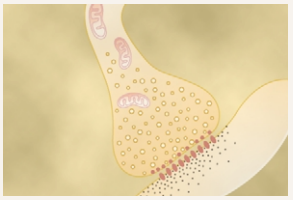
Organization of the Nervous System, Basic Functions of Synapses, "Transmitter Substances"



The nervous system is unique in the vast complexity of thought processes and control actions it can perform. It receives each minute literally millions of bits of information from the different sensory nerves and sensory organs and then integrates all these to determine responses to be made by the body.

However, before beginning this discussion of the nervous system, the reader should review Chapters 5 and 7, which present the principles of membrane potentials and transmission of signals in nerves and through neuromuscular junctions.

General Design of the Nervous System

Central Nervous System Neuron: The Basic Functional Unit

The central nervous system contains more than 100 billion neurons. Figure 45–1 shows a typical neuron of a type found in the brain motor cortex. Incoming signals enter this neuron through synapses located mostly on the neuronal dendrites, but also on the cell body. For different types of neurons, there may be only a few hundred or as many as 200,000 such synaptic connections from input fibers. Conversely, the output signal travels by way of a single axon leaving the neuron. Then, this axon has many separate branches to other parts of the nervous system or peripheral body.

A special feature of most synapses is that the signal normally passes only in the forward direction (from the axon of a preceding neuron to dendrites on cell membranes of subsequent neurons). This forces the signal to travel in required directions for performing specific nervous functions.

Sensory Part of the Nervous System—Sensory Receptors

Most activities of the nervous system are initiated by sensory experience exciting *sensory receptors*, whether visual receptors in the eyes, auditory receptors in the ears, tactile receptors on the surface of the body, or other kinds of receptors. This sensory experience can either cause immediate reaction from the brain, or memory of the experience can be stored in the brain for minutes, weeks, or years and determine bodily reactions at some future date.

Figure 45–2 shows the *somatic* portion of the sensory system, which transmits sensory information from the receptors of the entire body surface and from some deep structures. This information enters the central nervous system through peripheral nerves and is conducted immediately to multiple sensory areas in (1) the spinal cord at all levels; (2) the reticular substance of the medulla, pons, and mesencephalon of the brain; (3) the cerebellum; (4) the thalamus; and (5) areas of the cerebral cortex.

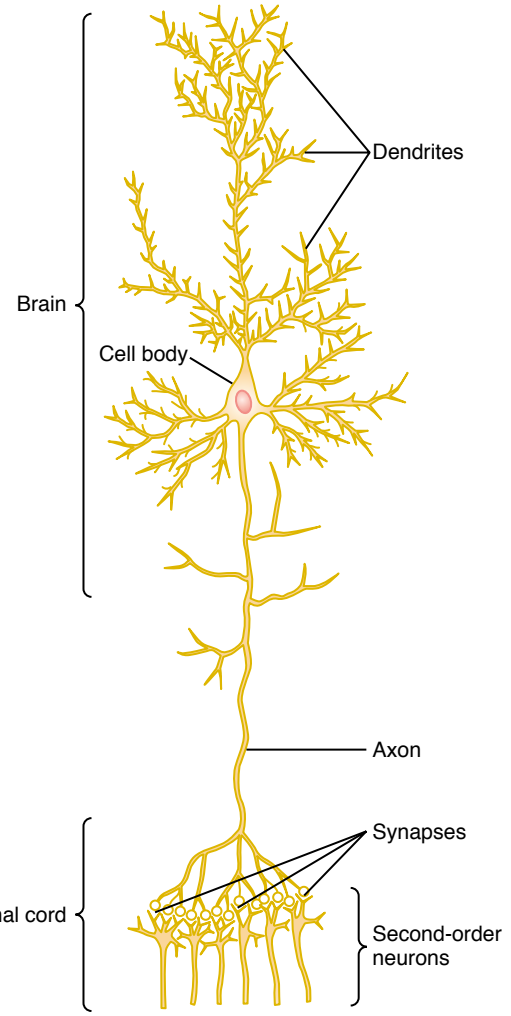


Figure 45–1

Structure of a large neuron in the brain, showing its important functional parts. (Redrawn from Guyton AC: Basic Neuroscience: Anatomy and Physiology. Philadelphia: WB Saunders Co, 1987.)

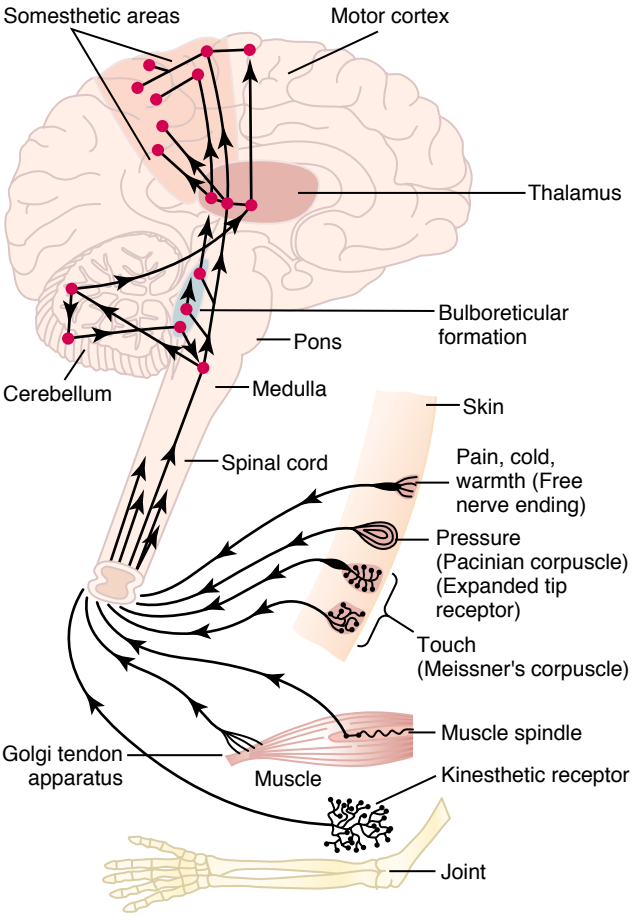


Figure 45–2

Somatosensory axis of the nervous system.

Motor Part of the Nervous System—Effectors

The most important eventual role of the nervous system is to control the various bodily activities. This is achieved by controlling (1) contraction of appropriate skeletal muscles throughout the body, (2) contraction of smooth muscle in the internal organs, and (3) secretion of active chemical substances by both exocrine and endocrine glands in many parts of the body. These activities are collectively called *motor functions* of the nervous system, and the muscles and glands are called *effectors* because they are the actual anatomical structures that perform the functions dictated by the nerve signals.

Figure 45–3 shows the *"skeletal" motor nerve axis* of the nervous system for controlling skeletal muscle contraction. Operating parallel to this axis is another system, called the *autonomic nervous system*, for controlling smooth muscles, glands, and other internal bodily systems; this is discussed in Chapter 60.

Note in Figure 45–3 that the skeletal muscles can be controlled from many levels of the central nervous system, including (1) the spinal cord; (2) the reticular substance of the medulla, pons, and mesencephalon; (3) the basal ganglia; (4) the cerebellum; and (5) the motor cortex. Each of these areas plays its own specific role, the lower regions concerned primarily with automatic, instantaneous muscle responses to sensory stimuli, and the higher regions with deliberate complex muscle movements controlled by the thought processes of the brain.

Processing of Information—"Integrative" Function of the Nervous System

One of the most important functions of the nervous system is to process incoming information in such a way that *appropriate* mental and motor responses will occur. More than 99 per cent of all sensory information is discarded by the brain as irrelevant and unimportant. For instance, one is ordinarily unaware of the

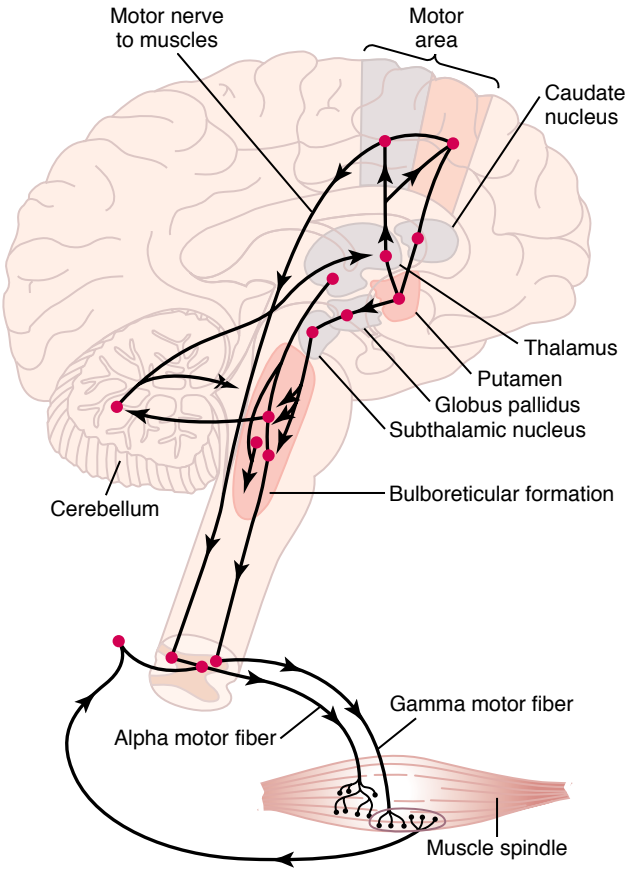


Figure 45–3

Skeletal motor nerve axis of the nervous system.

parts of the body that are in contact with clothing, as well as of the seat pressure when sitting. Likewise, attention is drawn only to an occasional object in one's field of vision, and even the perpetual noise of our surroundings is usually relegated to the subconscious.

But, when important sensory information excites the mind, it is immediately channeled into proper integrative and motor regions of the brain to cause desired responses. This channeling and processing of information is called the *integrative function* of the nervous system. Thus, if a person places a hand on a hot stove, the desired instantaneous response is to lift the hand. And other associated responses follow, such as moving the entire body away from the stove, and perhaps even shouting with pain.

Role of Synapses in Processing Information. The synapse is the junction point from one neuron to the next. Later in this chapter, we will discuss the details of synaptic function. However, it is important to point out here that synapses determine the directions that the nervous signals will spread through the nervous system. Some synapses transmit signals from one neuron to the next with ease, whereas others transmit signals only with difficulty. Also, *facilitatory* and *inhibitory* signals from other areas in the nervous system can control synaptic transmission, sometimes opening the synapses for transmission and at other times closing them. In addition, some postsynaptic neurons respond with large numbers of output impulses, and others respond with only a few. Thus, the synapses perform a selective action, often blocking weak signals while allowing strong signals to pass, but at other times selecting and amplifying certain weak signals, and often channeling these signals in many directions rather than only one direction.

Storage of Information—Memory

Only a small fraction of even the most important sensory information usually causes immediate motor response. But much of the information is stored for future control of motor activities and for use in the thinking processes. Most storage occurs in the *cerebral cortex*, but even the basal regions of the brain and the spinal cord can store small amounts of information.

The storage of information is the process we call *memory*, and this, too, is a function of the synapses. That is, each time certain types of sensory signals pass through sequences of synapses, these synapses become more capable of transmitting the same type of signal the next time, a process called *facilitation*. After the sensory signals have passed through the synapses a large number of times, the synapses become so facilitated that signals generated within the brain itself can also cause transmission of impulses through the same sequences of synapses, even when the sensory input is not excited. This gives the person a perception of experiencing the original sensations, although the perceptions are only memories of the sensations.

We know little about the precise mechanisms by which long-term facilitation of synapses occurs in the memory process, but what is known about this and other details of the sensory memory process are discussed in Chapter 57.

Once memories have been stored in the nervous system, they become part of the brain processing mechanism for future "thinking." That is, the thinking processes of the brain compare new sensory experiences with stored memories; the memories then help to select the important new sensory information and to channel this into appropriate memory storage areas for future use or into motor areas to cause immediate bodily responses.

Major Levels of Central Nervous System Function

The human nervous system has inherited special functional capabilities from each stage of human evolutionary development. From this heritage, three major levels of the central nervous system have specific functional characteristics: (1) the *spinal cord level*, (2) the *lower brain* or *subcortical level*, and (3) the *higher brain* or *cortical level*.

Spinal Cord Level

We often think of the spinal cord as being only a conduit for signals from the periphery of the body to the brain, or in the opposite direction from the brain back to the body. This is far from the truth. Even after the spinal cord has been cut in the high neck region, many highly organized spinal cord functions still occur. For instance, neuronal circuits in the cord can cause (1) walking movements, (2) reflexes that withdraw portions of the body from painful objects, (3) reflexes that stiffen the legs to support the body against gravity, and (4) reflexes that control local blood vessels, gastrointestinal movements, or urinary excretion. In fact, the upper levels of the nervous system often operate not by sending signals directly to the periphery of the body but by sending signals to the control centers of the cord, simply "commanding" the cord centers to perform their functions.

Lower Brain or Subcortical Level

Many, if not most, of what we call subconscious activities of the body are controlled in the lower areas of the brain—in the medulla, pons, mesencephalon, hypothalamus, thalamus, cerebellum, and basal ganglia. For instance, subconscious control of arterial pressure and respiration is achieved mainly in the medulla and pons. Control of equilibrium is a combined function of the older portions of the cerebellum and the reticular substance of the medulla, pons, and mesencephalon. Feeding reflexes, such as salivation and licking of the lips in response to the taste of food, are controlled by areas in the medulla, pons, mesencephalon, amygdala, and hypothalamus. And many emotional patterns, such as anger, excitement, sexual response, reaction to pain, and reaction to pleasure, can still occur after destruction of much of the cerebral cortex.

Higher Brain or Cortical Level

After the preceding account of the many nervous system functions that occur at the cord and lower brain levels, one may ask, what is left for the cerebral cortex to do? The answer to this is complex, but it begins with the fact that the cerebral cortex is an extremely large memory storehouse. The cortex never functions alone but always in association with lower centers of the nervous system.

Without the cerebral cortex, the functions of the lower brain centers are often imprecise. The vast storehouse of cortical information usually converts these functions to determinative and precise operations.

Finally, the cerebral cortex is essential for most of our thought processes, but it cannot function by itself. In fact, it is the lower brain centers, not the cortex, that initiate *wakefulness* in the cerebral cortex, thus opening its bank of memories to the thinking machinery of the brain. Thus, each portion of the nervous system performs specific functions. But it is the cortex that opens a world of stored information for use by the mind.

Comparison of the Nervous System with a Computer

When computers were first developed, it soon became apparent that these machines have many features in common with the nervous system. First, all computers have input circuits that are comparable to the sensory portion of the nervous system, and output circuits that are comparable to the motor portion of the nervous system.

In simple computers, the output signals are controlled directly by the input signals, operating in a manner similar to that of simple reflexes of the spinal cord. In more complex computers, the output is determined both by input signals and by information that has already been stored in memory in the computer, which is analogous to the more complex reflex and processing mechanisms of our higher nervous system. Furthermore, as computers become even more complex, it is necessary to add still another unit, called the *central processing unit*, that determines the sequence of all operations. This unit is analogous to the control mechanisms in our brain that direct our attention first to one thought or sensation or motor activity, then to another, and so forth, until complex sequences of thought or action take place.

Figure 45–4 is a simple block diagram of a computer. Even a rapid study of this diagram demonstrates its similarity to the nervous system. The fact that the basic components of the general-purpose computer are analogous to those of the human nervous system demonstrates that the brain is basically a computer that continuously collects sensory information and uses this along with stored information to compute the daily course of bodily activity.

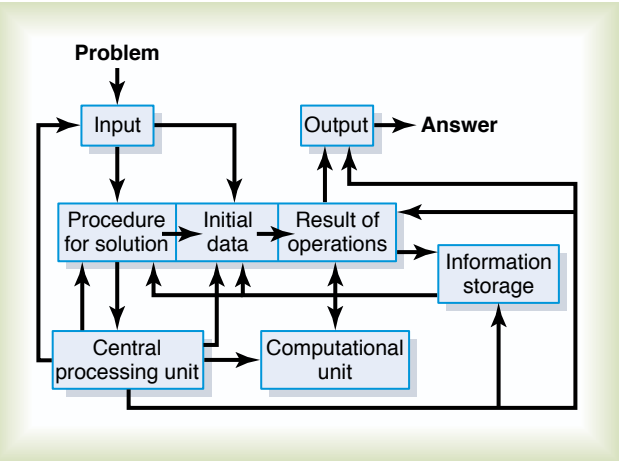


Figure 45–4

Block diagram of a general-purpose computer, showing the basic components and their interrelations.

Central Nervous System Synapses

Every medical student is aware that information is transmitted in the central nervous system mainly in the form of nerve action potentials, called simply "nerve impulses," through a succession of neurons, one after another. However, in addition, each impulse (1) may be blocked in its transmission from one neuron to the next, (2) may be changed from a single impulse into repetitive impulses, or (3) may be integrated with impulses from other neurons to cause highly intricate patterns of impulses in successive neurons. All these functions can be classified as *synaptic functions of neurons*.

Types of Synapses—Chemical and Electrical

There are two major types of synapses: (1) the *chemical synapse* and (2) the *electrical synapse*.

Almost all the synapses used for signal transmission in the central nervous system of the human being are *chemical synapses*. In these, the first neuron secretes at its nerve ending synapse a chemical substance called a *neurotransmitter* (or often called simply *transmitter substance*), and this transmitter in turn acts on receptor proteins in the membrane of the next neuron to excite the neuron, inhibit it, or modify its sensitivity in some other way. More than 40 important transmitter substances have been discovered thus far. Some of the best known are acetylcholine, norepinephrine, epinephrine, histamine, gamma-aminobutyric acid (GABA), glycine, serotonin, and glutamate.

Electrical synapses, in contrast, are characterized by direct open fluid channels that conduct electricity from one cell to the next. Most of these consist of small protein tubular structures called *gap junctions* that allow free movement of ions from the interior of one cell to the interior of the next. Such junctions were discussed in Chapter 4. Only a few examples of gap junctions have been found in the central nervous system. However, it is by way of gap junctions and other similar junctions that action potentials are transmitted from one smooth muscle fiber to the next in visceral smooth muscle (Chapter 8) and from one cardiac muscle cell to the next in cardiac muscle (Chapter 10).

"One-Way" Conduction at Chemical Synapses. Chemical synapses have one exceedingly important characteristic that makes them highly desirable for transmitting most nervous system signals: they always transmit the signals in one direction: that is, from the neuron that secretes the transmitter substance, called the *presynaptic neuron*, to the neuron on which the transmitter acts, called the *postsynaptic neuron*. This is the *principle of one-way conduction* at chemical synapses, and it is quite different from conduction through electrical synapses, which often transmit signals in either direction.

Think for a moment about the extreme importance of the one-way conduction mechanism. It allows signals to be directed toward specific goals. Indeed, it is this specific transmission of signals to discrete and highly focused areas both within the nervous system and at the terminals of the peripheral nerves that allows the nervous system to perform its myriad functions of sensation, motor control, memory, and many others.

Physiologic Anatomy of the Synapse

Figure 45–5 shows a typical *anterior motor neuron* in the anterior horn of the spinal cord. It is composed of three major parts: the *soma*, which is the main body of the neuron; a single *axon*, which extends from the soma into a peripheral nerve that leaves the spinal cord; and the *dendrites*, which are great numbers of branching projections of the soma that extend as much as 1 millimeter into the surrounding areas of the cord.

As many as 10,000 to 200,000 minute synaptic knobs called *presynaptic terminals* lie on the surfaces of the dendrites and soma of the motor neuron, about 80 to 95 per cent of them on the dendrites and only 5 to 20 per cent on the soma. These presynaptic terminals are the ends of nerve fibrils that originate from many other neurons. Later, it will become evident that many

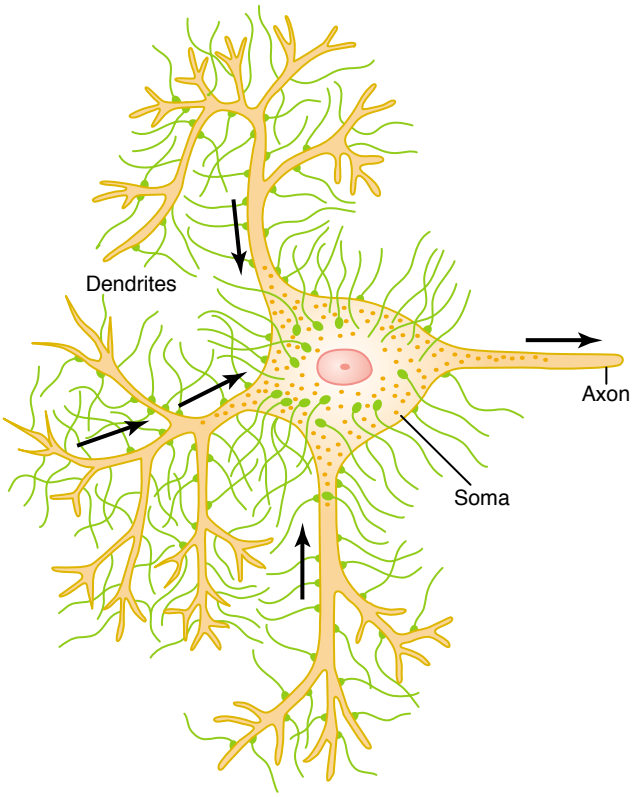


Figure 45–5

Typical anterior motor neuron, showing presynaptic terminals on the neuronal soma and dendrites. Note also the single axon.

of these presynaptic terminals are *excitatory*—that is, they secrete a transmitter substance that excites the postsynaptic neuron. But other presynaptic terminals are *inhibitory*—they secrete a transmitter substance that inhibits the postsynaptic neuron.

Neurons in other parts of the cord and brain differ from the anterior motor neuron in (1) the size of the cell body; (2) the length, size, and number of dendrites, ranging in length from almost zero to many centimeters; (3) the length and size of the axon; and (4) the number of presynaptic terminals, which may range from only a few to as many as 200,000. These differences make neurons in different parts of the nervous system react differently to incoming synaptic signals and, therefore, perform many different functions.

Presynaptic Terminals. Electron microscopic studies of the presynaptic terminals show that they have varied anatomical forms, but most resemble small round or oval knobs and, therefore, are sometimes called *terminal knobs*, *boutons, end-feet*, or *synaptic knobs*.

Figure 45–6 illustrates the basic structure of a synapse, showing a single presynaptic terminal on the membrane surface of a postsomatic neuron. The presynaptic terminal is separated from the postsynaptic neuronal soma by a *synaptic cleft* having a width usually of 200 to 300 angstroms. The terminal has two internal structures important to the excitatory or inhibitory function of the synapse: the *transmitter vesicles* and the *mitochondria*. The transmitter vesicles contain the *transmitter substance* that, when released into the synaptic cleft, either *excites* or *inhibits* the postsynaptic neuron—excites if the neuronal membrane contains *excitatory receptors*, inhibits if the membrane contains *inhibitory receptors*. The mitochondria provide adenosine triphosphate (ATP), which in turn supplies the energy for synethesizing new transmitter substance.

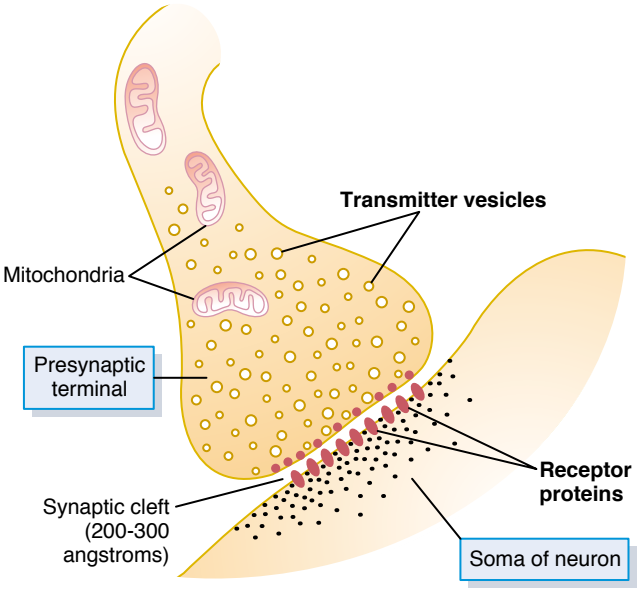


Figure 45–6

Physiologic anatomy of the synapse.

When an action potential spreads over a presynaptic terminal, depolarization of its membrane causes a small number of vesicles to empty into the cleft. The released transmitter in turn causes an immediate change in permeability characteristics of the postsynaptic neuronal membrane, and this leads to excitation or inhibition of the postsynaptic neuron, depending on the neuronal receptor characteristics.

Mechanism by Which an Action Potential Causes Transmitter Release from the Presynaptic Terminals—Role of Calcium Ions

The membrane of the presynaptic terminal is called the *presynaptic membrane*. It contains large numbers of *voltage-gated calcium channels*. When an action potential depolarizes the presynaptic membrane, these calcium channels open and allow large numbers of calcium ions to flow into the terminal. The quantity of transmitter substance that is then released from the terminal into the synaptic cleft is directly related to the number of calcium ions that enter. The precise mechanism by which the calcium ions cause this release is not known, but it is believed to be the following.

When the calcium ions enter the presynaptic terminal, it is believed that they bind with special protein molecules on the inside surface of the presynaptic membrane, called *release sites*. This binding in turn causes the release sites to open through the membrane, allowing a few transmitter vesicles to release their transmitter into the cleft after each single action potential. For those vesicles that store the neurotransmitter acetylcholine, between 2000 and 10,000 molecules of acetylcholine are present in each vesicle, and there are enough vesicles in the presynaptic terminal to transmit from a few hundred to more than 10,000 action potentials.

Action of the Transmitter Substance on the Postsynaptic Neuron—Function of "Receptor Proteins"

The membrane of the postsynaptic neuron contains large numbers of *receptor proteins*, also shown in Figure 45–6. The molecules of these receptors have two important components: (1) a *binding component* that protrudes outward from the membrane into the synaptic cleft—here it binds the neurotransmitter coming from the presynaptic terminal—and (2) an *ionophore component* that passes all the way through the postsynaptic membrane to the interior of the postsynaptic neuron. The ionophore in turn is one of two types: (1) an *ion channel* that allows passage of specified types of ions through the membrane or (2) a *"second messenger" activator* that is not an ion channel but instead is a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron. These substances in turn serve as "second messengers" to increase or decrease specific cellular functions.

Ion Channels. The ion channels in the postsynaptic neuronal membrane are usually of two types: (1) *cation channels* that most often allow sodium ions to pass when opened, but sometimes allow potassium and/or calcium ions as well, and (2) *anion channels* that allow mainly chloride ions to pass but also minute quantities of other anions.

The *cation channels* that conduct sodium ions are lined with negative charges. These charges attract the positively charged sodium ions into the channel when the channel diameter increases to a size larger than that of the hydrated sodium ion. But those same negative charges *repel chloride ions and other anions* and prevent their passage.

For the *anion channels*, when the channel diameters become large enough, chloride ions pass into the channels and on through to the opposite side, whereas sodium, potassium, and calcium cations are blocked, mainly because their hydrated ions are too large to pass.

We will learn later that when cation channels open and allow positively charged sodium ions to enter, the positive electrical charges of the sodium ions will in turn excite this neuron. Therefore, a transmitter substance that opens cation channels is called an *excitatory transmitter*. Conversely, opening anion channels allows negative electrical charges to enter, which inhibits the neuron. Therefore, transmitter substances that open these channels are called *inhibitory transmitters*.

When a transmitter substance activates an ion channel, the channel usually opens within a fraction of a millisecond; when the transmitter substance is no longer present, the channel closes equally rapidly. The opening and closing of ion channels provide a means for very rapid control of postsynaptic neurons.

"Second Messenger" System in the Postsynaptic Neuron. Many functions of the nervous system—for instance, the process of memory—require prolonged changes in neurons for seconds to months after the initial transmitter substance is gone. The ion channels are not suitable for causing prolonged postsynaptic neuronal changes because these channels close within milliseconds after the transmitter substance is no longer present. However, in many instances, prolonged postsynaptic neuronal excitation or inhibition is achieved by activating a "second messenger" chemical system inside the postsynaptic neuronal cell itself, and then it is the second messenger that causes the prolonged effect.

There are several types of second messenger systems. One of the most common types uses a group of proteins called *G-proteins*. Figure 45–7 shows in the upper left corner a membrane receptor protein. A G-protein is attached to the portion of the receptor that protrudes into the interior of the cell. The G-protein in turn consists of three components: an alpha (α) component that is the *activator* portion of the G-protein, and beta (β) and gamma (γ) components that are attached to the alpha component and also to the inside of the cell membrane adjacent to the receptor protein. On activation by a nerve impulse, the alpha portion of the G-protein separates from the beta and gamma portions and then is free to move within the cytoplasm of the cell.

Inside the cytoplasm, the separated alpha component performs one or more of multiple functions, depending on the specific characteristic of each type of neuron. Shown in Figure 45–7 are four changes that can occur. They are as follows:

1. *Opening specific ion channels through the postsynaptic cell membrane*. Shown in the upper right of the figure is a potassium channel that is opened in response to the G-protein; this channel often stays open for a prolonged time, in contrast to rapid closure of directly activated ion channels that do not use the second messenger system.

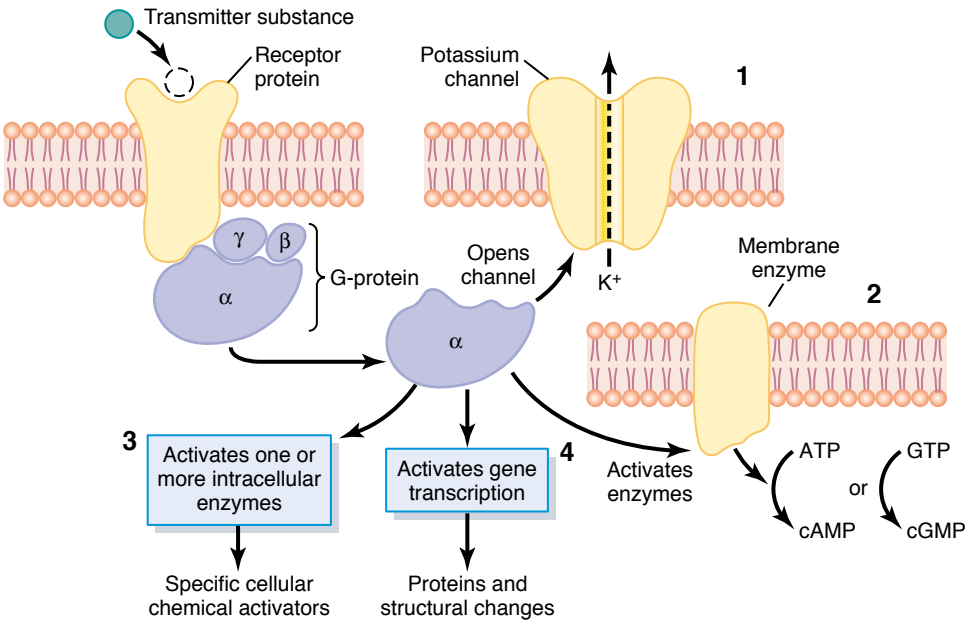


Figure 45–7

"Second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first releasing a "G-protein" into the second neuron's cytoplasm. Four subsequent possible effects of the G-protein are shown, including 1, opening an ion channel in the membrane of the second neuron; 2, activating an enzyme system in the neuron's membrane; 3, activating an intracellular enzyme system; and/or 4, causing gene transcription in the second neuron.

2. *Activation of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) in the neuronal cell*. Recall that either cyclic AMP or cyclic GMP can activate highly specific metabolic machinery in the neuron and, therefore, can initiate any one of many chemical results, including long-term changes in cell structure itself, which in turn alters long-term excitability of the neuron.
3. *Activation of one or more intracellular enzymes*. The G-protein can directly activate one or more intracellular enzymes. In turn the enzymes can cause any one of many specific chemical functions in the cell.
4. *Activation of gene transcription.* This is one of the most important effects of activation of the second messenger systems because gene transcription can cause formation of new proteins within the neuron, thereby changing its metabolic machinery or its structure. Indeed, it is well known that structural changes of appropriately activated neurons do occur, especially in long-term memory processes.

It is clear that activation of second messenger systems within the neuron, whether they be of the G-protein type or of other types, is extremely important for changing the long-term response characteristics of different neuronal pathways. We will return to this subject in more detail in Chapter 57 when we discuss memory functions of the nervous system.

Excitatory or Inhibitory Receptors in the Postsynaptic Membrane

Some postsynaptic receptors, when activated, cause excitation of the postsynaptic neuron, and others cause inhibition. The importance of having inhibitory as well as excitatory types of receptors is that this gives an additional dimension to nervous function, allowing restraint of nervous action as well as excitation.

The different molecular and membrane mechanisms used by the different receptors to cause excitation or inhibition include the following.

Excitation

1. *Opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell*. This raises the intracellular membrane potential in the positive direction up toward the threshold level for excitation. It is by far the most widely used means for causing excitation.
2. *Depressed conduction through chloride or potassium channels, or both*. This decreases the diffusion of negatively charged chloride ions to the inside of the postsynaptic neuron or decreases the diffusion of positively charged potassium ions to the outside. In either instance, the effect is to make the internal membrane potential more positive than normal, which is excitatory.
3. *Various changes in the internal metabolism of the postsynaptic neuron* to excite cell activity or, in some instances, to increase the number of excitatory membrane receptors or decrease the number of inhibitory membrane receptors.

Inhibition

1. *Opening of chloride ion channels through the postsynaptic neuronal membrane*. This allows rapid diffusion of negatively charged chloride ions from outside the postsynaptic neuron to the inside, thereby carrying negative charges inward and increasing the negativity inside, which is inhibitory.
2. *Increase in conductance of potassium ions out of the neuron*. This allows positive ions to diffuse to the exterior, which causes increased negativity inside the neuron; this is inhibitory.
3. *Activation of receptor enzymes* that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

Chemical Substances That Function as Synaptic Transmitters

More than 50 chemical substances have been proved or postulated to function as synaptic transmitters. Many of them are listed in Tables 45–1 and 45–2, which give two groups of synaptic transmitters. One group comprises *small-molecule, rapidly acting transmitters*. The other is made up of a large number of *neuropeptides* of much larger molecular size that are usually much more slowly acting.

The small-molecule, rapidly acting transmitters are the ones that cause most acute responses of the nervous system, such as transmission of sensory signals to the brain and of motor signals back to the muscles. The neuropeptides, in contrast, usually cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, and possibly even long-term changes in numbers of synapses or sizes of synapses.

Table 45–1

Small-Molecule, Rapidly Acting Transmitters

Class I
Acetylcholine
Class II: The Amines
Norepinephrine
Epinephrine
Dopamine
Serotonin
Histamine
Class III: Amino Acids
Gamma-aminobutyric acid (GABA)
Glycine
Glutamate
Aspartate
Class IV
Nitric oxide (NO)

Table 45–2

Neuropeptide, Slowly Acting Transmitters or Growth Factors

Hypothalamic-releasing hormones
Thyrotropin-releasing hormone
Luteinizing hormone–releasing hormone
Somatostatin (growth hormone inhibitory factor)
Pituitary peptides
Adrenocorticotropic hormone (ACTH)
β-Endorphin
α-Melanocyte-stimulating hormone
Prolactin
Luteinizing hormone
Thyrotropin
Growth hormone
Vasopressin
Oxytocin
Peptides that act on gut and brain
Leucine enkephalin
Methionine enkephalin
Substance P
Gastrin
Cholecystokinin
Vasoactive intestinal polypeptide (VIP)
Nerve growth factor
Brain-derived neurotropic factor
Neurotensin
Insulin
Glucagon
From other tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

Small-Molecule, Rapidly Acting Transmitters

In most cases, the small-molecule types of transmitters are synthesized in the cytosol of the presynaptic terminal and are absorbed by means of active transport into the many transmitter vesicles in the terminal. Then, each time an action potential reaches the presynaptic terminal, a few vesicles at a time release their transmitter into the synaptic cleft. This usually occurs within a millisecond or less by the mechanism described earlier. The subsequent action of the small-molecule type of transmitter on the membrane receptors of the postsynaptic neuron usually also occurs within another millisecond or less. Most often the effect is to increase or decrease conductance through ion channels; an example is to increase sodium conductance, which causes excitation, or to increase potassium or chloride conductance, which causes inhibition.

Recycling of the Small-Molecule Types of Vesicles. The vesicles that store and release small-molecule transmitters are continually recycled and used over and over again. After they fuse with the synaptic membrane and open to release their transmitter substance, the vesicle membrane at first simply becomes part of the synaptic membrane. However, within seconds to minutes, the vesicle portion of the membrane invaginates back to the inside of the presynaptic terminal and pinches off to form a new vesicle. And the new vesicular membrane still contains appropriate enzyme proteins or transport proteins required for synthesizing and/or concentrating new transmitter substance inside the vesicle.

Acetylcholine is a typical small-molecule transmitter that obeys the principles of synthesis and release stated earlier. This transmitter substance is synthesized in the presynaptic terminal from acetyl coenzyme A and choline in the presence of the enzyme *choline acetyltransferase*. Then it is transported into its specific vesicles. When the vesicles later release the acetylcholine into the synaptic cleft during synaptic neuronal signal transmission, the acetylcholine is rapidly split again to acetate and choline by the enzyme *cholinesterase*, which is present in the proteoglycan reticulum that fills the space of the synaptic cleft. And then again, inside the presynaptic terminal, the vesicles are recycled; choline is actively transported back into the terminal to be used again for synthesis of new acetylcholine.

Characteristics of Some of the More Important Small-Molecule Transmitters. The most important of the small-molecule transmitters are the following.

Acetylcholine is secreted by neurons in many areas of the nervous system but specifically by (1) the terminals of the large pyramidal cells from the motor cortex, (2) several different types of neurons in the basal ganglia, (3) the motor neurons that innervate the skeletal muscles, (4) the preganglionic neurons of the autonomic nervous system, (5) the postganglionic neurons of the parasympathetic nervous system, and (6) some of the postganglionic neurons of the sympathetic nervous system. In most instances, acetylcholine has an excitatory effect; however, it is known to have inhibitory effects at some peripheral parasympathetic nerve endings, such as inhibition of the heart by the vagus nerves.

Norepinephrine is secreted by the terminals of many neurons whose cell bodies are located in the brain stem and hypothalamus. Specifically, norepinephrine-secreting neurons located in the *locus ceruleus* in the pons send nerve fibers to widespread areas of the brain to help control overall activity and mood of the mind, such as increasing the level of wakefulness. In most of these areas, norepinephrine probably activates excitatory receptors, but in a few areas, it activates inhibitory receptors instead. Norepinephrine is also secreted by most postganglionic neurons of the sympathetic nervous system, where it excites some organs but inhibits others.

Dopamine is secreted by neurons that originate in the substantia nigra. The termination of these neurons is mainly in the striatal region of the basal ganglia. The effect of dopamine is usually inhibition.

Glycine is secreted mainly at synapses in the spinal cord. It is believed to always act as an inhibitory transmitter.

GABA (*gamma-aminobutyric acid*) is secreted by nerve terminals in the spinal cord, cerebellum, basal ganglia, and many areas of the cortex. It is believed always to cause inhibition.

Glutamate is secreted by the presynaptic terminals in many of the sensory pathways entering the central nervous system, as well as in many areas of the cerebral cortex. It probably always causes excitation.

Serotonin is secreted by nuclei that originate in the median raphe of the brain stem and project to many brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus. Serotonin acts as an inhibitor of pain pathways in the cord, and an inhibitor action in the higher regions of the nervous system is believed to help control the mood of the person, perhaps even to cause sleep.

Nitric oxide is especially secreted by nerve terminals in areas of the brain responsible for long-term behavior and for memory. Therefore, this transmitter system might in the future explain some behavior and memory functions that thus far have defied understanding. Nitric oxide is different from other small-molecule transmitters in its mechanism of formation in the presynaptic terminal and in its actions on the postsynaptic neuron. It is not preformed and stored in vesicles in the presynaptic terminal as are other transmitters. Instead, it is synthesized almost instantly as needed, and it then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets. Next, it diffuses into postsynaptic neurons nearby. In the postsynaptic neuron, it usually does not greatly alter the membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or perhaps even longer.

Neuropeptides

The neuropeptides are an entirely different class of transmitters that are synthesized differently and whose actions are usually slow and in other ways quite different from those of the small-molecule transmitters. The neuropeptides are not synthesized in the cytosol of the presynaptic terminals. Instead, they are synthesized as integral parts of large-protein molecules by ribosomes in the neuronal cell body.

The protein molecules then enter the spaces inside the endoplasmic reticulum of the cell body and subsequently inside the Golgi apparatus, where two changes occur: First, the neuropeptide-forming protein is enzymatically split into smaller fragments, some of which are either the neuropeptide itself or a precursor of it. Second, the Golgi apparatus packages the neuropeptide into minute transmitter vesicles that are released into the cytoplasm. Then the transmitter vesicles are transported all the way to the tips of the nerve fibers by *axonal streaming* of the axon cytoplasm, traveling at the slow rate of only a few centimeters per day. Finally, these vesicles release their transmitter at the neuronal terminals in response to action potentials in the same manner as for small-molecule transmitters. However, the vesicle is autolyzed and is not reused.

Because of this laborious method of forming the neuropeptides, much smaller quantities of them are usually released than of the small-molecule transmitters. This is partly compensated for by the fact that the neuropeptides are generally a thousand or more times as potent as the small-molecule transmitters. Another important characteristic of the neuropeptides is that they often cause much more prolonged actions. Some of these actions include prolonged closure of calcium channels, prolonged changes in the metabolic machinery of cells, prolonged changes in activation or deactivation of specific genes in the cell nucleus, and/or prolonged alterations in numbers of excitatory or inhibitory receptors. Some of these effects last for days, but others perhaps for months or years. Our knowledge of the functions of the neuropeptides is only beginning to develop.

Electrical Events During Neuronal Excitation

The electrical events in neuronal excitation have been studied especially in the large motor neurons of the anterior horns of the spinal cord. Therefore, the events described in the next few sections pertain essentially to these neurons. Except for quantitative differences, they apply to most other neurons of the nervous system as well.

Resting Membrane Potential of the Neuronal Soma. Figure 45–8 shows the soma of a spinal motor neuron, indicating a *resting membrane potential* of about –65 millivolts. This is somewhat less negative than the –90 millivolts found in large peripheral nerve fibers and in skeletal muscle fibers; the lower voltage is important because it allows both positive and negative control of the degree of excitability of the neuron. That is, decreasing the voltage to a less negative value makes the membrane of the neuron more excitable, whereas increasing this voltage to a more negative value makes the neuron less excitable. This is the basis for the two

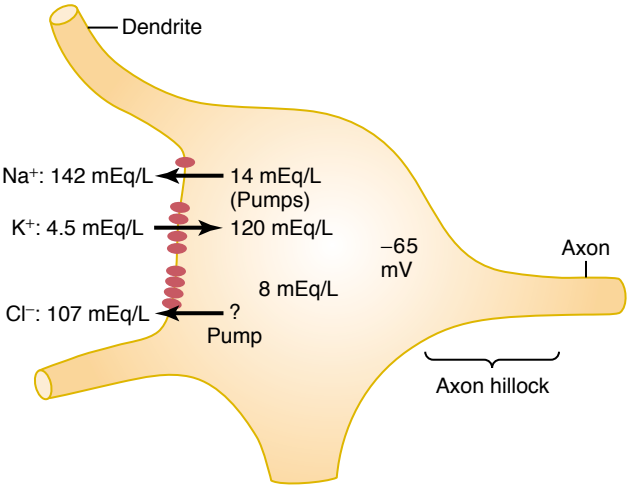


Figure 45–8

Distribution of sodium, potassium, and chloride ions across the neuronal somal membrane; origin of the intrasomal membrane potential.

modes of function of the neuron—either excitation or inhibition—as explained in detail in the next sections.

Concentration Differences of Ions Across the Neuronal Somal Membrane. Figure 45–8 also shows the concentration differences across the neuronal somal membrane of the three ions that are most important for neuronal function: sodium ions, potassium ions, and chloride ions. At the top, the *sodium ion concentration* is shown to be *high in the extracellular fluid* (142 mEq/L) but *low inside the neuron* (14 mEq/L). This sodium concentration gradient is caused by a strong somal membrane sodium pump that continually pumps sodium out of the neuron.

The figure also shows that *potassium ion concentration is high inside the neuronal soma* (120 mEq/L) but *low in the extracellular fluid* (4.5 mEq/L). It shows that there is a potassium pump (the other half of the Na^+-K^+ pump) that pumps potassium to the interior.

Figure 45–8 shows the *chloride ion* to be of *high concentration in the extracellular fluid* but *low concentration inside the neuron*. It also shows that the membrane is quite permeable to chloride ions and that there may be a weak chloride pump. Yet most of the reason for the low concentration of chloride ions inside the neuron is the –65 millivolts in the neuron. That is, this negative voltage repels the negatively charged chloride ions, forcing them outward through the pores until the concentration is much less inside the membrane than outside.

Let us recall at this point what we learned in Chapters 4 and 5 about the relation of ionic concentration differences to membrane potentials. It will be recalled that an electrical potential across the cell membrane can oppose movement of ions through a membrane if the potential is of proper polarity and magnitude. A potential that *exactly* opposes movement of an ion is called the *Nernst potential* for that ion; the equation for this is the following:

$$\text{EMF (mV)} = \pm 61 \times \log\left(\frac{\text{Concentration inside}}{\text{Concentration outside}}\right)$$

where EMF is the Nernst potential in millivolts on the *inside of the membrane*. The potential will be negative (–) for positive ions and positive (+) for negative ions.

Now, let us calculate the Nernst potential that will exactly oppose the movement of each of the three separate ions: sodium, potassium, and chloride.

For the sodium concentration difference shown in Figure 45–8, 142 mEq/L on the exterior and 14 mEq/L on the interior, the membrane potential that will exactly oppose sodium ion movement through the sodium channels calculates to be +61 millivolts. However, the actual membrane potential is –65 millivolts, not +61 millivolts. Therefore, those sodium ions that leak to the interior are immediately pumped back to the exterior by the sodium pump, thus maintaining the –65 millivolt negative potential inside the neuron.

For potassium ions, the concentration gradient is 120 mEq/L inside the neuron and 4.5 mEq/L outside. This calculates to a Nernst potential of –86 millivolts inside the neuron, which is more negative than the –65 that actually exists. Therefore, because of the high intracellular potassium ion concentration, there is a net tendency for potassium ions to diffuse to the outside of the neuron, but this is opposed by continual pumping of these potassium ions back to the interior.

Finally, the chloride ion gradient, 107 mEq/L outside and 8 mEq/L inside, yields a Nernst potential of –70 millivolts inside the neuron, which is only *slightly* more negative than the actual measured value of –65 millivolts. Therefore, chloride ions tend to leak very slightly to the interior of the neuron, but those few that do leak are moved back to the exterior, perhaps by an active chloride pump.

Keep these three Nernst potentials in mind and remember the direction in which the different ions tend to diffuse because this information is important in understanding both excitation and inhibition of the neuron by synapse activation or inactivation of ion channels.

Uniform Distribution of Electrical Potential Inside the Soma. The interior of the neuronal soma contains a highly conductive electrolytic solution, the *intracellular fluid* of the neuron. Furthermore, the diameter of the neuronal soma is large (from 10 to 80 micrometers), causing almost no resistance to conduction of electric current from one part of the somal interior to another part. Therefore, any change in potential in any part of the intrasomal fluid causes an almost exactly equal change in potential at all other points inside the soma (that is, as long as the neuron is not transmitting an action potential). This is an important principle, because it plays a major role in "summation" of signals entering the neuron from multiple sources, as we shall see in subsequent sections of this chapter.

Effect of Synaptic Excitation on the Postsynaptic Membrane—Excitatory Postsynaptic Potential. Figure 45–9*A* shows the resting neuron with an unexcited presynaptic terminal resting on its surface. The resting membrane potential everywhere in the soma is –65 millivolts.

Figure 45–9*B* shows a presynaptic terminal that has secreted an excitatory transmitter into the cleft between the terminal and the neuronal somal membrane. This transmitter acts on the membrane excitatory receptor *to increase the membrane's permeability to* Na^+. Because of the large sodium concentration gradient and large electrical negativity inside the neuron, sodium ions diffuse rapidly to the inside of the membrane.

The rapid influx of positively charged sodium ions to the interior neutralizes part of the negativity of the resting membrane potential. Thus, in Figure 45–9*B,* the resting membrane potential has increased in the positive direction from –65 to –45 millivolts. This positive increase in voltage above the normal resting neuronal potential—that is, to a less negative value—is called the *excitatory postsynaptic potential* (or EPSP), because if this potential rises high enough in the positive direction, it will elicit an action potential in the postsynaptic neuron, thus exciting it. (In this case, the

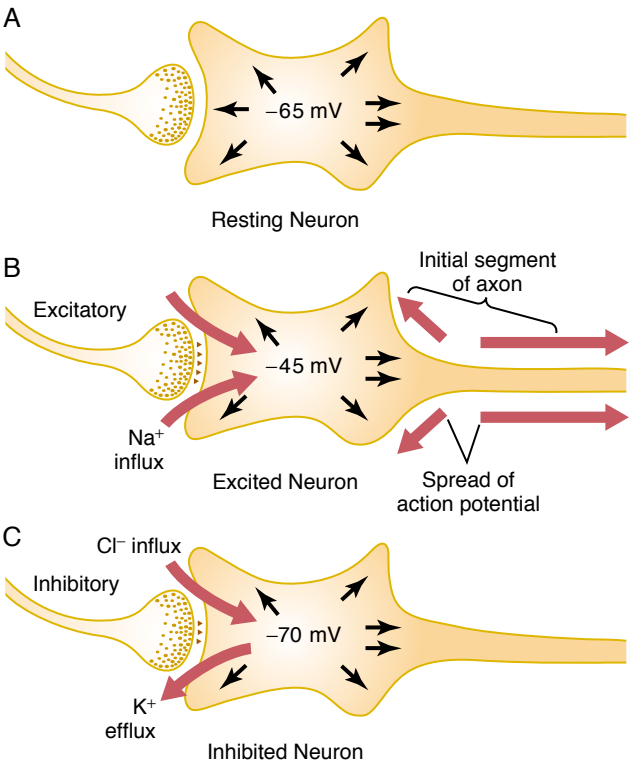


Figure 45–9

Three states of a neuron. *A*, *Resting neuron*, with a normal intraneuronal potential of –65 millivolts. *B*, Neuron in an *excited state*, with a less negative intraneuronal potential (–45 millivolts) caused by sodium influx. *C*, Neuron in an *inhibited state*, with a more negative intraneuronal membrane potential (–70 millivolts) caused by potassium ion efflux, chloride ion influx, or both.

EPSP is +20 millivolts—that is, 20 millivolts more positive than the resting value.)

However, we must issue a word of warning. Discharge of a single presynaptic terminal can never increase the neuronal potential from –65 millivolts all the way up to –45 millivolts. An increase of this magnitude requires simultaneous discharge of many terminals—about 40 to 80 for the usual anterior motor neuron—at the same time or in rapid succession. This occurs by a process called *summation*, which is discussed in detail in the next sections.

Generation of Action Potentials in the Initial Segment of the Axon Leaving the Neuron—Threshold for Excitation. When the EPSP rises high enough in the positive direction, there comes a point at which this initiates an action potential in the neuron. However, the action potential does not begin adjacent to the excitatory synapses. Instead, *it begins in the initial segment of the axon* where the axon leaves the neuronal soma. The main reason for this point of origin of the action potential is that the soma has relatively few voltage-gated sodium channels in its membrane, which makes it difficult for the EPSP to open the required number of sodium channels to elicit an action potential. Conversely, *the membrane of the initial segment* has seven times as great a concentration of voltage-gated sodium channels as does the soma and, therefore, can generate an action potential with much greater ease than can the soma. The EPSP that will elicit an action potential in the axon initial segment is between +10 and +20 millivolts. This is in contrast to the +30 or +40 millivolts or more required on the soma.

Once the action potential begins, it travels peripherally along the axon and usually also backward over the soma. In some instances, it travels backward into the dendrites, too, but not into all of them, because they, like the neuronal soma, have very few voltage-gated sodium channels and therefore frequently cannot generate action potentials at all. Thus, in Figure 45–9*B,* the *threshold* for excitation of the neuron is shown to be about –45 millivolts, which represents an EPSP of +20 millivolts—that is, 20 millivolts more positive than the normal resting neuronal potential of –65 millivolts.

Electrical Events During Neuronal Inhibition

Effect of Inhibitory Synapses on the Postsynaptic Membrane—Inhibitory Postsynaptic Potential. The inhibitory synapses *open mainly chloride channels,* allowing easy passage of chloride ions. Now, to understand how the inhibitory synapses inhibit the postsynaptic neuron, we must recall what we learned about the Nernst potential for chloride ions. We calculated the Nernst potential for chloride ions to be about –70 millivolts. This potential is more negative than the –65 millivolts normally present inside the resting neuronal membrane. Therefore, opening the chloride channels will allow negatively charged chloride ions to move from the extracellular fluid to the interior, which will make the interior membrane potential more negative than normal, approaching the –70 millivolt level.

Opening potassium channels will allow positively charged potassium ions to move to the exterior, and this will also make the interior membrane potential more negative than usual. Thus, both chloride influx and potassium efflux increase the degree of intracellular negativity, which is called *hyperpolarization*. This inhibits the neuron because the membrane potential is even more negative than the normal intracellular potential. Therefore, an increase in negativity beyond the normal resting membrane potential level is called an *inhibitory postsynaptic potential (IPSP)*.

Figure 45–9*C* shows the effect on the membrane potential caused by activation of inhibitory synapses, allowing chloride influx into the cell and/or potassium efflux out of the cell, with the membrane potential decreasing from its normal value of –65 millivolts to the more negative value of –70 millivolts. This membrane potential is 5 millivolts more negative than normal and is therefore an IPSP of –5 millivolts, which inhibits transmission of the nerve signal through the synapse.

Presynaptic Inhibition

In addition to inhibition caused by inhibitory synapses operating at the neuronal membrane, which is called *postsynaptic inhibition*, another type of inhibition often occurs at the presynaptic terminals before the signal ever reaches the synapse. This type of inhibition, called *presynaptic inhibition*, occurs in the following way.

Presynaptic inhibition is caused by release of an inhibitory substance onto the outsides of the presynaptic nerve fibrils before their own endings terminate on the postsynaptic neuron. In most instances, the inhibitory transmitter substance is GABA (gamma-aminobutyric acid). This has a specific effect of opening anion channels, allowing large numbers of chloride ions to diffuse into the terminal fibril. The negative charges of these ions inhibit synaptic transmission because they cancel much of the excitatory effect of the positively charged sodium ions that also enter the terminal fibrils when an action potential arrives.

Presynaptic inhibition occurs in many of the sensory pathways in the nervous system. In fact, adjacent sensory nerve fibers often mutually inhibit one another, which minimizes sideways spread and mixing of signals in sensory tracts. We discuss the importance of this phenomenon more fully in subsequent chapters.

Time Course of Postsynaptic Potentials

When an excitatory synapse excites the anterior motor neuron, the neuronal membrane becomes highly permeable to sodium ions for 1 to 2 milliseconds. During this very short time, enough sodium ions diffuse rapidly to the interior of the postsynaptic motor neuron to increase its intraneuronal potential by a few millivolts, thus creating the excitatory postsynaptic potential (EPSP) shown by the blue and green curves of Figure 45–10. This potential then slowly declines over the next 15 milliseconds because this is the time required for the excess positive charges to leak out of the excited neuron and to re-establish the normal resting membrane potential.

Precisely the opposite effect occurs for an IPSP; that is, the inhibitory synapse increases the permeability of the membrane to potassium or chloride ions, or both, for 1 to 2 milliseconds, and this decreases the intraneuronal potential to a more negative value than normal, thereby creating the IPSP. This potential also dies away in about 15 milliseconds.

Other types of transmitter substances can excite or inhibit the postsynaptic neuron for much longer periods—for hundreds of milliseconds or even for seconds, minutes, or hours. This is especially true for some of the neuropeptide types of transmitter substances.

"Spatial Summation" in Neurons—Threshold for Firing

Excitation of a single presynaptic terminal on the surface of a neuron almost never excites the neuron. The reason for this is that sufficient transmitter substance is released by a single terminal to cause an EPSP usually no greater than 0.5 to 1 millivolt, instead of the 10 to 20 millivolts normally required to reach threshold for excitation. However, many presynaptic terminals are usually stimulated at the same time. Even though these terminals are spread over wide areas of the neuron, their effects can still *summate;* that is, they can add to one another until neuronal excitation does occur. The reason for this is the following: It was pointed out earlier that a change in potential at any single point within the soma will cause the potential to change everywhere inside the soma almost exactly equally. This is true because of the very high electrical conductivity inside the large neuronal cell body. Therefore, for each excitatory synapse that discharges simultaneously, the total intrasomal potential becomes more positive by 0.5 to 1.0 millivolt. When

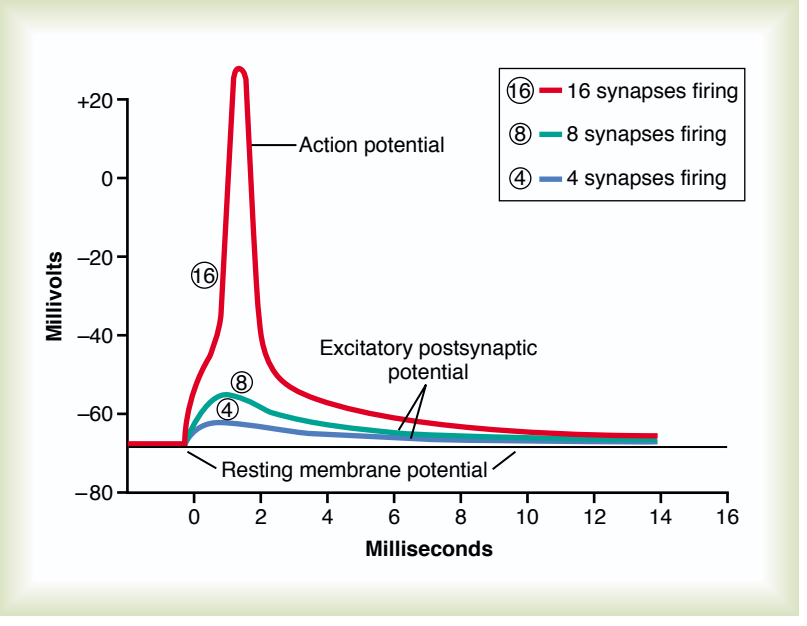


Figure 45–10

Excitatory postsynaptic potentials, showing that simultaneous firing of only a few synapses will not cause sufficient summated potential to elicit an action potential, but that simultaneous firing of many synapses will raise the summated potential to threshold for excitation and cause a superimposed action potential.

the EPSP becomes great enough, the *threshold for firing* will be reached and an action potential will develop spontaneously in the initial segment of the axon. This is demonstrated in Figure 45–10. The bottom postsynaptic potential in the figure was caused by simultaneous stimulation of 4 synapses; the next higher potential was caused by stimulation of 8 synapses; finally, a still higher EPSP was caused by stimulation of 16 synapses. In this last instance, the firing threshold had been reached, and an action potential was generated in the axon.

This effect of summing simultaneous postsynaptic potentials by activating multiple terminals on widely spaced areas of the neuronal membrane is called *spatial summation*.

"Temporal Summation"

Each time a presynaptic terminal fires, the released transmitter substance opens the membrane channels for at most a millisecond or so. But the changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed. Therefore, a second opening of the same channels can increase the postsynaptic potential to a still greater level, and the more rapid the rate of stimulation, the greater the postsynaptic potential becomes. Thus, successive discharges from a single presynaptic terminal, if they occur rapidly enough, can add to one another; that is, they can "summate." This type of summation is called *temporal summation*.

Simultaneous Summation of Inhibitory and Excitatory Postsynaptic Potentials. If an IPSP is tending to *decrease* the membrane potential to a more negative value while an EPSP is tending to *increase* the potential at the same time, these two effects can either completely or partially nullify each other. Thus, if a neuron is being excited by an EPSP, an inhibitory signal from another source can often reduce the postsynaptic potential to less than threshold value for excitation, thus turning off the activity of the neuron.

"Facilitation" of Neurons

Often the summated postsynaptic potential is excitatory but has not risen high enough to reach the threshold for firing by the postsynaptic neuron. When this happens, the neuron is said to be *facilitated*. That is, its membrane potential is nearer the threshold for firing than normal, but not yet at the firing level. Consequently, another excitatory signal entering the neuron from some other source can then excite the neuron very easily. Diffuse signals in the nervous system often do facilitate large groups of neurons so that they can respond quickly and easily to signals arriving from other sources.

Special Functions of Dendrites for Exciting Neurons

Large Spatial Field of Excitation of the Dendrites. The dendrites of the anterior motor neurons often extend 500 to 1000 micrometers in all directions from the neuronal soma. And these dendrites can receive signals from a large spatial area around the motor neuron. This provides a vast opportunity for summation of signals from many separate presynaptic nerve fibers.

It is also important that between 80 and 95 per cent of all the presynaptic terminals of the anterior motor neuron terminate on dendrites, in contrast to only 5 to 20 per cent terminating on the neuronal soma. Therefore, the preponderant share of the excitation is provided by signals transmitted by way of the dendrites.

Most Dendrites Cannot Transmit Action Potentials—But They Can Transmit Signals Within the Same Neuron by Electrotonic Conduction. Most dendrites fail to transmit action potentials because their membranes have relatively few voltage-gated sodium channels, and their thresholds for excitation are too high for action potentials to occur. Yet they do transmit *electrotonic current* down the dendrites to the soma. Transmission of electrotonic current means direct spread of electrical current by ion conduction in the fluids of the dendrites but without generation of action potentials. Stimulation (or inhibition) of the neuron by this current has special characteristics, as follows.

Decrement of Electrotonic Conduction in the Dendrites—Greater Excitatory (or Inhibitory) Effect by Synapses Located Near the Soma. In Figure 45–11, multiple excitatory and inhibitory synapses are shown stimulating the dendrites of a neuron. On the two dendrites to the left, there are excitatory effects near the tip ends; note the high levels of excitatory postsynaptic potentials at these ends—that is, note the *less negative* membrane potentials at these points. However, a

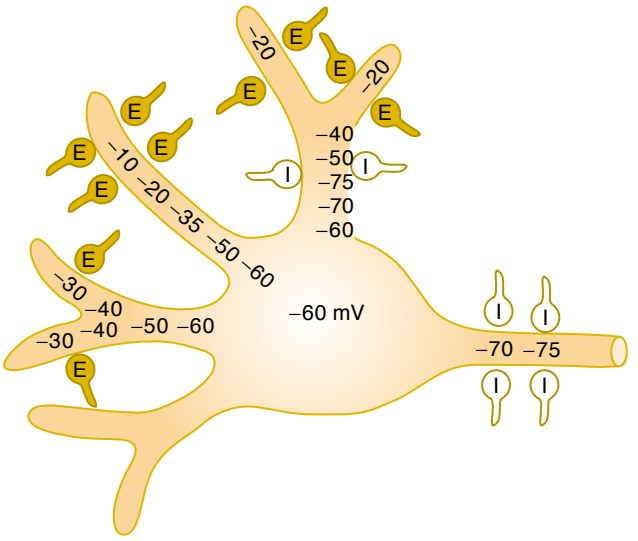


Figure 45–11

Stimulation of a neuron by presynaptic terminals located on dendrites, showing, especially, decremental conduction of excitatory (E) electrotonic potentials in the two dendrites to the left and inhibition (I) of dendritic excitation in the dendrite that is uppermost. A powerful effect of inhibitory synapses at the initial segment of the axon is also shown.

large share of the excitatory postsynaptic potential is lost before it reaches the soma. The reason is that the dendrites are long, and their membranes are thin and at least partially permeable to potassium and chloride ions, making them "leaky" to electric current. Therefore, before the excitatory potentials can reach the soma, a large share of the potential is lost by leakage through the membrane. This decrease in membrane potential as it spreads electrotonically along dendrites toward the soma is called *decremental conduction*.

The farther the excitatory synapse is from the soma of the neuron, the greater will be the decrement, and the less will be excitatory signal reaching the soma. Therefore, those synapses that lie near the soma have far more effect in causing neuron excitation or inhibition than those that lie far away from the soma.

Summation of Excitation and Inhibition in Dendrites. The uppermost dendrite of Figure 45–11 is shown to be stimulated by both excitatory and inhibitory synapses. At the tip of the dendrite is a strong excitatory postsynaptic potential, but nearer the soma are two inhibitory synapses acting on the same dendrite. These inhibitory synapses provide a hyperpolarizing voltage that completely nullifies the excitatory effect and indeed transmits a small amount of inhibition by electrotonic conduction toward the soma. Thus, dendrites can summate excitatory and inhibitory postsynaptic potentials in the same way that the soma can. Also shown in the figure are several inhibitory synapses located directly on the axon hillock and initial axon segment. This location provides especially powerful inhibition because it has the direct effect of increasing the threshold for excitation at the very point where the action potential is normally generated.

Relation of State of Excitation of the Neuron to Rate of Firing

"Excitatory State." The "excitatory state" of a neuron is defined as the summated degree of excitatory drive to the neuron. If there is a higher degree of excitation than inhibition of the neuron at any given instant, then it is said that there is an *excitatory state*. Conversely, if there is more inhibition than excitation, then it is said that there is an *inhibitory state*.

When the excitatory state of a neuron rises above the threshold for excitation, the neuron will fire repetitively as long as the excitatory state remains at that level. Figure 45–12 shows responses of three types of neurons to varying levels of excitatory state. Note that neuron 1 has a low threshold for excitation, whereas neuron 3 has a high threshold. But note also that neuron 2 has the lowest maximum frequency of discharge, whereas neuron 3 has the highest maximum frequency.

Some neurons in the central nervous system fire continuously because even the normal excitatory state is above the threshold level. Their frequency of firing can usually be increased still more by further increasing their excitatory state. The frequency can be decreased, or firing can even be stopped, by superimposing an inhibitory state on the neuron. Thus, different neurons respond differently, have different thresholds for excitation, and have widely differing maximum frequencies of discharge. With a little imagination, one can readily understand the importance of having different neurons with these many types of response characteristics to perform the widely varying functions of the nervous system.

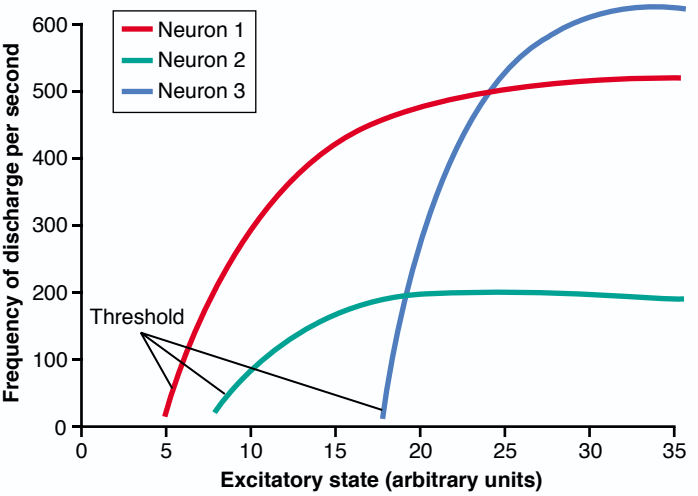


Figure 45–12

Response characteristics of different types of neurons to different levels of excitatory state.

Some Special Characteristics of Synaptic Transmission

Fatigue of Synaptic Transmission. When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the postsynaptic neuron is at first very great, but the firing rate becomes progressively less in succeeding milliseconds or seconds. This is called *fatigue* of synaptic transmission.

Fatigue is an exceedingly important characteristic of synaptic function because when areas of the nervous system become overexcited, fatigue causes them to lose this excess excitability after awhile. For example, fatigue is probably the most important means by which the excess excitability of the brain during an epileptic seizure is finally subdued so that the seizure ceases. Thus, the development of fatigue is a protective mechanism against excess neuronal activity. This is discussed further in the description of reverberating neuronal circuits in Chapter 46.

The mechanism of fatigue is mainly exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals. The excitatory terminals on many neurons can store enough excitatory transmitter to cause only about 10,000 action potentials, and the transmitter can be exhausted in only a few seconds to a few minutes of rapid stimulation. Part of the fatigue process probably results from two other factors as well: (1) progressive inactivation of many of the postsynaptic membrane receptors and (2) slow development of abnormal concentrations of ions inside the *postsynaptic* neuronal cell.

Effect of Acidosis or Alkalosis on Synaptic Transmission. Most neurons are highly responsive to changes in pH of the surrounding interstitial fluids. *Normally*, *alkalosis greatly increases neuronal excitability.* For instance, a rise in arterial blood pH from the 7.4 norm to 7.8 to 8.0 often causes cerebral epileptic seizures because of increased excitability of some or all of the cerebral neurons. This can be demonstrated especially well by asking a person who is predisposed to epileptic seizures to overbreathe. The overbreathing blows off carbon dioxide and therefore elevates the pH of the blood momentarily, but even this short time can often precipitate an epileptic attack.

Conversely, *acidosis greatly depresses neuronal activity;* a fall in pH from 7.4 to below 7.0 usually causes a comatose state. For instance, in very severe diabetic or uremic acidosis, coma virtually always develops.

Effect of Hypoxia on Synaptic Transmission. Neuronal excitability is also highly dependent on an adequate supply of oxygen. Cessation of oxygen for only a few seconds can cause complete inexcitability of some neurons. This is observed when the brain's blood flow is temporarily interrupted, because within 3 to 7 seconds, the person becomes unconscious.

Effect of Drugs on Synaptic Transmission. Many drugs are known to increase the excitability of neurons, and others are known to decrease excitability. For instance, *caffeine*, *theophylline*, and *theobromine*, which are found in coffee, tea, and cocoa, respectively, all *increase* neuronal excitability, presumably by reducing the threshold for excitation of neurons.

Strychnine is one of the best known of all agents that increase excitability of neurons. However, it does not do this by reducing the threshold for excitation of the neurons; instead, it *inhibits the action of some normally inhibitory transmitter substances*, especially the inhibitory effect of glycine in the spinal cord. Therefore, the effects of the excitatory transmitters become overwhelming, and the neurons become so excited that they go into rapidly repetitive discharge, resulting in severe tonic muscle spasms.

Most anesthetics increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system. Because many of the anesthetics are especially lipid-soluble, it has been reasoned that some of them might change the physical characteristics of the neuronal membranes, making them less responsive to excitatory agents.

Synaptic Delay. During transmission of a neuronal signal from a presynaptic neuron to a postsynaptic neuron, a certain amount of time is consumed in the process of (1) discharge of the transmitter substance by the presynaptic terminal, (2) diffusion of the transmitter to the postsynaptic neuronal membrane, (3) action of the transmitter on the membrane receptor, (4) action of the receptor to increase the membrane permeability, and (5) inward diffusion of sodium to raise the excitatory postsynaptic potential to a high enough level to elicit an action potential. The *minimal* period of time required for all these events to take place, even when large numbers of excitatory synapses are stimulated simultaneously, is about 0.5 millisecond. This is called the *synaptic delay.* Neurophysiologists can measure the *minimal* delay time between an input volley of impulses into a pool of neurons and the consequent output volley. From the measure of delay time, one can then estimate the number of series neurons in the circuit.

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