reticular system, explaining why treatment with psychostimulants is often successful. We will discuss this in more detail in our chapter on attention disorders.

Some of the neural circuits that carry sensory messages from the lower regions of the brain to the higher brain areas have ancillary or detouring fibers that connect with the reticular system. Impulses from these fibers prompt the reticular formation to send signals upward, making us more responsive and alert to our environment. Experiments have shown that mild electrical stimulation of certain areas within this network causes sleeping animals to awaken slowly, whereas stronger stimulation causes animals to awaken rapidly, with greater alertness.

The reticular formation also seems to be linked to sleep cycles. When we fall asleep, our reticular systems cease to send alerting messages to our brains. While sleeping, we may screen out our extraneous stimuli, with the possible exception of critical messages such as the sounds of a squeaking floor or a baby's cry. Although the role of the reticular formation in sleep is still not fully understood, we do know that reticular neurons inhibit sleep-active neurons during wakefulness (Osaka, 1994) and that serious damage to this structure may cause a person to be extremely lethargic or to enter into a prolonged coma.

Recent evidence also suggests that patients in a severe coma may be aroused by electrical stimulation of the reticular system (Cooper et al., 1999).

LIMBIC SYSTEM

The **limbic system** is the portion of the brain most closely associated with emotional expression and motivation; it also plays a significant role in learning, and memory. The limbic system is a collection of structures located around the central core of the brain, along the innermost edge of the cerebral hemispheres. The key structures of the limbic system include the amygdala, the hippocampus, the nucleus accumbens, parts of the hypothalamus, and the bundles of axons that connect these structures. The limbic system also includes the cingulate gurus which is located above the corpus callosum within the fissure that separates the two cerebral hemispheres. Damage to, or stimulation of sites within this system may profoundly affect emotional expression, either by causing excessive reactions to situations or by greatly reducing emotional responses. Limbic structures are also implicated in major depression and drugs we discuss later on will act on some of these structures.

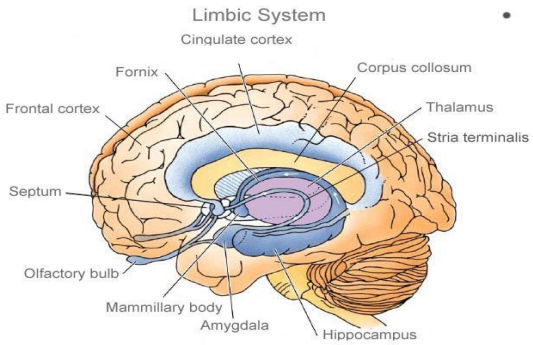

Figure 26*: Limbic Structures revealed from a sagital section of the brain.*

Amygdala

The amygdala, a small structure located in the inferior temporal lobe, plays an important role in the expression of anger, rage, and aggressive and learning fear-motivated behavior. Electrical stimulation or surgical damage to areas within the amygdala may cause an animal to go into a blind rage, whereas in other parts of the amygdala the same procedures may produce extreme passivity. The amygdala also plays significant roles in social cognition and in decision-making. Amygdala damage in humans results in the inability of memories to trigger emotional states. These emotional states are essential to normal social functioning and decision-making. For example, when you make a decision to invest a large sum of money an emotional state induced by the thought of either making more or losing it all, guides your decision to invest or not. People with amygdala damage lose these functions making normal decisions difficult (Bechara et al., 2002, 2003; Adolphs et al., 1995).

Nucleus Accumbens

The nucleus accumbens, located near the amygdala, is part of a group of structures which form the pathway for dopamine neurons originating in the upper pons and terminating in the frontal cortex. This pathway, referred to as the **mesolimbic-cortical**

system, begins in ventral tegmental area of the pons and passes through the nucleus accumbens where it is routed to the frontal cortex. The nucleus accumbens is associated with the reinforcing properties of a category of highly valued stimuli including addictive drugs. The dopamine containing neurons of the mesolimbic system have an excitatory effect on the frontal cortex.

Hippocampus

The hippocampus is also located in the inferior temporal lobe. This structure plays significant roles in the formation of new memories. Individuals who experience damage to this structure have difficulty storing new information in memory. Recent evidence suggests that the hippocampus may also undergo significant alterations as a result of stress and its size may be smaller in patients who have experienced prolonged periods of stress, have post traumatic stress disorder, or who may have schizophrenia. The stress hormone cortisol, a glucocorticoid, can cause neuronal atrophy in the hippocampus as well as inhibit the growth of new neurons in adults. Both of these consequences result in a decline in memory.

Hypothalamus

The hypothalamus is a grape-sized structure that lies inferior to the thalamus and above the optic chiasm. Although it is relatively small, it is essential for many physiological functions and for the motivation of behavior. The hypothalamus integrates information from a number neurotransmitters and hormones that indicate changes in body states. The maintenance of a relatively constant internal environment, including fluid and nutrient levels, requires the integration of information about the status of these systems as well as the initiation of motivational systems to ensure they remain relatively stable. For

example, neurons in the lateral hypothalamus secrete the peptide neurotransmitter **orexin** in response to signals indicating a depletion in energy stores. Orexin, in turn, stimulates appetite and a reduction in metabolic rate to conserve remaining energy.

Shivering when we are cold and perspiring when we are hot are both homeostatic processes that act to restore normal body temperature, and are controlled by neurons in the anterior hypothalamus. The hypothalamus also is critical to sexual motivation and it contains distinct nuclei for males and females that are critical for normal sexual motivation. The medial preoptic nucleus of the hypothalamus contains a greater number of cells in males than in females. The growth of these neurons depends on androgens during development and they are responsible for normal male sexual behaviors. In females it is the ventromedial hypothalamus that controls sexual motivation and this region contains large numbers of estrogen receptors.

The hypothalamus is also the center of neuroendocrine system, which controls the activity of the pituitary gland and various other hormone-secreting endocrine glands. The hypothalamus contains specialized secretory cells that produce and release hormones that stimulate the **pituitary gland**. The pituitary gland produces and secretes a variety of essential hormones including male and female sex hormones, growth hormone, adrenocorticotropic hormone, antidiuretic hormone, and oxytocin. Figure 6 illustrates the hypothalamus and many of its nuclei.

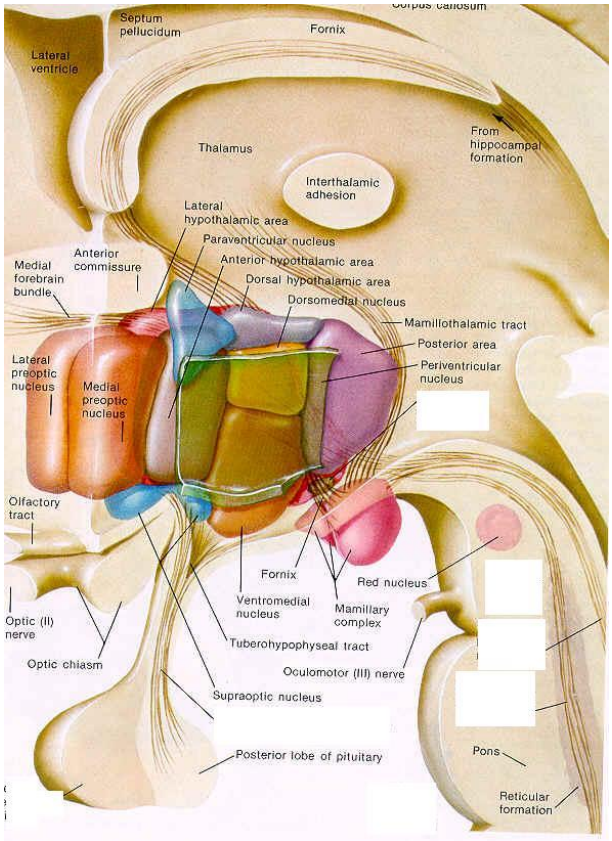

***Figure 27**: Hypothalamus and thalamus revealed from an animated sagital section.*

Thalamus

The thalamus is located above the hypothalamus in the center of the cerebral hemispheres. It is composed of two oval-shaped lobes that lie side by side, one in each hemisphere. Sensory input to the cortex is routed through specific regions within the thalamus with the sole exception of the sense of smell. These distinct regions are specialized for certain kinds of sensory information. Auditory messages from the inner ear travel to the medial geniculate nucleus of the thalamus before being routed to the

primary auditory cortex and visual messages transmitted from your eyes pass through the lateral geniculate nucleus in route to the primary visual cortex. In addition to this function, the thalamus also appears to work in conjunction with the reticular formation to help regulate sleep cycles and to control the excitability of all regions of the cortex. We will have more to say about the thalamus and its control over the excitability of the cortex in the chapter on attention disorders.

BASAL GANGLIA

The basal ganglia consist of several subcortical brain structures including the caudate nucleus, the putamen, and the substantia nigra. These structures receive messages from the cortex and the thalamus. The primary function of the basal ganglia is in the control and initiation of motor movement. One of the most common disorders of the basal ganglia is a condition referred to as Parkinson's disease. Parkinson's disease results from the progressive destruction of the dopamine-containing neurons of the substantia nigra. This destruction leads to decreased activity of other structures within the basal ganglia including the caudate nucleus and putamen. This disease occurs most often in the elderly; however, it may occur in individuals in their late forties or fifties like Michael J. Fox. Parkinson's disease is characterized by difficulty in initiating movement, rigidity, and tremors often in the hands. Parkinson’s disease is commonly treated with drugs that increase dopamine neural transmission such as L-DOPA, but embryonic and stem cell transplants into the substantia nigra are perhaps the most promising treatments for the future (Correia et al., 2006).

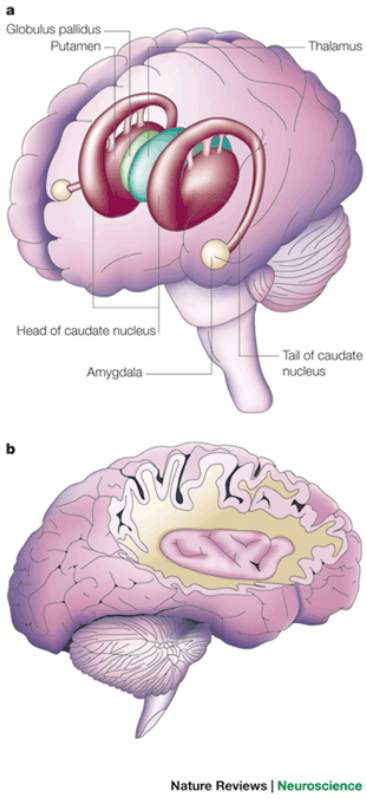

Figure 28: *The structures of the basal ganglia include the caudate nucleus, the putamen, and the globus pallidus.*

A related movement disorder, **tardive dyskinesia**, may result from long-term use of antipsychotic medication. These drugs block a subset of dopamine receptors referred to as D2 receptors. As a result, these dopamine receptors may become sensitized causing the excessive movement associated with this disease. In a sense Parkinson's and tardive dyskinesia are opposite diseases—Parkinson's occurring when dopamine pathways begin to degenerate in the basal ganglia and tardive dyskinesia when dopamine receptors in the same region become too sensitive. We will have more to say about tardive dyskinesia in the chapter on antipsychotic medication.

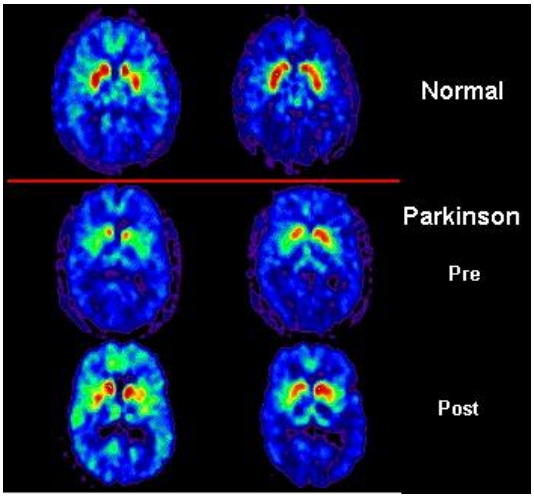

Figure 29*: PET scans revealing the activity of neurons within the caudate nucleus in normal subjects as well a patient with Parkinson's disease before (pre) and after (post) L-DOPA treatment. Red and yellow colors indicate more neural activity than green and blue colored areas.*

Chapter 1: Glossary of terms

central nervous system (CNS) consists of the entire brain and the spinal cord.

peripheral nervous system (PNS) transmits and receives information to and from our muscles, our glands, internal organs, and to our skin.

neocortex neo is Latin for new cortex since it was the last part of the brain to develop during evolution. It consists of the outer layers of the cerebral cortex.

reticular activating system noradrenergic and cholinergic neurons originating in the brainstem and projecting via the thalamus to the cortex.

limbic system is the portion of the brain most closely associated with emotional expression and motivation. It structures also plays a significant role in learning and memory.

mesolimbic-cortical system dopamine neurons which originate in ventral tegmental area of the pons and pass through the nucleus accumbens where they are routed to the frontal cortex.

tardive dyskinesia a severe motor disorder characterized by facial tics, lip smacking, tongue extensions, and rapid eye blinking. Can be caused by long-term use of antipsychotic medication.

interneurons reside only within the central nervous system and function to bridge communication between sensory and motor neurons.

resting potential the state of a neuron when the ionic electrostatic and diffusion forces are at equilibrium. The resting potential may vary between -60 and -70 millivolts depending on the neuron and its location.

graded potential small changes in a membrane's resting potential. Graded potentials may be excitatory and depolarize the membrane from -70 mV to -60 mV or they may be inhibitory and hyperpolarize the membrane to -75 or -80 mV. See also excitatory and inhibitory postsynaptic potentials.

action potential a complete depolarization of the neuronal membrane from -70 mV to approximately +40 mV.

node of Ranvier a small gap in the myelin the surrounds the axon of a neuron. The membrane of the axon is exposed to the extracellular environment at these gaps.

ionotropic receptor a receptor that directly controls an ion channel on the cell membrane.

metabotropic receptor a receptor that controls a variety of internal cell processes mediated by second messengers within the cell.

neurotransmitter reuptake the process of removing neurotransmitter substance from the synaptic gap back into the terminal button by a transporter protein.

excitatory postsynaptic potentials graded membrane potentials that depolarize the neuron bringing it closer to its firing threshold.

inhibitory postsynaptic potentials graded membrane potentials that hyperpolarize polarize the neuron making it less likely to fire.

autoreceptors receptors located on the terminal button or cell body that receive neurotransmitter released from its terminal button. Autoreceptors control neurotransmitter synthesis and release.

heteroreceptors receptors located on the terminal button or cell body that receive neurotransmitter released from another neuron. Heteroreceptors control neurotransmitter synthesis and release.

nigrostriatal pathway dopamine neurons originating in the substantia nigra of the brainstem and project to the striatum or basal ganglia.

mesolimbic system dopamine neurons which originate in ventral tegmental area of the pons and pass through the nucleus accumbens.

mesocortical system dopamine neurons originating in the nucleus accumbens and project to the cortex.. Also see mesolimbic-cortical system.

long-term potentiation (LTP) a change in a neurons ability to depolarize because of the ejection of Mg^{++} ions that previously prevented ion flow into the neuron. Long-term potentiation occurs on postsynaptic membranes when they are depolarized by a strong stimulus at the same time a presynaptic neuron is releasing neurotransmitter. Long-term potentiation is believed to be the neural mechanism for associative (Pavlovian conditioning) learning.

excitotoxicity a consequence of a high rate of presynaptic activity on a neuron resulting in excessive Ca^{++} influx and eventual cell death.

ion channel a protein embedded in the cell membrane that controls the movement of charged ions across the cell's membrane.

second messenger a substance within the cell that becomes activated during cell signaling. Second messengers initiate biochemical processes that result in opening or closing ion channels, the activation of cell enzymes or hormones, and the expression of genes.

neuromodulator a substance produced and released by neurons or glia that alter cell functioning. Neuromodulators may alter the effects of neurotransmitters at synapses and unlike neurotransmitters they may act a greater distances from the releasing cell.

pituitary gland attached to the base of the hypothalamus by the pituitary stalk the pituitary gland is responsible to the production and secretion of a variety of essential hormones.

orexin a peptide neurotransmitter produced by cells within the lateral hypothalamus. Orexin is a powerful appetite stimulant and plays a significant role in sleep-wake cycles.