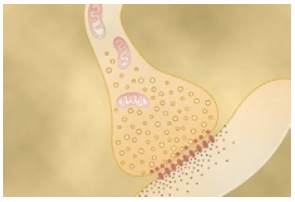
Organization of the Nervous System, Basic Functions of Synapses, and Neurotransmitters



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.

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 experiences that excite *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. These sensory experiences can either cause immediate reactions from the brain, or memories of the experiences 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.

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

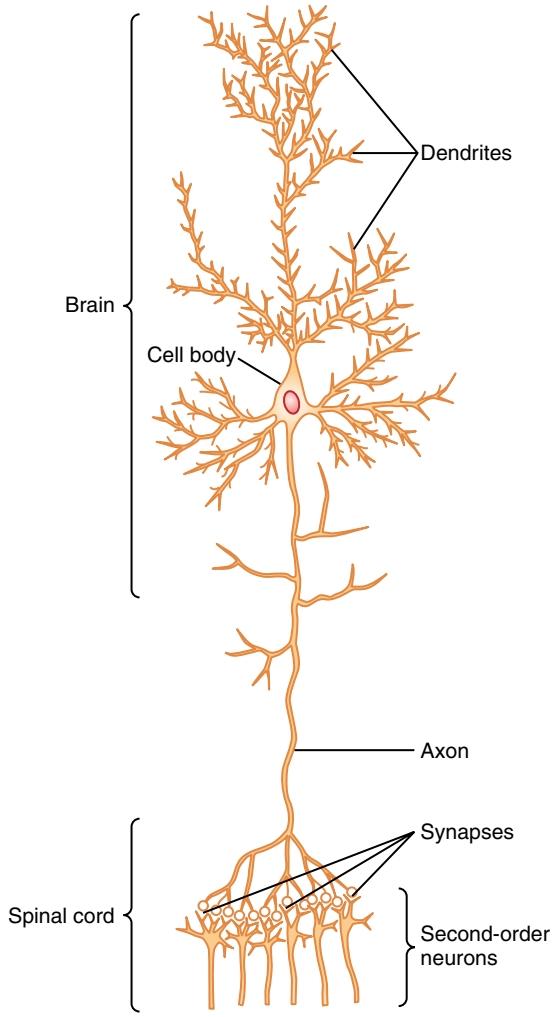


Figure 45-1 Structure of a large neuron in the brain, showing its important functional parts. (Redrawn from Guyton AC: Basic Neuroscience: Anatomy and Physiology. Philadelphia: WB Saunders, 1987.)

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 percent of all sensory information is discarded by the brain as irrelevant and unimportant. For instance, one is ordinarily unaware of the 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,

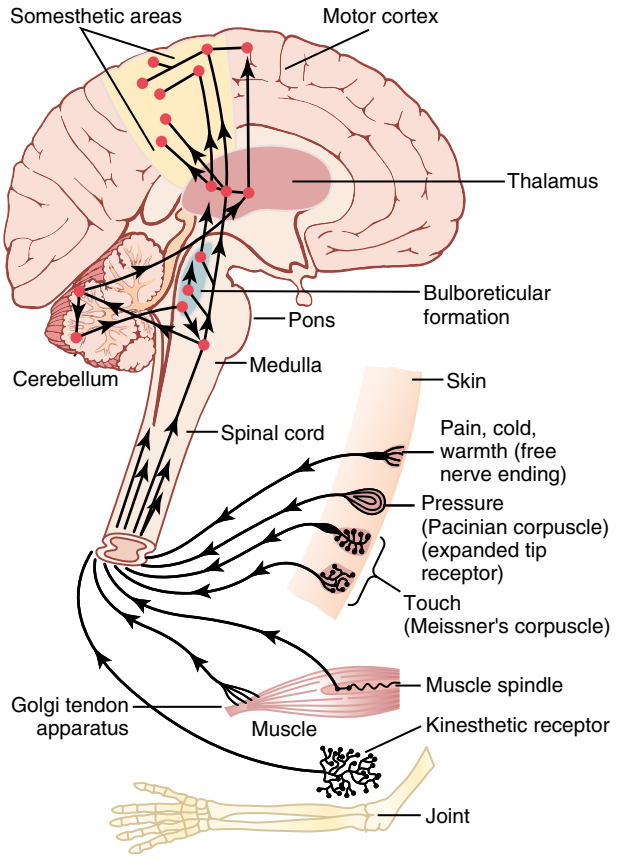


Figure 45-2 Somatosensory axis of the nervous system.

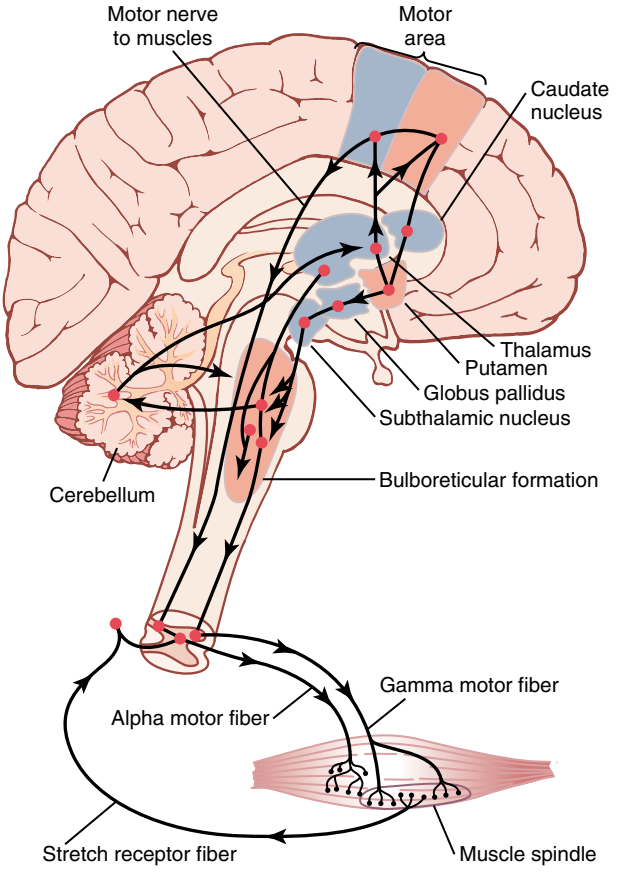


Figure 45-3 Skeletal motor nerve axis of the nervous system.

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 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 in 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. 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.

The precise mechanisms by which long-term facilitation of synapses occurs in the memory process are still uncertain, but what is known about this and other details of the sensory memory process is 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, as well as 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,* which 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.

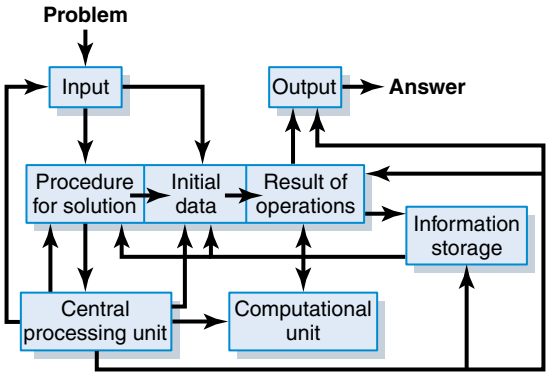


Figure 45-4 Block diagram of a general-purpose computer, showing the basic components and their interrelations.

Central Nervous System Synapses

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 percent of them on the dendrites and only 5 to 20 percent on the soma. These presynaptic terminals are the ends of nerve fibrils that originate from many other neurons. Many 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 postsynaptic 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 synthesizing new transmitter substance.

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

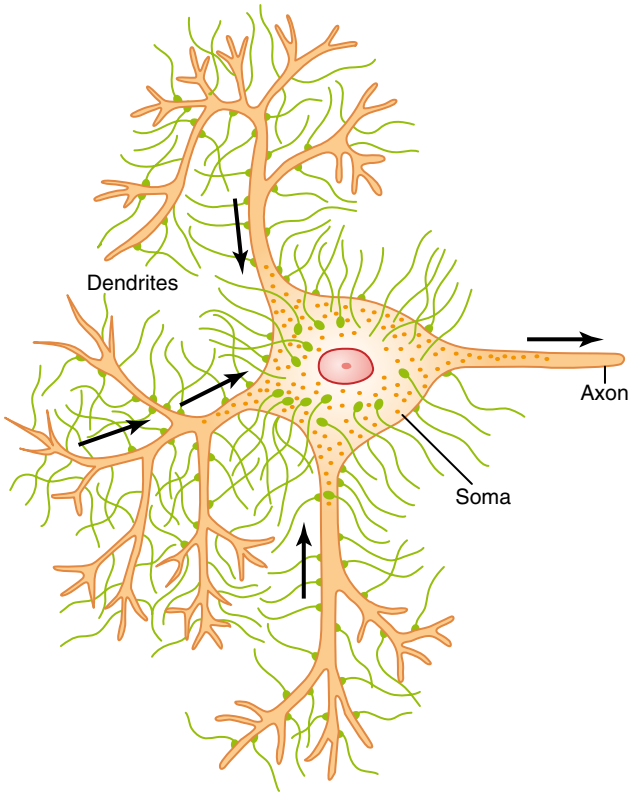


Figure 45-5 Typical anterior motor neuron, showing presynaptic terminals on the neuronal soma and dendrites. Note also the single axon.

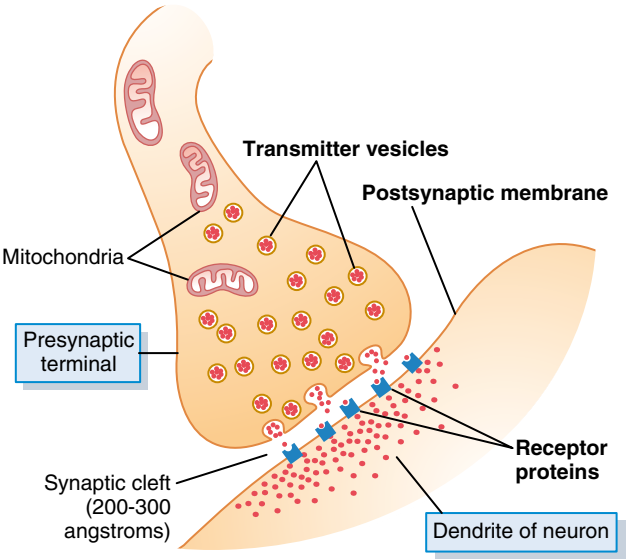


Figure 45-6 Physiologic anatomy of the synapse.

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

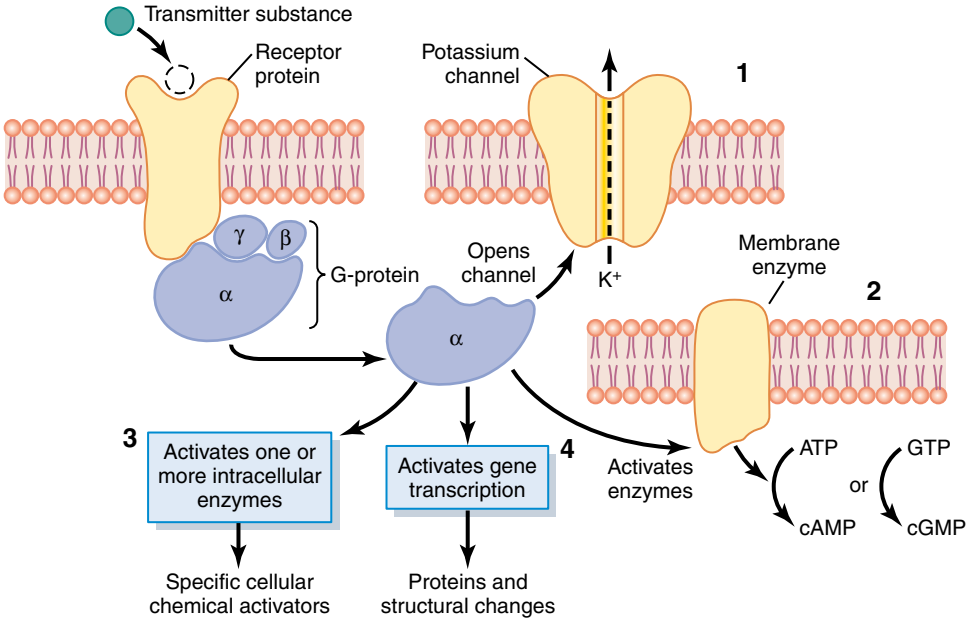


Figure 45-7 "Second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first releasing a "G-protein" into the second neuron's cytoplasm. Four subsequent possible effects of the G-protein are shown, including *1,* opening an ion channel in the membrane 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.

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.
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 and 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.

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

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.

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. 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

Neuropeptides are synthesized differently and have actions that 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 modes of function of the neuron—either excitation or inhibition—as explained in detail in the next sections.

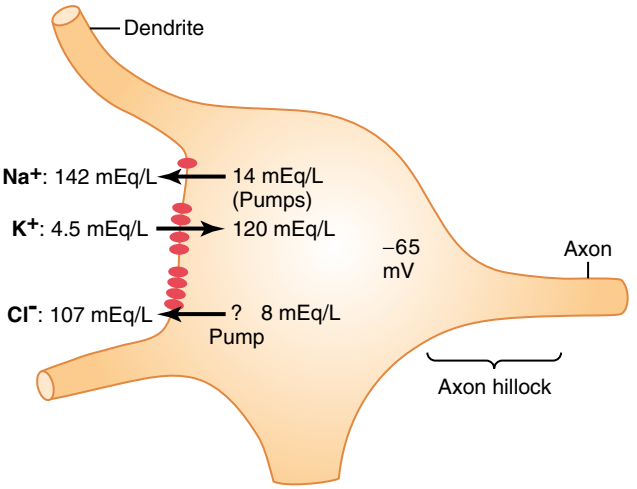


Figure 45-8 Distribution of sodium, potassium, and chloride ions across the neuronal somal membrane; origin of the intrasomal membrane potential.

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.* The membrane may be somewhat permeable to chloride ions and 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 from Chapters 4 and 5 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 be 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 (i.e., 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

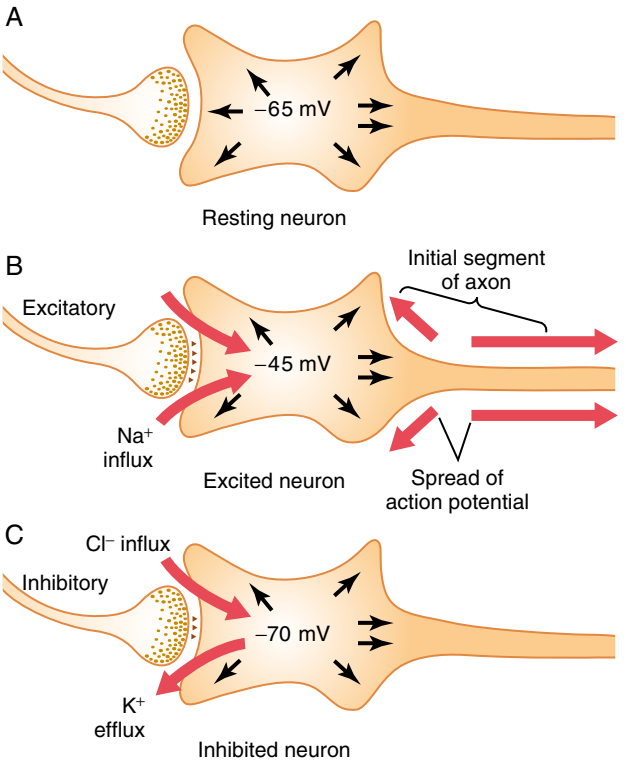


Figure 45-9 Three states of a neuron. *A*, *Resting neuron,* with a normal intraneuronal potential of −65 millivolts. *B*, Neuron in an *excited state,* with a less negative intraneuronal potential (−45 millivolts) caused by sodium influx. *C*, Neuron in an *inhibited state,* with a more negative intraneuronal membrane potential (−70 millivolts) caused by potassium ion efflux, chloride ion influx, or both.

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 EPSP is +20 millivolts—i.e., 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 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

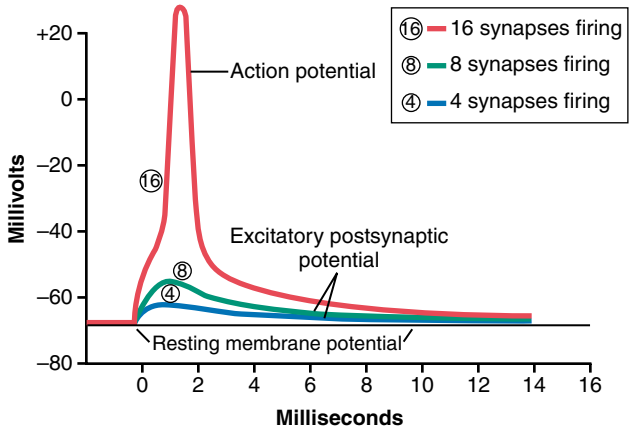


Figure 45-10 Excitatory postsynaptic potentials, showing that simultaneous firing of only a few synapses will not cause sufficient summated potential to elicit an action potential, but that simultaneous firing of many synapses will raise the summated potential to threshold for excitation and cause a superimposed action potential.

periods—for hundreds of milliseconds or even for seconds, minutes, or hours. This is especially true for some of the neuropeptide transmitters.

"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 the amount of transmitter substance released by a single terminal to cause an EPSP is 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 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 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" Caused by Successive Discharges of a Presynaptic Terminal

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 percent of all the presynaptic terminals of the anterior motor neuron terminate on dendrites, in contrast to only 5 to 20 percent terminating on the neuronal soma. Therefore, a large

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 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

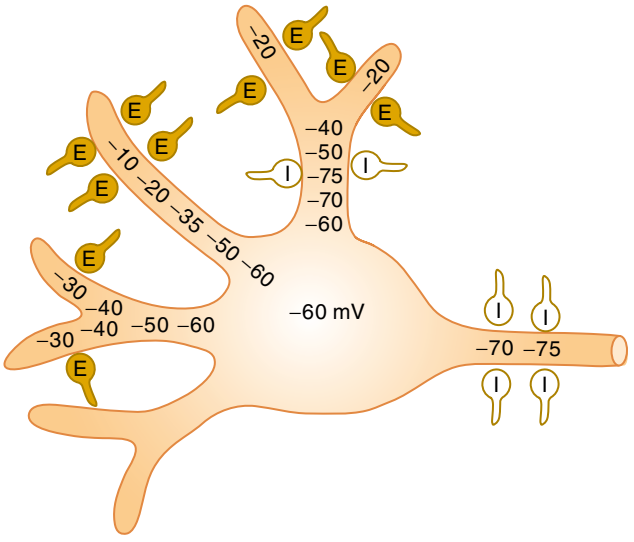


Figure 45-11 Stimulation of a neuron by presynaptic terminals located on dendrites, showing, especially, decremental conduction of excitatory (*E*) electrotonic potentials in the two dendrites to the left and inhibition (*I*) of dendritic excitation in the dendrite that is uppermost. A powerful effect of inhibitory synapses at the initial segment of the axon is also shown.

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 lesser 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

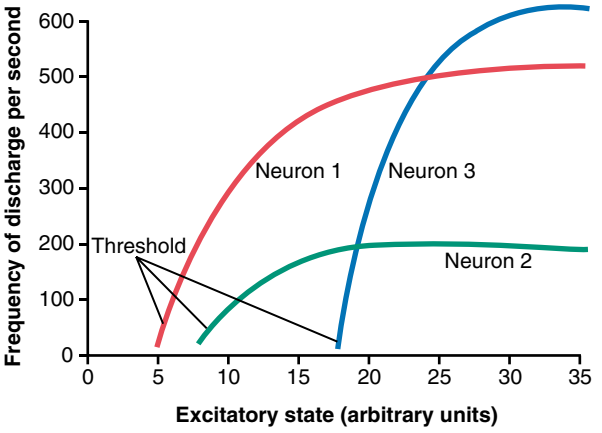


Figure 45-12 Response characteristics of different types of neurons to different levels of excitatory state.

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.

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 a while. 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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CHAPTER 46

Sensory Receptors, Neuronal Circuits for Processing Information

Input to the nervous system is provided by sensory receptors that detect such sensory stimuli as touch, sound, light, pain, cold, and warmth. The purpose of this chapter is to discuss the basic mechanisms by which these receptors change sensory stimuli into nerve signals that are then conveyed to and processed in the central nervous system.

Types of Sensory Receptors and the Stimuli They Detect

Table 46-1 lists and classifies five basic types of sensory receptors: (1) *mechanoreceptors,* which detect mechanical compression or stretching of the receptor or of tissues adjacent to the receptor; (2) *thermoreceptors,* which detect changes in temperature, with some receptors detecting cold and others warmth; (3) *nociceptors* (pain receptors), which detect damage occurring in the tissues, whether physical damage or chemical damage; (4) *electromagnetic receptors,* which detect light on the retina of the eye; and (5) *chemoreceptors,* which detect taste in the mouth, smell in the nose, oxygen level in the arterial blood, osmolality of the body fluids, carbon dioxide concentration, and other factors that make up the chemistry of the body.

In this chapter, we discuss the function of a few specific types of receptors, primarily peripheral mechanoreceptors, to illustrate some of the principles by which receptors operate. Other receptors are discussed in other chapters in relation to the sensory systems that they subserve. Figure 46-1 shows some of the types of mechanoreceptors found in the skin or in deep tissues of the body.

Differential Sensitivity of Receptors

How do two types of sensory receptors detect different types of sensory stimuli? The answer is, by *"differential sensitivities."* That is, each type of receptor is highly sensitive to one type of stimulus for which it is designed and yet is almost nonresponsive to other types of sensory stimuli. Thus, the rods and cones of the eyes are highly responsive to light but are almost completely nonresponsive to normal ranges of heat, cold, pressure on the eyeballs, or chemical changes in the blood. The osmoreceptors of the supraoptic nuclei in the hypothalamus detect minute changes in the osmolality of the body fluids but have never been known to respond to sound. Finally, pain receptors in the skin are almost never stimulated by usual touch or pressure stimuli but do become highly active the moment tactile stimuli become severe enough to damage the tissues.

Modality of Sensation—The "Labeled Line" Principle

Each of the principal types of sensation that we can experience—pain, touch, sight, sound, and so forth—is called a *modality* of sensation. Yet despite the fact that we experience these different modalities of sensation, nerve fibers transmit only impulses. Therefore, how do different nerve fibers transmit different modalities of sensation?

The answer is that each nerve tract terminates at a specific point in the central nervous system, and the type of sensation felt when a nerve fiber is stimulated is determined by the point in the nervous system to which the fiber leads. For instance, if a pain fiber is stimulated, the person perceives pain regardless of what type of stimulus excites the fiber. The stimulus can be electricity, overheating of the fiber, crushing of the fiber, or stimulation of the pain nerve ending by damage to the tissue cells. In all these instances, the person perceives pain. Likewise, if a touch fiber is stimulated by electrical excitation of a touch receptor or in any other way, the person perceives touch because touch fibers lead to specific touch areas in the brain. Similarly, fibers from the retina of the eye terminate in the vision areas of the brain, fibers from the ear terminate in the auditory areas of the brain, and temperature fibers terminate in the temperature areas.

This specificity of nerve fibers for transmitting only one modality of sensation is called the *labeled line principle.*

Table 46-1 Classification of Sensory Receptors

- **I. Mechanoreceptors**
  - Skin tactile sensibilities (epidermis and dermis)
    - Free nerve endings
    - Expanded tip endings
      - Merkel's discs
      - Plus several other variants
    - Spray endings
    - Ruffini's endings
    - Encapsulated endings
      - Meissner's corpuscles
      - Krause's corpuscles
    - Hair end-organs
  - Deep tissue sensibilities
    - Free nerve endings
    - Expanded tip endings
    - Spray endings
      - Ruffini's endings
    - Encapsulated endings
      - Pacinian corpuscles
      - Plus a few other variants
    - Muscle endings
      - Muscle spindles
      - Golgi tendon receptors
  - Hearing
    - Sound receptors of cochlea
  - Equilibrium
    - Vestibular receptors
  - Arterial pressure
    - Baroreceptors of carotid sinuses and aorta
- **II. Thermoreceptors**
  - Cold
    - Cold receptors
  - Warmth
    - Warm receptors
- **III. Nociceptors**
  - Pain
    - Free nerve endings
- **IV. Electromagnetic receptors**
  - Vision
    - Rods
    - Cones
- **V. Chemoreceptors**
  - Taste
    - Receptors of taste buds
  - Smell
    - Receptors of olfactory epithelium
  - Arterial oxygen
    - Receptors of aortic and carotid bodies
  - Osmolality
    - Neurons in or near supraoptic nuclei
  - Blood CO_2
    - Receptors in or on surface of medulla and in aortic and carotid bodies
  - Blood glucose, amino acids, fatty acids
    - Receptors in hypothalamus

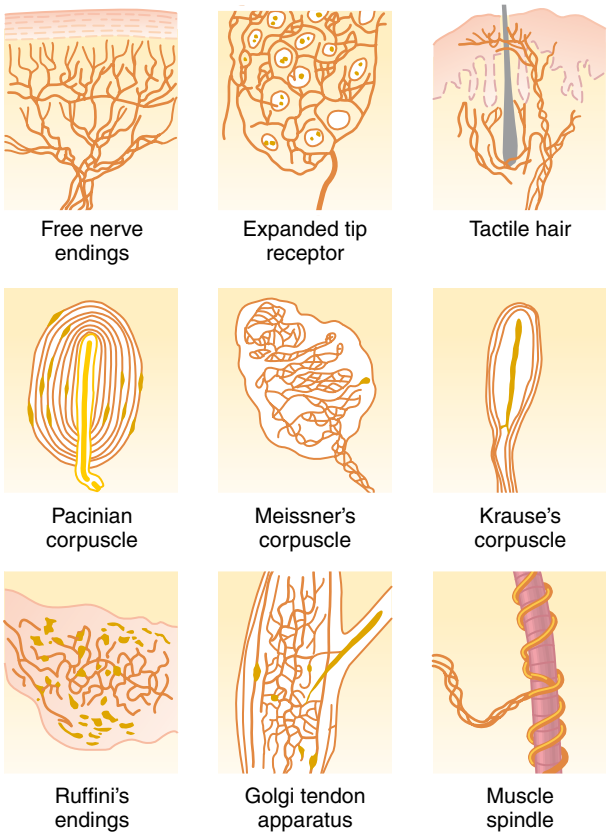

Figure 46-1 Several types of somatic sensory nerve endings.

Transduction of Sensory Stimuli into Nerve Impulses

Local Electrical Currents at Nerve Endings—Receptor Potentials

All sensory receptors have one feature in common. Whatever the type of stimulus that excites the receptor, its immediate effect is to change the membrane electrical potential of the receptor. This change in potential is called a *receptor potential.*

Mechanisms of Receptor Potentials. Different receptors can be excited in one of several ways to cause receptor potentials: (1) by mechanical deformation of the receptor, which stretches the receptor membrane and opens ion channels; (2) by application of a chemical to the membrane, which also opens ion channels; (3) by change of the temperature of the membrane, which alters the permeability of the membrane; or (4) by the effects of electromagnetic radiation, such as light on a retinal visual receptor, which either directly or indirectly changes the receptor membrane characteristics and allows ions to flow through membrane channels.

These four means of exciting receptors correspond in general with the different types of known sensory receptors. In all instances, the basic cause of the change in membrane potential is a change in membrane permeability of the receptor, which allows ions to diffuse more or

less readily through the membrane and thereby to change the *transmembrane potential.*

Maximum Receptor Potential Amplitude. The maximum amplitude of most sensory receptor potentials is about 100 millivolts, but this level occurs only at an extremely high intensity of sensory stimulus. This is about the same maximum voltage recorded in action potentials and is also the change in voltage when the membrane becomes maximally permeable to sodium ions.

Relation of the Receptor Potential to Action Potentials. When the receptor potential rises above the *threshold* for eliciting action potentials in the nerve fiber attached to the receptor, then action potentials occur, as illustrated in Figure 46-2. Note also that the more the receptor potential rises above the threshold level, the greater becomes the *action potential frequency.*

Receptor Potential of the Pacinian Corpuscle—An Example of Receptor Function

The student should at this point restudy the anatomical structure of the pacinian corpuscle shown in Figure 46-1. Note that the corpuscle has a central nerve fiber extending through its core. Surrounding this are multiple concentric capsule layers, so compression anywhere on the outside of the corpuscle will elongate, indent, or otherwise deform the central fiber.

Now study Figure 46-3, which shows only the central fiber of the pacinian corpuscle after all capsule layers but one have been removed. The tip of the central fiber inside the capsule is unmyelinated, but the fiber does become myelinated (the blue sheath shown in the figure) shortly before leaving the corpuscle to enter a peripheral sensory nerve.

The figure also shows the mechanism by which a receptor potential is produced in the pacinian corpuscle. Observe the small area of the terminal fiber that has been deformed by compression of the corpuscle, and note that ion channels have opened in the membrane, allowing

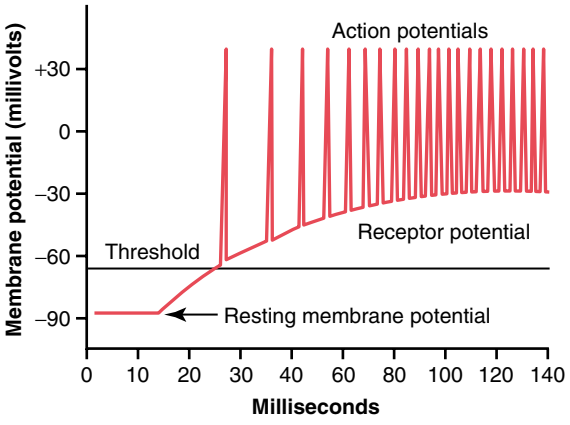

Figure 46-2 Typical relation between receptor potential and action potentials when the receptor potential rises above threshold level.

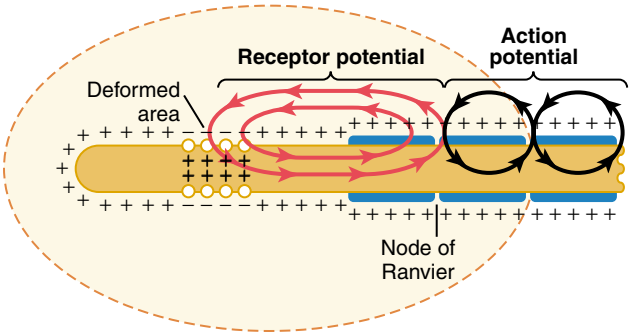

Figure 46-3 Excitation of a sensory nerve fiber by a receptor potential produced in a pacinian corpuscle. (Modified from Loëwenstein WR: Excitation and inactivation in a receptor membrane. Ann N Y Acad Sci 94:510, 1961.)

positively charged sodium ions to diffuse to the interior of the fiber. This creates increased positivity inside the fiber, which is the "receptor potential." The receptor potential in turn induces a *local circuit* of current flow, shown by the arrows, that spreads along the nerve fiber. At the first node of Ranvier, which itself lies inside the capsule of the pacinian corpuscle, the local current flow depolarizes the fiber membrane at this node, which then sets off typical action potentials that are transmitted along the nerve fiber toward the central nervous system.

Relation Between Stimulus Intensity and the Receptor Potential. Figure 46-4 shows the changing amplitude of the receptor potential caused by progressively stronger mechanical compression (increasing "stimulus strength") applied experimentally to the central core of a pacinian corpuscle. Note that the amplitude increases rapidly at first but then progressively less rapidly at high stimulus strength.

In turn, the *frequency of repetitive action potentials* transmitted from sensory receptors increases approximately in

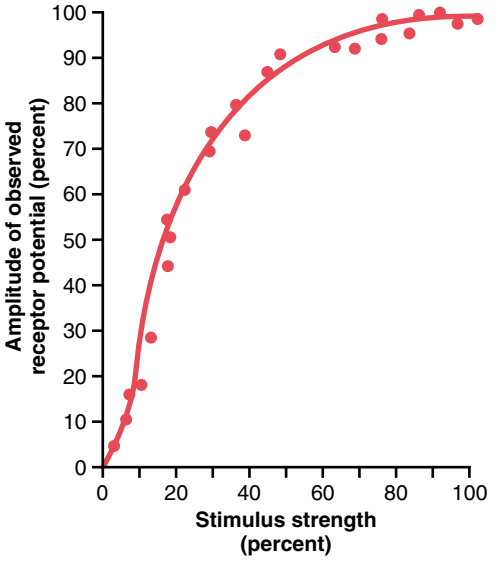

Figure 46-4 Relation of amplitude of receptor potential to strength of a mechanical stimulus applied to a pacinian corpuscle. (Data from Loëwenstein WR: Excitation and inactivation in a receptor membrane. Ann N Y Acad Sci 94:510, 1961.)

proportion to the increase in receptor potential. Putting this principle together with the data in Figure 46-4, one can see that very intense stimulation of the receptor causes progressively less and less additional increase in numbers of action potentials. This is an exceedingly important principle that is applicable to almost all sensory receptors. It allows the receptor to be sensitive to very weak sensory experience and yet not reach a maximum firing rate until the sensory experience is extreme. This allows the receptor to have an extreme range of response, from very weak to very intense.

Adaptation of Receptors

Another characteristic of all sensory receptors is that they *adapt* either partially or completely to any constant stimulus after a period of time. That is, when a continuous sensory stimulus is applied, the receptor responds at a high impulse rate at first and then at a progressively slower rate until finally the rate of action potentials decreases to very few or often to none at all.

Figure 46-5 shows typical adaptation of certain types of receptors. Note that the pacinian corpuscle adapts very rapidly, hair receptors adapt within a second or so, and some joint capsule and muscle spindle receptors adapt slowly.

Furthermore, some sensory receptors adapt to a far greater extent than others. For example, the pacinian corpuscles adapt to "extinction" within a few hundredths of a second, and the receptors at the bases of the hairs adapt to extinction within a second or more. It is probable that all other *mechanoreceptors* eventually adapt almost completely, but some require hours or days to do so, for which reason they are called "nonadapting" receptors. The longest measured time for almost complete adaptation of a mechanoreceptor is about 2 days, which is the adaptation time for many carotid and aortic baroreceptors. Conversely, some of the nonmechanoreceptors—the chemoreceptors and pain receptors, for instance—probably never adapt completely.

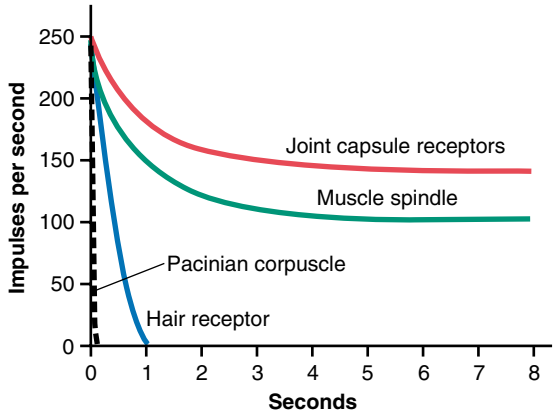

Figure 46-5 Adaptation of different types of receptors, showing rapid adaptation of some receptors and slow adaptation of others.

Mechanisms by Which Receptors Adapt. The mechanism of receptor adaptation is different for each type of receptor, in much the same way that development of a receptor potential is an individual property. For instance, in the eye, the rods and cones adapt by changing the concentrations of their light-sensitive chemicals (which is discussed in Chapter 50).

In the case of the mechanoreceptors, the receptor that has been studied in greatest detail is the pacinian corpuscle. Adaptation occurs in this receptor in two ways. First, the pacinian corpuscle is a viscoelastic structure, so that when a distorting force is suddenly applied to one side of the corpuscle, this force is instantly transmitted by the viscous component of the corpuscle directly to the same side of the central nerve fiber, thus eliciting a receptor potential. However, within a few hundredths of a second, the fluid within the corpuscle redistributes and the receptor potential is no longer elicited. Thus, the receptor potential appears at the onset of compression but disappears within a small fraction of a second even though the compression continues.

The second mechanism of adaptation of the pacinian corpuscle, but a much slower one, results from a process called *accommodation,* which occurs in the nerve fiber itself. That is, even if by chance the central core fiber should continue to be distorted, the tip of the nerve fiber itself gradually becomes "accommodated" to the stimulus. This probably results from progressive "inactivation" of the sodium channels in the nerve fiber membrane, which means that sodium current flow through the channels causes them gradually to close, an effect that seems to occur for all or most cell membrane sodium channels, as was explained in Chapter 5.

Presumably, these same two general mechanisms of adaptation apply also to the other types of mechanoreceptors. That is, part of the adaptation results from readjustments in the structure of the receptor itself, and part from an electrical type of accommodation in the terminal nerve fibril.

Slowly Adapting Receptors Detect Continuous Stimulus Strength—The "Tonic" Receptors. Slowly adapting receptors continue to transmit impulses to the brain as long as the stimulus is present (or at least for many minutes or hours). Therefore, they keep the brain constantly apprised of the status of the body and its relation to its surroundings. For instance, impulses from the muscle spindles and Golgi tendon apparatuses allow the nervous system to know the status of muscle contraction and load on the muscle tendon at each instant.

Other slowly adapting receptors include (1) receptors of the macula in the vestibular apparatus, (2) pain receptors, (3) baroreceptors of the arterial tree, and (4) chemoreceptors of the carotid and aortic bodies.

Because the slowly adapting receptors can continue to transmit information for many hours, they are called *tonic* receptors.

Rapidly Adapting Receptors Detect Change in Stimulus Strength—The "Rate Receptors," "Movement Receptors," or "Phasic Receptors." Receptors that adapt rapidly cannot be used to transmit a continuous signal because these receptors are stimulated only when the stimulus strength changes. Yet they react strongly *while a change is actually taking place*. Therefore, these receptors are called *rate* receptors, *movement* receptors, or *phasic* receptors. Thus, in the case of the pacinian corpuscle, sudden pressure applied to the tissue excites this receptor for a few milliseconds, and then its excitation is over even though the pressure continues. But later, it transmits a signal again when the pressure is released. In other words, the pacinian corpuscle is exceedingly important in apprising the nervous system of rapid tissue deformations, but it is useless for transmitting information about constant conditions in the body.

Importance of the Rate Receptors—Their Predictive Function. If one knows the rate at which some change in bodily status is taking place, one can predict in one's mind the state of the body a few seconds or even a few minutes later. For instance, the receptors of the semicircular canals in the vestibular apparatus of the ear detect the rate at which the head begins to turn when one runs around a curve. Using this information, a person can predict how much he or she will turn within the next 2 seconds and can adjust the motion of the legs *ahead of time* to keep from losing balance. Likewise, receptors located in or near the joints help detect the rates of movement of the different parts of the body. For instance, when one is running, information from the joint rate receptors allows the nervous system to predict where the feet will be during any precise fraction of the next second. Therefore, appropriate motor signals can be transmitted to the muscles of the legs to make any necessary anticipatory corrections in position so that the person will not fall. Loss of this predictive function makes it impossible for the person to run.

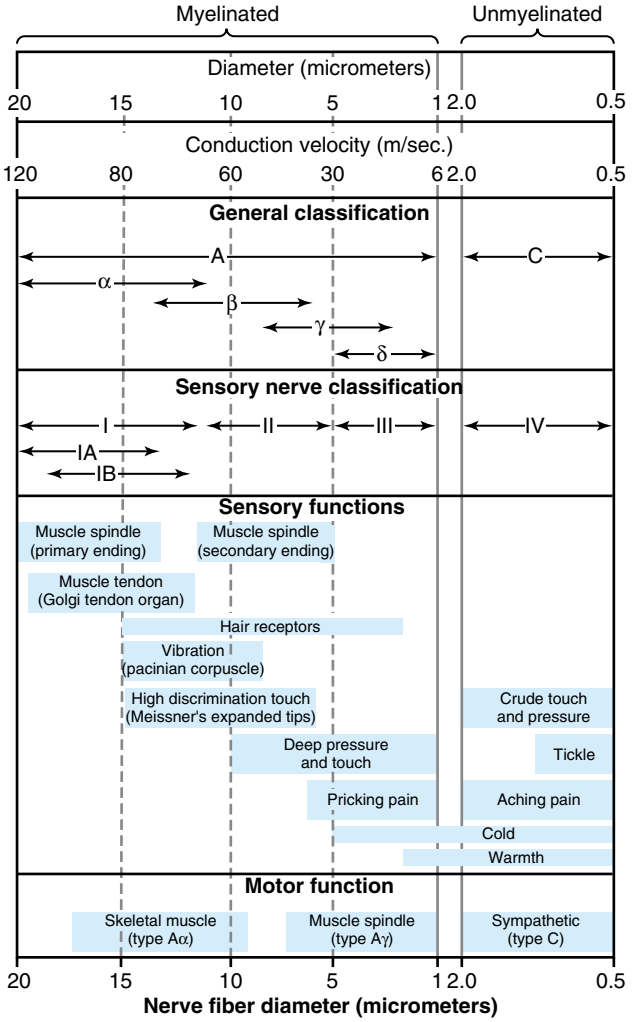

Figure 46-6 Physiologic classifications and functions of nerve fibers.

Nerve Fibers That Transmit Different Types of Signals and Their Physiologic Classification

Some signals need to be transmitted to or from the central nervous system extremely rapidly; otherwise, the information would be useless. An example of this is the sensory signals that apprise the brain of the momentary positions of the legs at each fraction of a second during running. At the other extreme, some types of sensory information, such as that depicting prolonged, aching pain, do not need to be transmitted rapidly, so slowly conducting fibers will suffice. As shown in Figure 46-6, nerve fibers come in all sizes between 0.5 and 20 micrometers in diameter—the larger the diameter, the greater the conducting velocity. The range of conducting velocities is between 0.5 and 120 m/sec.

General Classification of Nerve Fibers. Shown in Figure 46-6 is a "general classification" and a "sensory nerve classification" of the different types of nerve fibers. In the general classification, the fibers are divided into types A and C, and the type A fibers are further subdivided into α, β, γ, and δ fibers.

Type A fibers are the typical large and medium-sized *myelinated* fibers of spinal nerves. Type C fibers are the small *unmyelinated* nerve fibers that conduct impulses at low velocities. The C fibers constitute more than one half of the sensory fibers in most peripheral nerves, as well as all the postganglionic autonomic fibers.

The sizes, velocities of conduction, and functions of the different nerve fiber types are also given in Figure 46-6. Note that a few large myelinated fibers can transmit impulses at velocities as great as 120 m/sec, a distance in 1 second that is longer than a football field. Conversely, the smallest fibers transmit impulses as slowly as 0.5 m/sec, requiring about 2 seconds to go from the big toe to the spinal cord.

Alternative Classification Used by Sensory Physiologists. Certain recording techniques have made it possible to separate the type Aα fibers into two subgroups; yet these same recording techniques cannot distinguish easily between Aβ and Aγ fibers. Therefore, the following classification is frequently used by sensory physiologists:

Group Ia
Fibers from the annulospiral endings of muscle spindles (average about 17 microns in diameter; these are α-type A fibers in the general classification).

Group Ib
Fibers from the Golgi tendon organs (average about 16 micrometers in diameter; these also are α-type A fibers).

Group II
Fibers from most discrete cutaneous tactile receptors and from the flower-spray endings of the muscle spindles (average about 8 micrometers in diameter; these are β- and γ-type A fibers in the general classification).

Group III
Fibers carrying temperature, crude touch, and pricking pain sensations (average about 3 micrometers in diameter; they are δ-type A fibers in the general classification).

Group IV
Unmyelinated fibers carrying pain, itch, temperature, and crude touch sensations (0.5 to 2 micrometers in diameter; they are type C fibers in the general classification).

Transmission of Signals of Different Intensity in Nerve Tracts—Spatial and Temporal Summation

One of the characteristics of each signal that always must be conveyed is signal intensity—for instance, the intensity of pain. The different gradations of intensity can be transmitted either by using increasing numbers of parallel fibers or by sending more action potentials along a single fiber. These two mechanisms are called, respectively, *spatial summation* and *temporal summation*.

Spatial Summation. Figure 46-7 shows the phenomenon of *spatial summation,* whereby increasing signal strength is transmitted by using progressively greater numbers of fibers. This figure shows a section of skin innervated by a large number of parallel pain fibers. Each of these arborizes into hundreds of minute *free nerve endings* that serve as pain receptors. The entire cluster of fibers from one pain fiber frequently covers an area of skin as large as 5 centimeters in diameter. This area is called the *receptor field* of that fiber. The number of endings is large in the center of the field but diminishes toward the periphery. One can also see from the figure that the arborizing fibrils overlap those from other pain fibers. Therefore, a pinprick of the skin usually stimulates endings from many different pain fibers simultaneously. When the pinprick is in the center of the receptive field of a particular pain fiber, the degree of stimulation of that fiber is far greater than when it is in the periphery of the field because the number of free nerve endings in the middle of the field is much greater than at the periphery.

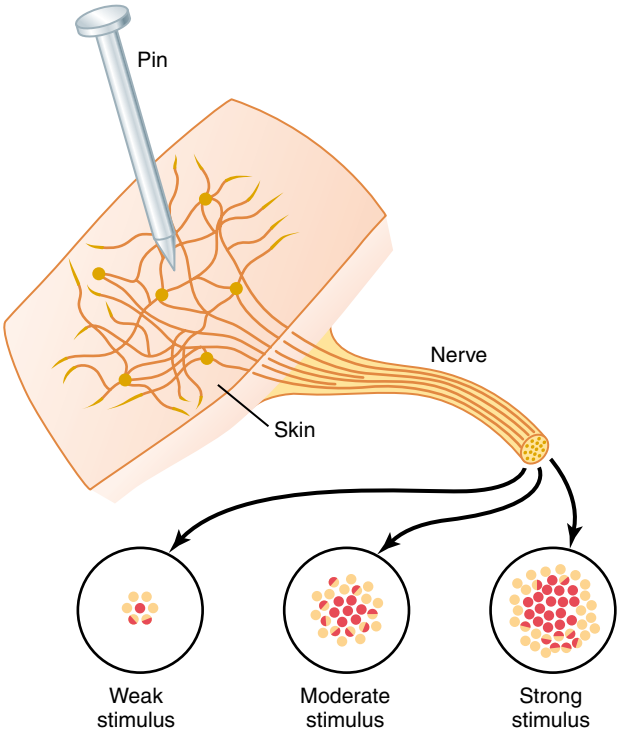

Figure 46-7 Pattern of stimulation of pain fibers in a nerve leading from an area of skin pricked by a pin. This is an example of *spatial summation*.

Thus, the lower part of Figure 46-7 shows three views of the cross section of the nerve bundle leading from the skin area. To the left is the effect of a weak stimulus, with only a single nerve fiber in the middle of the bundle stimulated strongly (represented by the red-colored fiber), whereas several adjacent fibers are stimulated weakly (half-red fibers). The other two views of the nerve cross section show the effect of a moderate stimulus and a strong stimulus, with progressively more fibers being stimulated. Thus, the stronger signals spread to more and more fibers. This is the phenomenon of *spatial summation*.

Temporal Summation. A second means for transmitting signals of increasing strength is by increasing the *frequency* of nerve impulses in each fiber, which is called *temporal summation*. Figure 46-8 demonstrates this, showing in the upper part a changing strength of signal and in the lower part the actual impulses transmitted by the nerve fiber.

Transmission and Processing of Signals in Neuronal Pools

The central nervous system is composed of thousands to millions of neuronal pools; some of these contain few neurons, whereas others have vast numbers. For instance, the entire cerebral cortex could be considered to be a single large neuronal pool. Other neuronal pools include the different basal ganglia and the specific nuclei in the thalamus,

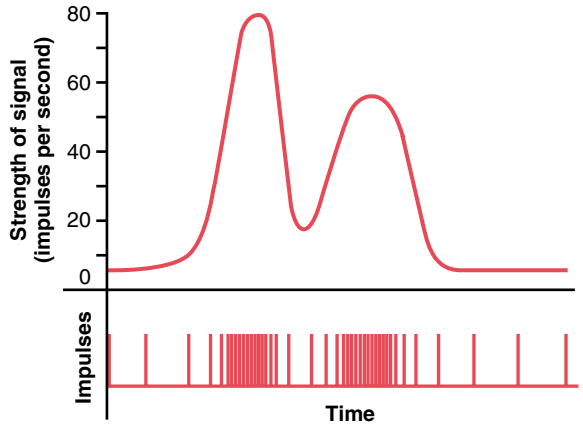

Figure 46-8 Translation of signal strength into a frequency-modulated series of nerve impulses, showing the strength of signal (*above*) and the separate nerve impulses (*below*). This is an example of *temporal summation*.

cerebellum, mesencephalon, pons, and medulla. Also, the entire dorsal gray matter of the spinal cord could be considered one long pool of neurons.

Each neuronal pool has its own special organization that causes it to process signals in its own unique way, thus allowing the total consortium of pools to achieve the multitude of functions of the nervous system. Yet despite their differences in function, the pools also have many similar principles of function, described in the following pages.

Relaying of Signals Through Neuronal Pools

Organization of Neurons for Relaying Signals. Figure 46-9 is a schematic diagram of several neurons in a neuronal pool, showing "input" fibers to the left and "output" fibers to the right. Each input fiber divides hundreds to thousands of times, providing a thousand or more terminal fibrils that spread into a large area in the pool to synapse with dendrites or cell bodies of the neurons in the pool. The dendrites usually also arborize and spread hundreds to thousands of micrometers in the pool.

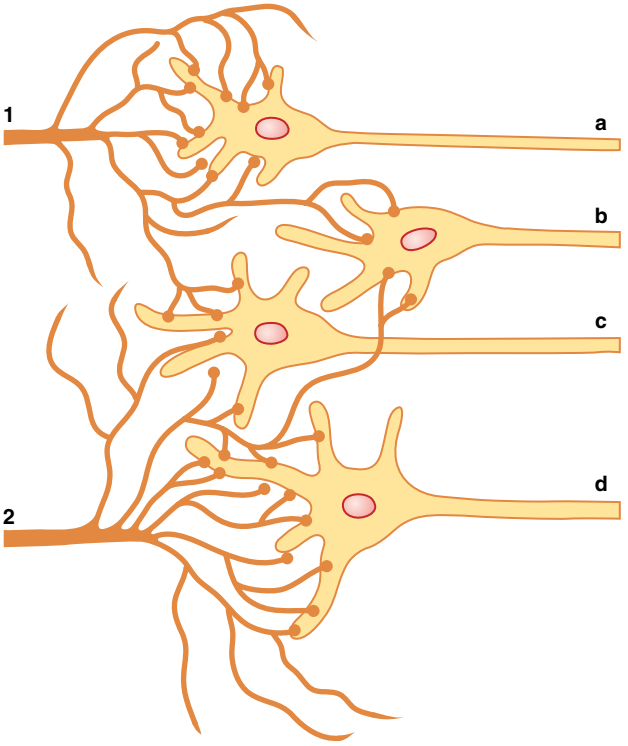

Figure 46-9 Basic organization of a neuronal pool.

The neuronal area stimulated by each incoming nerve fiber is called its *stimulatory field.* Note in Figure 46-9 that large numbers of the terminals from each input fiber lie on the nearest neuron in its "field," but progressively fewer terminals lie on the neurons farther away.

Threshold and Subthreshold Stimuli—Excitation or Facilitation. From the discussion of synaptic function in Chapter 45, it will be recalled that discharge of a single excitatory presynaptic terminal almost never causes an action potential in a postsynaptic neuron. Instead, large numbers of input terminals must discharge on the same neuron either simultaneously or in rapid succession to cause excitation. For instance, in Figure 46-9, let us assume that six terminals must discharge almost simultaneously to excite any one of the neurons. If the student counts the number of terminals on each one of the neurons from each input fiber, he or she will see that *input fiber 1* has more than enough terminals to cause *neuron a* to discharge. The stimulus from input fiber 1 to this neuron is said to be an *excitatory stimulus;* it is also called a *suprathreshold stimulus* because it is above the threshold required for excitation.

Input fiber 1 also contributes terminals to neurons b and c, but not enough to cause excitation. Nevertheless, discharge of these terminals makes both these neurons more likely to be excited by signals arriving through other incoming nerve fibers. Therefore, the stimuli to these neurons are said to be *subthreshold,* and the neurons are said to be *facilitated.*

Similarly, for *input fiber 2,* the stimulus to *neuron d* is a suprathreshold stimulus, and the stimuli to *neurons b* and *c* are subthreshold, but facilitating, stimuli.

Figure 46-9 represents a highly condensed version of a neuronal pool because each input nerve fiber usually provides massive numbers of branching terminals to hundreds or thousands of neurons in its distribution "field," as shown in Figure 46-10. In the central portion of the field in this figure, designated by the circled area, all the neurons are stimulated by the incoming fiber. Therefore, this is said to be the *discharge zone* of the incoming fiber, also called the *excited zone* or *liminal zone.* To each side,

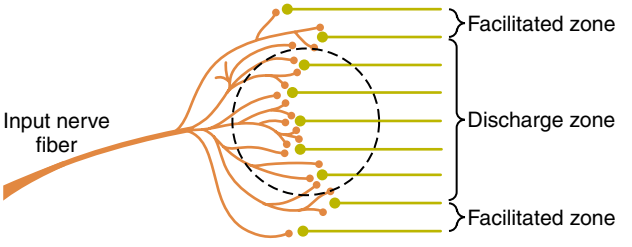

Figure 46-10 "Discharge" and "facilitated" zones of a neuronal pool.

the neurons are facilitated but not excited, and these areas are called the *facilitated zone,* also called the *subthreshold zone* or *subliminal zone.*

Inhibition of a Neuronal Pool. We must also remember that some incoming fibers inhibit neurons, rather than exciting them. This is the opposite of facilitation, and the entire field of the inhibitory branches is called the *inhibitory zone.* The degree of inhibition in the center of this zone is great because of large numbers of endings in the center; it becomes progressively less toward its edges.

Divergence of Signals Passing Through Neuronal Pools

Often it is important for weak signals entering a neuronal pool to excite far greater numbers of nerve fibers leaving the pool. This phenomenon is called *divergence.* Two major types of divergence occur and have entirely different purposes.

An *amplifying* type of divergence is shown in Figure 46-11*A.* This means simply that an input signal spreads to an increasing number of neurons as it passes through successive orders of neurons in its path. This type of divergence is characteristic of the corticospinal pathway in its control of skeletal muscles, with a single large pyramidal cell in the motor cortex capable, under highly facilitated conditions, of exciting as many as 10,000 muscle fibers.

The second type of divergence, shown in Figure 46-11*B,* is *divergence into multiple tracts.* In this case, the signal is transmitted in two directions from the pool. For instance, information transmitted up the dorsal columns of the spinal cord takes two courses in the lower part of the brain: (1) into the cerebellum and (2) on through the lower regions of the brain to the thalamus and cerebral cortex. Likewise, in the thalamus, almost all sensory information is relayed both into still deeper structures of the thalamus and at the same time to discrete regions of the cerebral cortex.

Convergence of Signals

Convergence means signals from multiple inputs uniting to excite a single neuron. Figure 46-12*A* shows *convergence from a single source.* That is, multiple terminals from a single incoming fiber tract terminate on the same neuron. The importance of this is that neurons are almost never excited by an action potential from a single input terminal. But action potentials converging on the neuron from multiple terminals provide enough spatial summation to bring the neuron to the threshold required for discharge.

Convergence can also result from input signals (excitatory or inhibitory) *from multiple sources,* as shown in Figure 46-12*B.* For instance, the interneurons of the spinal cord receive converging signals from (1) peripheral nerve fibers entering the cord, (2) propriospinal fibers passing from one segment of the cord to another, (3) corticospinal fibers from the cerebral cortex, and (4) several other long pathways descending from the brain into the spinal cord. Then the signals from the interneurons converge on the anterior motor neurons to control muscle function.

Such convergence allows *summation* of information from different sources, and the resulting response is a summated effect of all the different types of information. Convergence is one of the important means by which the central nervous system correlates, summates, and sorts different types of information.

Neuronal Circuit with both Excitatory and Inhibitory Output Signals

Sometimes an incoming signal to a neuronal pool causes an output excitatory signal going in one direction and at the same time an inhibitory signal going elsewhere. For instance, at the same time that an excitatory signal is transmitted by one set of neurons in the spinal cord to cause forward movement of a leg, an inhibitory signal is transmitted through a separate set of neurons to inhibit the muscles on the back of the leg so that they will not oppose the forward movement. This type of circuit is characteristic for controlling all antagonistic pairs of muscles, and it is called the *reciprocal inhibition circuit.*

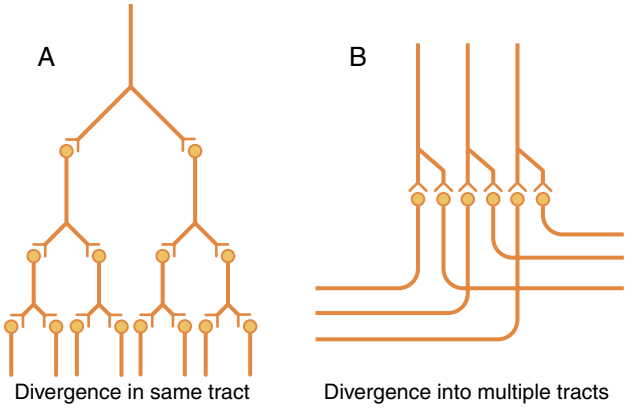

Figure 46-11 "Divergence" in neuronal pathways. *A,* Divergence within a pathway to cause "amplification" of the signal. *B,* Divergence into multiple tracts to transmit the signal to separate areas.

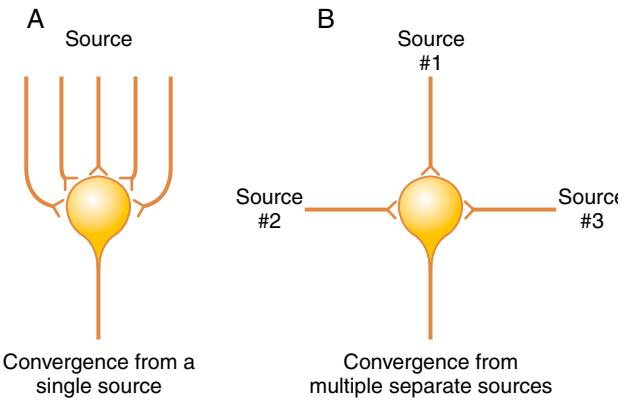

Figure 46-12 "Convergence" of multiple input fibers onto a single neuron. *A,* Multiple input fibers from a single source. *B,* Input fibers from multiple separate sources.

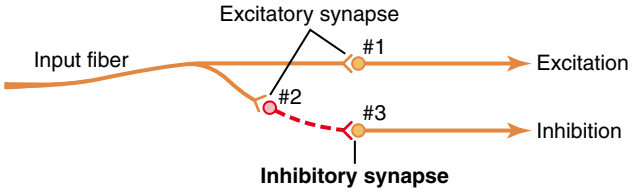

Figure 46-13 Inhibitory circuit. Neuron 2 is an inhibitory neuron.

Figure 46-13 shows the means by which the inhibition is achieved. The input fiber directly excites the excitatory output pathway, but it stimulates an intermediate *inhibitory neuron* (neuron 2), which secretes a different type of transmitter substance to inhibit the second output pathway from the pool. This type of circuit is also important in preventing overactivity in many parts of the brain.

Prolongation of a Signal by a Neuronal Pool—"Afterdischarge"

Thus far, we have considered signals that are merely relayed through neuronal pools. However, in many instances, a signal entering a pool causes a prolonged output discharge, called *afterdischarge,* lasting a few milliseconds to as long as many minutes after the incoming signal is over. The most important mechanisms by which afterdischarge occurs are the following.

Synaptic Afterdischarge. When excitatory synapses discharge on the surfaces of dendrites or soma of a neuron, a postsynaptic electrical potential develops in the neuron and lasts for many milliseconds, especially when some of the long-acting synaptic transmitter substances are involved. As long as this potential lasts, it can continue to excite the neuron, causing it to transmit a continuous train of output impulses, as was explained in Chapter 45. Thus, as a result of this synaptic "afterdischarge" mechanism alone, it is possible for a single instantaneous input signal to cause a sustained signal output (a series of repetitive discharges) lasting for many milliseconds.

Reverberatory (Oscillatory) Circuit as a Cause of Signal Prolongation. One of the most important of all circuits in the entire nervous system is the *reverberatory,* or *oscillatory, circuit.* Such circuits are caused by positive feedback within the neuronal circuit that feeds back to re-excite the input of the same circuit. Consequently, once stimulated, the circuit may discharge repetitively for a long time.

Several possible varieties of reverberatory circuits are shown in Figure 46-14. The simplest, shown in Figure 46-14*A,* involves only a single neuron. In this case, the output neuron simply sends a collateral nerve fiber back to its own dendrites or soma to restimulate itself. Although this type of circuit probably is not an important one, theoretically, once the neuron discharges, the feedback stimuli could keep the neuron discharging for a protracted time thereafter.

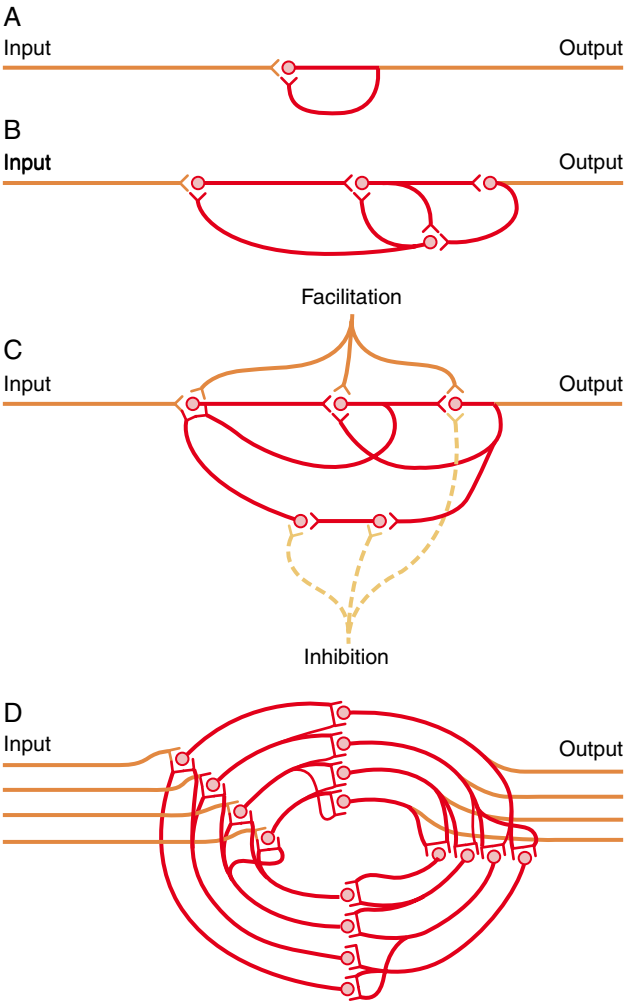

Figure 46-14 Reverberatory circuits of increasing complexity.

Figure 46-14*B* shows a few additional neurons in the feedback circuit, which causes a longer delay between initial discharge and the feedback signal. Figure 46-14*C* shows a still more complex system in which both facilitatory and inhibitory fibers impinge on the reverberating circuit. A facilitatory signal enhances the intensity and frequency of reverberation, whereas an inhibitory signal depresses or stops the reverberation.

Figure 46-14*D* shows that most reverberating pathways are constituted of many parallel fibers. At each cell station, the terminal fibrils spread widely. In such a system, the total reverberating signal can be either weak or strong, depending on how many parallel nerve fibers are momentarily involved in the reverberation.

Characteristics of Signal Prolongation from a Reverberatory Circuit. Figure 46-15 shows output signals from a typical reverberatory circuit. The input stimulus may last only 1 millisecond or so, and yet the output can last for many milliseconds or even minutes. The figure demonstrates that the intensity of the output signal usually increases to a high value early in reverberation and then decreases to a critical point, at which it suddenly ceases entirely. The cause of this sudden cessation of

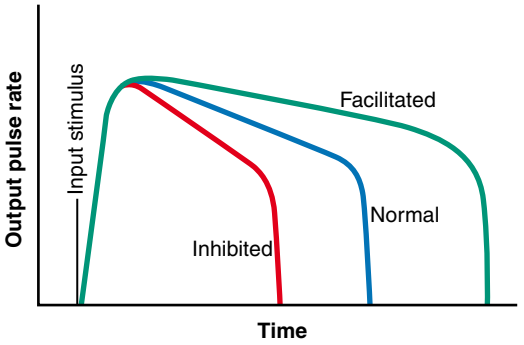

Figure 46-15 Typical pattern of the output signal from a reverberatory circuit after a single input stimulus, showing the effects of facilitation and inhibition.

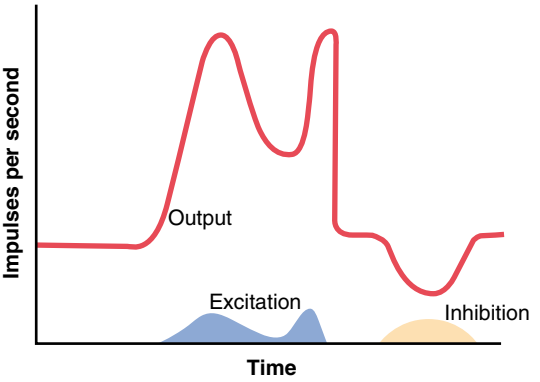

Figure 46-16 Continuous output from either a reverberating circuit or a pool of intrinsically discharging neurons. This figure also shows the effect of excitatory or inhibitory input signals.

reverberation is fatigue of synaptic junctions in the circuit. Fatigue beyond a certain critical level lowers the stimulation of the next neuron in the circuit below threshold level so that the circuit feedback is suddenly broken.

The duration of the total signal before cessation can also be controlled by signals from other parts of the brain that inhibit or facilitate the circuit. Almost these exact patterns of output signals are recorded from the motor nerves exciting a muscle involved in a flexor reflex after pain stimulation of the foot (as shown later in Figure 46-18).

Continuous Signal Output from Some Neuronal Circuits

Some neuronal circuits emit output signals continuously, even without excitatory input signals. At least two mechanisms can cause this effect: (1) continuous intrinsic neuronal discharge and (2) continuous reverberatory signals.

Continuous Discharge Caused by Intrinsic Neuronal Excitability. Neurons, like other excitable tissues, discharge repetitively if their level of excitatory membrane potential rises above a certain threshold level. The membrane potentials of many neurons even normally are high enough to cause them to emit impulses continually. This occurs especially in many of the neurons of the cerebellum, as well as in most of the interneurons of the spinal cord. The rates at which these cells emit impulses can be increased by excitatory signals or decreased by inhibitory signals; inhibitory signals often can decrease the rate of firing to zero.

Continuous Signals Emitted from Reverberating Circuits as a Means for Transmitting Information. A reverberating circuit that does not fatigue enough to stop reverberation is a source of continuous impulses. And excitatory impulses entering the reverberating pool can increase the output signal, whereas inhibition can decrease or even extinguish the signal.

Figure 46-16 shows a continuous output signal from a pool of neurons. The pool may be emitting impulses because of intrinsic neuronal excitability or as a result of reverberation. Note that an excitatory input signal greatly increases the output signal, whereas an inhibitory input signal greatly decreases the output. Those students who are familiar with radio transmitters will recognize this to be a *carrier wave* type of information transmission. That is, the excitatory and inhibitory control signals are not the *cause* of the output signal, but they do *control* its changing level of intensity. Note that this carrier wave system allows a *decrease* in signal intensity, as well as an increase, whereas up to this point, the types of information transmission we have discussed have been mainly positive information rather than negative information. This type of information transmission is used by the autonomic nervous system to control such functions as vascular tone, gut tone, degree of constriction of the iris in the eye, and heart rate. That is, the nerve excitatory signal to each of these can be either increased or decreased by accessory input signals into the reverberating neuronal pathway.

Rhythmical Signal Output

Many neuronal circuits emit rhythmical output signals—for instance, a rhythmical respiratory signal originates in the respiratory centers of the medulla and pons. This respiratory rhythmical signal continues throughout life. Other rhythmical signals, such as those that cause scratching movements by the hind leg of a dog or the walking movements of any animal, require input stimuli into the respective circuits to initiate the rhythmical signals.

All or almost all rhythmical signals that have been studied experimentally have been found to result from reverberating circuits or a succession of sequential reverberating circuits that feed excitatory or inhibitory signals in a circular pathway from one neuronal pool to the next.

Excitatory or inhibitory signals can also increase or decrease the amplitude of the rhythmical signal output. Figure 46-17, for instance, shows changes in the respiratory signal output in the phrenic nerve. When the carotid body is stimulated by arterial oxygen deficiency, both the frequency and the amplitude of the respiratory rhythmical output signal increase progressively.

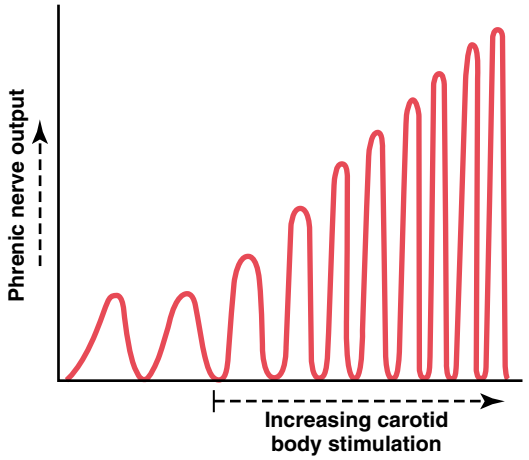

Figure 46-17 The rhythmical output of summated nerve impulses from the respiratory center, showing that progressively increasing stimulation of the carotid body increases both the intensity and the frequency of the phrenic nerve signal to the diaphragm to increase respiration.

Instability and Stability of Neuronal Circuits

Almost every part of the brain connects either directly or indirectly with every other part, and this creates a serious problem. If the first part excites the second, the second the third, the third the fourth, and so on until finally the signal re-excites the first part, it is clear that an excitatory signal entering any part of the brain would set off a continuous cycle of re-excitation of all parts. If this should occur, the brain would be inundated by a mass of uncontrolled reverberating signals—signals that would be transmitting no information but, nevertheless, would be consuming the circuits of the brain so that none of the informational signals could be transmitted. Such an effect occurs in widespread areas of the brain during *epileptic seizures.* How does the central nervous system prevent this from happening all the time? The answer lies mainly in two basic mechanisms that function throughout the central nervous system: (1) inhibitory circuits and (2) fatigue of synapses.

Inhibitory Circuits as a Mechanism for Stabilizing Nervous System Function

Two types of inhibitory circuits in widespread areas of the brain help prevent excessive spread of signals: (1) inhibitory feedback circuits that return from the termini of pathways back to the initial excitatory neurons of the same pathways—these circuits occur in virtually all sensory nervous pathways and inhibit either the input neurons or the intermediate neurons in the sensory pathway when the termini become overly excited; and (2) some neuronal pools that exert gross inhibitory control over widespread areas of the brain—for instance, many of the basal ganglia exert inhibitory influences throughout the muscle control system.

Synaptic Fatigue as a Means of Stabilizing the Nervous System

Synaptic fatigue means simply that synaptic transmission becomes progressively weaker the more prolonged and more intense the period of excitation. Figure 46-18 shows three successive records of a flexor reflex elicited in an animal caused by inflicting pain in the footpad of the paw. Note in each record that the strength of contraction progressively "decrements"—that is, its strength diminishes; much of this effect is caused by *fatigue* of synapses in the flexor reflex circuit. Furthermore, the shorter the interval between successive flexor reflexes, the less the intensity of the subsequent reflex response.

Automatic Short-Term Adjustment of Pathway Sensitivity by the Fatigue Mechanism. Now let us apply this phenomenon of fatigue to other pathways in the brain. Those that are overused usually become fatigued, so their sensitivities decrease. Conversely, those that are underused become rested and their sensitivities increase. Thus, fatigue and recovery from fatigue constitute an important short-term means of moderating the sensitivities of the different nervous system circuits. These help to keep the circuits operating in a range of sensitivity that allows effective function.

Long-Term Changes in Synaptic Sensitivity Caused by Automatic Down-regulation or Up-regulation of Synaptic Receptors. The long-term sensitivities of synapses can be changed tremendously by up-regulating the number of receptor proteins at the synaptic sites when there is underactivity and down-regulating the receptors when there is overactivity. The mechanism for this is the following: Receptor proteins are being formed constantly by the endoplasmic reticular–Golgi apparatus system and are constantly being inserted into the receptor neuron synaptic membrane. However, when the synapses are overused so that excesses of transmitter substance combine with the receptor proteins, many of these receptors are inactivated and removed from the synaptic membrane.

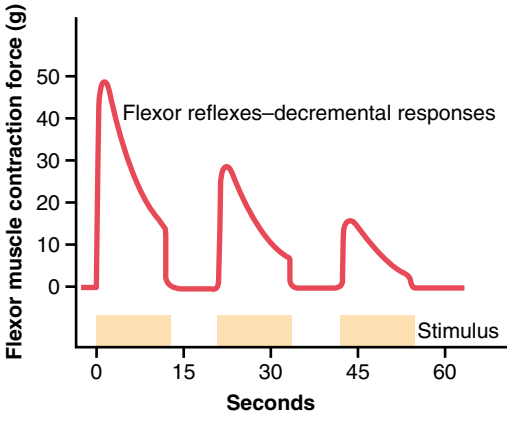

Figure 46-18 Successive flexor reflexes showing fatigue of conduction through the reflex pathway.

It is indeed fortunate that up-regulation and down-regulation of receptors, as well as other control mechanisms for adjusting synaptic sensitivity, continually adjust the sensitivity in each circuit to almost the exact level required for proper function. Think for a moment how serious it would be if the sensitivities of only a few of these circuits were abnormally high; one might then expect almost continual muscle cramps, seizures, psychotic disturbances, hallucinations, mental tension, or other nervous disorders. But fortunately, the automatic controls normally readjust the sensitivities of the circuits back to controllable ranges of reactivity any time the circuits begin to be too active or too depressed.

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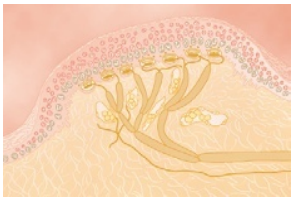
CHAPTER 47

Somatic Sensations: I. General Organization, the Tactile and Position Senses



The *somatic senses* are the nervous mechanisms that collect sensory information from all over the body. These senses are in contradistinction to the *special senses,* which mean specifically vision, hearing, smell, taste, and equilibrium.

Classification of Somatic Senses

The somatic senses can be classified into three physiologic types: (1) the *mechanoreceptive somatic senses,* which include both *tactile* and *position* sensations that are stimulated by mechanical displacement of some tissue of the body; (2) the *thermoreceptive senses,* which detect heat and cold; and (3) the *pain sense,* which is activated by factors that damage the tissues.

This chapter deals with the mechanoreceptive tactile and position senses. Chapter 48 discusses the thermoreceptive and pain senses. The tactile senses include *touch, pressure, vibration,* and *tickle* senses, and the position senses include *static position* and *rate of movement* senses.

Other Classifications of Somatic Sensations. Somatic sensations are also often grouped together in other classes, as follows.

Exteroreceptive sensations are those from the surface of the body. *Proprioceptive sensations* are those relating to the physical state of the body, including position sensations, tendon and muscle sensations, pressure sensations from the bottom of the feet, and even the sensation of equilibrium (which is often considered a "special" sensation rather than a somatic sensation).

Visceral sensations are those from the viscera of the body; in using this term, one usually refers specifically to sensations from the internal organs.

Deep sensations are those that come from deep tissues, such as from fasciae, muscles, and bone. These include mainly "deep" pressure, pain, and vibration.

Detection and Transmission of Tactile Sensations

Interrelations Among the Tactile Sensations of Touch, Pressure, and Vibration. Although touch, pressure, and vibration are frequently classified as separate sensations, they are all detected by the same types of receptors. There are three principal differences among them: (1) touch sensation generally results from stimulation of tactile receptors in the skin or in tissues immediately beneath the skin; (2) pressure sensation generally results from deformation of deeper tissues; and (3) vibration sensation results from rapidly repetitive sensory signals, but some of the same types of receptors as those for touch and pressure are used.

Tactile Receptors. There are at least six entirely different types of tactile receptors, but many more similar to these also exist. Some were shown in Figure 46-1 of the previous chapter; their special characteristics are the following.

First, some *free nerve endings,* which are found everywhere in the skin and in many other tissues, can detect touch and pressure. For instance, even light contact with the cornea of the eye, which contains no other type of nerve ending besides free nerve endings, can nevertheless elicit touch and pressure sensations.

Second, a touch receptor with great sensitivity is the *Meissner's corpuscle* (illustrated in Figure 46-1), an elongated encapsulated nerve ending of a large (type Aβ) myelinated sensory nerve fiber. Inside the capsulation are many branching terminal nerve filaments. These corpuscles are present in the nonhairy parts of the skin and are particularly abundant in the fingertips, lips, and other areas of the skin where one's ability to discern spatial locations of touch sensations is highly developed. Meissner's corpuscles adapt in a fraction of a second after they are stimulated, which means that they are particularly sensitive to movement of objects over the surface of the skin, as well as to low-frequency vibration.

Third, the fingertips and other areas that contain large numbers of Meissner's corpuscles usually also contain large numbers of *expanded tip tactile receptors,* one type of which is *Merkel's discs,* shown in Figure 47-1. The hairy parts of the skin also contain moderate numbers of expanded tip receptors, even though they have almost no Meissner's corpuscles. These receptors differ from Meissner's corpuscles in that they transmit an initially strong but partially adapting signal and then a continuing weaker signal that adapts only slowly. Therefore, they are responsible for giving steady-state signals that allow one to determine continuous touch of objects against the skin.

Merkel's discs are often grouped together in a receptor organ called the *Iggo dome receptor,* which projects upward against the underside of the epithelium of the skin, as also shown in Figure 47-1. This causes the epithelium at this point to protrude outward, thus creating a dome and constituting an extremely sensitive receptor. Also note that the entire group of Merkel's discs is innervated by a single large myelinated nerve fiber (type Aβ). These receptors, along with the Meissner's corpuscles discussed earlier, play extremely important roles in localizing touch sensations to specific surface areas of the body and in determining the texture of what is felt.

Fourth, slight movement of any hair on the body stimulates a nerve fiber entwining its base. Thus, each hair and its basal nerve fiber, called the *hair end-organ,* are also touch receptors. A receptor adapts readily and, like Meissner's corpuscles, detects mainly (a) movement of objects on the surface of the body or (b) initial contact with the body.

Fifth, located in the deeper layers of the skin and also in still deeper internal tissues are many *Ruffini's endings,* which are multibranched, encapsulated endings, as shown in Figure 46-1. These endings adapt very slowly and, therefore, are important for signaling continuous states of deformation of the tissues, such as heavy prolonged touch and pressure signals. They are also found in joint capsules and help to signal the degree of joint rotation.

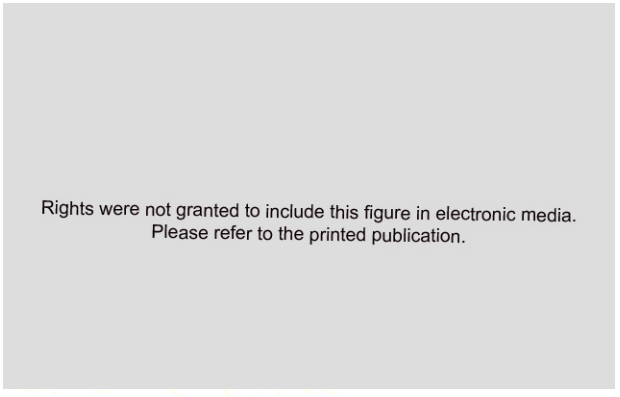


Figure 47-1 Iggo dome receptor. Note the multiple numbers of Merkel's discs connecting to a single large myelinated fiber and abutting tightly the undersurface of the epithelium. (From Iggo A, Muir AR: The structure and function of a slowly adapting touch corpuscle in hairy skin. J Physiol 200:763, 1969.)

Sixth, pacinian corpuscles, which were discussed in detail in Chapter 46, lie both immediately beneath the skin and deep in the fascial tissues of the body. They are stimulated only by rapid local compression of the tissues because they adapt in a few hundredths of a second. Therefore, they are particularly important for detecting tissue vibration or other rapid changes in the mechanical state of the tissues.

Transmission of Tactile Signals in Peripheral Nerve Fibers. Almost all specialized sensory receptors, such as Meissner's corpuscles, Iggo dome receptors, hair receptors, pacinian corpuscles, and Ruffini's endings, transmit their signals in type Aβ nerve fibers that have transmission velocities ranging from 30 to 70 m/sec. Conversely, free nerve ending tactile receptors transmit signals mainly by way of the small type Aδ myelinated fibers that conduct at velocities of only 5 to 30 m/sec.

Some tactile free nerve endings transmit by way of type C unmyelinated fibers at velocities from a fraction of a meter up to 2 m/sec; these send signals into the spinal cord and lower brain stem, probably subserving mainly the sensation of tickle.

Thus, the more critical types of sensory signals—those that help to determine precise localization on the skin, minute gradations of intensity, or rapid changes in sensory signal intensity—are all transmitted in more rapidly conducting types of sensory nerve fibers. Conversely, the cruder types of signals, such as pressure, poorly localized touch, and especially tickle, are transmitted by way of much slower, very small nerve fibers that require much less space in the nerve bundle than the fast fibers.

Detection of Vibration

All tactile receptors are involved in detection of vibration, although different receptors detect different frequencies of vibration. Pacinian corpuscles can detect signal vibrations from 30 to 800 cycles per second because they respond extremely rapidly to minute and rapid deformations of the tissues, and they also transmit their signals over type Aβ nerve fibers, which can transmit as many as 1000 impulses per second. Low-frequency vibrations from 2 up to 80 cycles per second, in contrast, stimulate other tactile receptors, especially Meissner's corpuscles, which are less rapidly adapting than pacinian corpuscles.

Detection of Tickle and Itch by Mechanoreceptive Free Nerve Endings

Neurophysiologic studies have demonstrated the existence of very sensitive, rapidly adapting mechanoreceptive free nerve endings that elicit only the tickle and itch sensations. Furthermore, these endings are found almost exclusively in superficial layers of the skin, which is also the only tissue from which the tickle and itch sensations usually can be elicited. These sensations are transmitted by very small type C, unmyelinated fibers similar to those that transmit the aching, slow type of pain.

The purpose of the itch sensation is presumably to call attention to mild surface stimuli such as a flea crawling on the skin or a fly about to bite, and the elicited signals then activate the scratch reflex or other maneuvers that rid the host of the irritant. Itch can be relieved by scratching if this removes the irritant or if the scratch is strong enough to elicit pain. The pain signals are believed to suppress the itch signals in the cord by lateral inhibition, as described in Chapter 48.

Sensory Pathways for Transmitting Somatic Signals into the Central Nervous System

Almost all sensory information from the somatic segments of the body enters the spinal cord through the dorsal roots of the spinal nerves. However, from the entry point into the cord and then to the brain, the sensory signals are carried through one of two alternative sensory pathways: (1) the *dorsal column*–medial lemniscal system or (2) the *anterolateral system*. These two systems come back together partially at the level of the thalamus.

The dorsal column–medial lemniscal system, as its name implies, carries signals upward to the medulla of the brain mainly in the *dorsal columns* of the cord. Then, after the signals synapse and cross to the opposite side in the medulla, they continue upward through the brain stem to the thalamus by way of the *medial lemniscus.*

Conversely, signals in the anterolateral system, immediately after entering the spinal cord from the dorsal spinal nerve roots, synapse in the dorsal horns of the spinal gray matter, then cross to the opposite side of the cord and ascend through the anterior and lateral white columns of the cord. They terminate at all levels of the lower brain stem and in the thalamus.

The dorsal column–medial lemniscal system is composed of large, myelinated nerve fibers that transmit signals to the brain at velocities of 30 to 110 m/sec, whereas the anterolateral system is composed of smaller myelinated fibers that transmit signals at velocities ranging from a few meters per second up to 40 m/sec.

Another difference between the two systems is that the dorsal column–medial lemniscal system has a high degree of spatial orientation of the nerve fibers with respect to their origin, while the anterolateral system has much less spatial orientation. These differences immediately characterize the types of sensory information that can be transmitted by the two systems. That is, sensory information that must be transmitted rapidly and with temporal and spatial fidelity is transmitted mainly in the dorsal column–medial lemniscal system; that which does not need to be transmitted rapidly or with great spatial fidelity is transmitted mainly in the anterolateral system.

The anterolateral system has a special capability that the dorsal system does not have: the ability to transmit a broad spectrum of sensory modalities—pain, warmth, cold, and crude tactile sensations; most of these are discussed in detail in Chapter 48. The dorsal system is limited to discrete types of mechanoreceptive sensations.

With this differentiation in mind, we can now list the types of sensations transmitted in the two systems.

Dorsal Column—Medial Lemniscal System

1. Touch sensations requiring a high degree of localization of the stimulus
2. Touch sensations requiring transmission of fine gradations of intensity
3. Phasic sensations, such as vibratory sensations
4. Sensations that signal movement against the skin
5. Position sensations from the joints
6. Pressure sensations related to fine degrees of judgment of pressure intensity

Anterolateral System

1. Pain
2. Thermal sensations, including both warmth and cold sensations
3. Crude touch and pressure sensations capable only of crude localizing ability on the surface of the body
4. Tickle and itch sensations
5. Sexual sensations

Transmission in the Dorsal Column–Medial Lemniscal System

Anatomy of the Dorsal Column–Medial Lemniscal System

On entering the spinal cord through the spinal nerve dorsal roots, the large myelinated fibers from the specialized mechanoreceptors divide almost immediately to form a *medial branch* and a *lateral branch,* shown by the right-hand fiber entering through the spinal root in Figure 47-2.

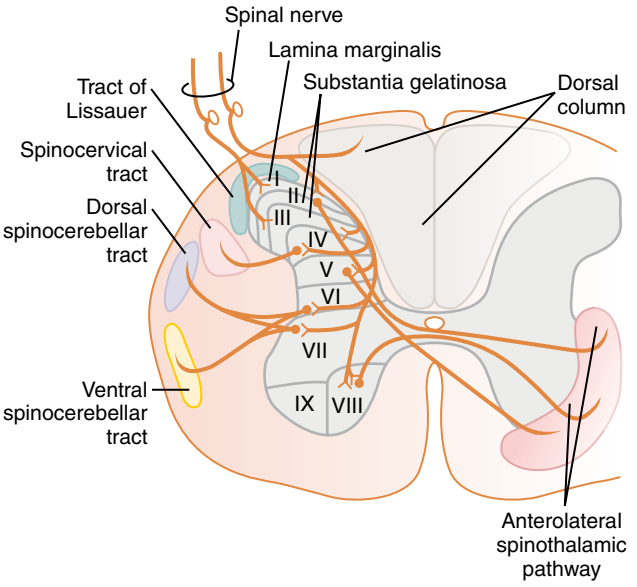


Figure 47-2 Cross section of the spinal cord, showing the anatomy of the cord gray matter and of ascending sensory tracts in the white columns of the spinal cord.

The medial branch turns medially first and then upward in the dorsal column, proceeding by way of the dorsal column pathway all the way to the brain.

The lateral branch enters the dorsal horn of the cord gray matter, then divides many times to provide terminals that synapse with local neurons in the intermediate and anterior portions of the cord gray matter. These local neurons in turn serve three functions: (1) A major share of them give off fibers that enter the dorsal columns of the cord and then travel upward to the brain. (2) Many of the fibers are very short and terminate locally in the spinal cord gray matter to elicit local spinal cord reflexes, which are discussed in Chapter 54. (3) Others give rise to the spinocerebellar tracts, which we discuss in Chapter 56 in relation to the function of the cerebellum.

Dorsal Column—Medial Lemniscal Pathway. Note in Figure 47-3 that nerve fibers entering the dorsal columns pass uninterrupted up to the dorsal medulla, where they synapse in the *dorsal column nuclei* (the *cuneate* and *gracile nuclei*). From there, *second-order neurons* decussate immediately to the opposite side of the brain stem and continue upward through the *medial lemnisci* to the thalamus. In this pathway through the brain stem, each medial lemniscus is joined by additional fibers from the *sensory nuclei of the trigeminal nerve;* these fibers subserve the same sensory functions for the head that the dorsal column fibers subserve for the body.

In the thalamus, the medial lemniscal fibers terminate in the thalamic sensory relay area, called the *ventrobasal complex.* From the ventrobasal complex, *third-order nerve fibers* project, as shown in Figure 47-4, mainly to the *postcentral gyrus* of the *cerebral cortex,* which is called *somatic sensory area I* (as shown in Figure 47-6, these fibers also project to a smaller area in the lateral parietal cortex called *somatic sensory area II*).

Spatial Orientation of the Nerve Fibers in the Dorsal Column–Medial Lemniscal System

One of the distinguishing features of the dorsal column–medial lemniscal system is a distinct spatial orientation of nerve fibers from the individual parts of the body that is maintained throughout. For instance, in the dorsal columns of the spinal cord, the fibers from the lower parts of the body lie toward the center of the cord, whereas those that enter the cord at progressively higher segmental levels form successive layers laterally.

In the thalamus, distinct spatial orientation is still maintained, with the tail end of the body represented by the most lateral portions of the ventrobasal complex and the head and face represented by the medial areas of the complex. Because of the crossing of the medial lemnisci in the medulla, the left side of the body is represented in the right side of the thalamus, and the right side of the body in the left side of the thalamus.

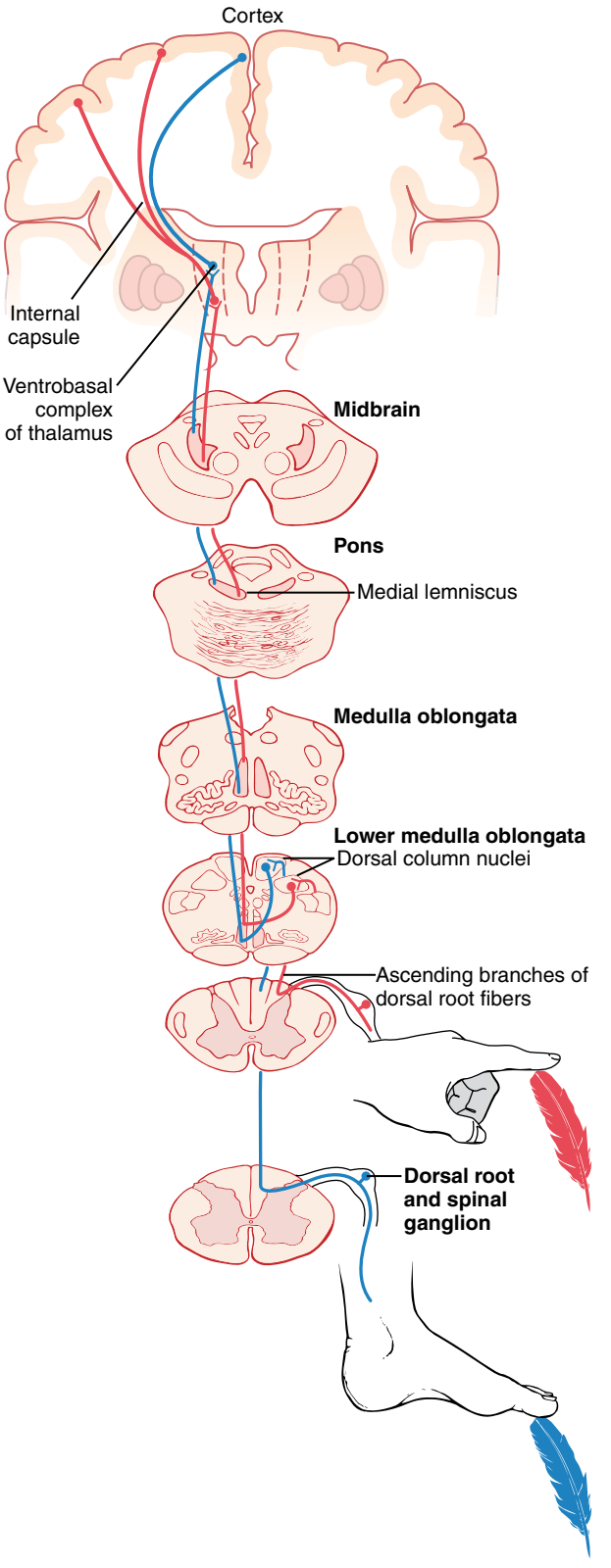


Figure 47-3 The dorsal column–medial lemniscal pathway for transmitting critical types of tactile signals.

Somatosensory Cortex

Before discussing the role of the cerebral cortex in somatic sensation, we need to give an orientation to the various areas of the cortex. Figure 47-5 is a map of the human cerebral cortex, showing that it is divided into about 50 distinct areas called *Brodmann's areas* based on histological structural differences. This map is important because virtually all neurophysiologists and neurologists use it to

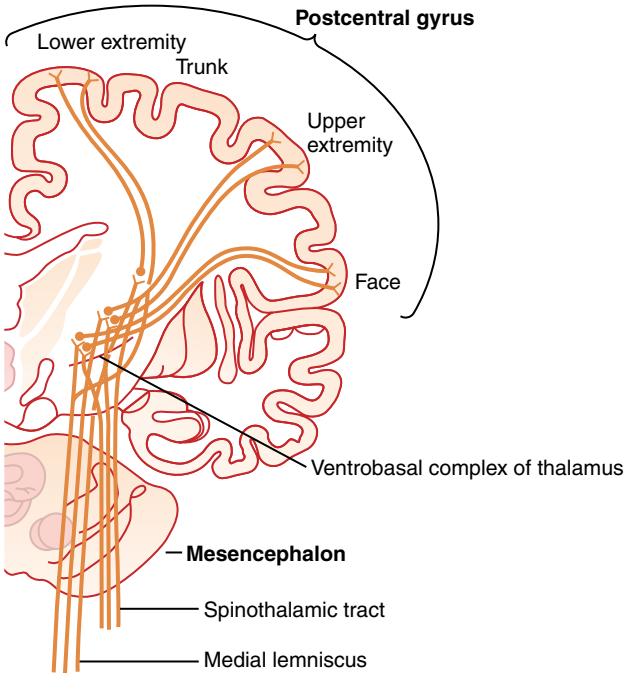


Figure 47-4 Projection of the dorsal column–medial lemniscal system through the thalamus to the somatosensory cortex. (Modified from Brodal A: Neurological Anatomy in Relation to Clinical Medicine. New York: Oxford University Press, 1969, by permission of Oxford University Press.)

refer by number to many of the different functional areas of the human cortex.

Note in the figure the large *central fissure* (also called *central sulcus*) that extends horizontally across the brain. In general, sensory signals from all modalities of sensation terminate in the cerebral cortex immediately posterior to the central fissure. And, generally, the anterior half of the *parietal lobe* is concerned almost entirely with reception and interpretation of *somatosensory signals.* But the posterior half of the parietal lobe provides still higher levels of interpretation.

Visual signals terminate in the *occipital lobe,* and *auditory signals* terminate in the *temporal lobe.*

Conversely, that portion of the cerebral cortex anterior to the central fissure and constituting the posterior half of the frontal lobe is called the *motor cortex* and is devoted almost entirely to control of muscle contractions and body movements. A major share of this motor control is in response to somatosensory signals received from the sensory portions of the cortex, which keep the motor cortex informed at each instant about the positions and motions of the different body parts.

Somatosensory Areas I and II. Figure 47-6 shows two separate sensory areas in the anterior parietal lobe called *somatosensory area I* and *somatosensory area II.* The reason for this division into two areas is that a distinct and separate spatial orientation of the different parts of the body is found in each of these two areas. However, somatosensory area I is so much more extensive and so much more important than somatosensory area II that in popular usage, the term "somatosensory cortex" almost always means area I.

Somatosensory area I has a high degree of localization of the different parts of the body, as shown by the names of virtually all parts of the body in Figure 47-6. By contrast, localization is poor in somatosensory area II, although roughly, the face is represented anteriorly, the arms centrally, and the legs posteriorly.

Little is known about the function of somatosensory area II. It is known that signals enter this area from the brain stem, transmitted upward from both sides of the body. In addition, many signals come secondarily from somatosensory area I, as well as from other sensory areas of the brain, even from the visual and auditory areas. Projections from somatosensory area I are required for function of somatosensory area II. However, removal of parts of somatosensory area II has no apparent effect on the response of neurons in somatosensory area I. Thus, much of what we know about somatic sensation appears to be explained by the functions of somatosensory area I.

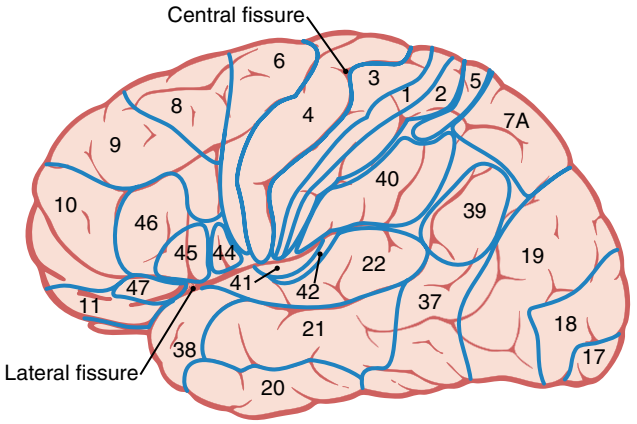


Figure 47-5 Structurally distinct areas, called *Brodmann's areas,* of the human cerebral cortex. Note specifically areas *1, 2,* and *3,* which constitute *primary somatosensory area I,* and areas *5* and *7,* which constitute the *somatosensory association area.*

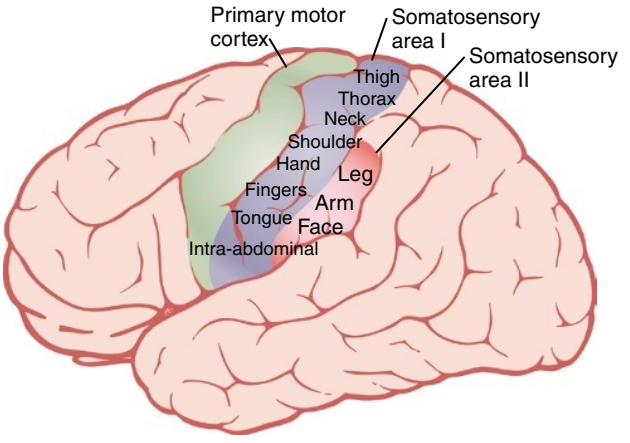


Figure 47-6 Two somatosensory cortical areas, somatosensory areas I and II.

Spatial Orientation of Signals from Different Parts of the Body in Somatosensory Area I. Somatosensory area I lies immediately behind the central fissure, located in the postcentral gyrus of the human cerebral cortex (in Brodmann's areas 3, 1, and 2).

Figure 47-7 shows a cross section through the brain at the level of the *postcentral gyrus,* demonstrating representations of the different parts of the body in separate regions of somatosensory area I. Note, however, that each lateral side of the cortex receives sensory information almost exclusively from the opposite side of the body.

Some areas of the body are represented by large areas in the somatic cortex—the lips the greatest of all, followed by the face and thumb—whereas the trunk and lower part of the body are represented by relatively small areas. The sizes of these areas are directly proportional to the number of specialized sensory receptors in each respective peripheral area of the body. For instance, a great number of specialized nerve endings are found in the lips and thumb, whereas only a few are present in the skin of the body trunk.

Note also that the head is represented in the most lateral portion of somatosensory area I, and the lower part of the body is represented medially.

Layers of the Somatosensory Cortex and Their Function

The cerebral cortex contains *six* layers of neurons, beginning with layer I next to the brain surface and extending progressively deeper to layer VI, shown in Figure 47-8.

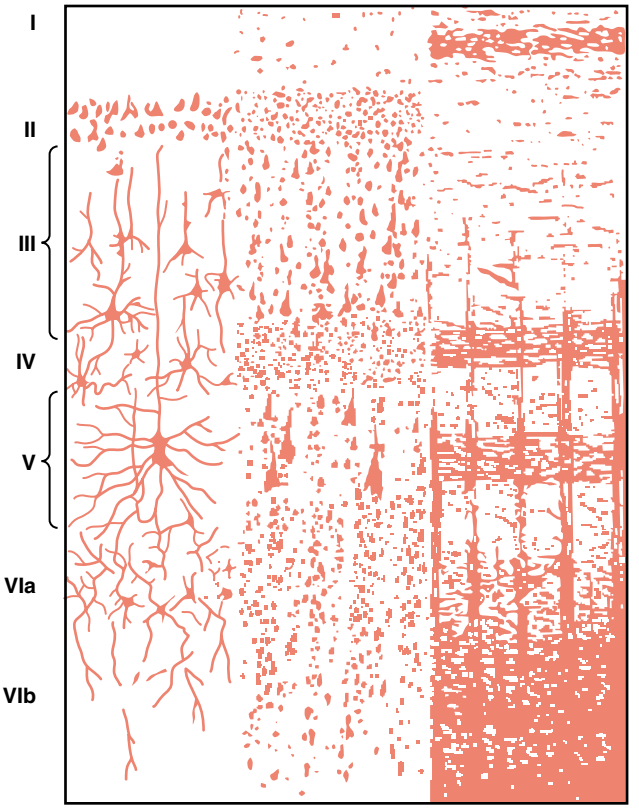


Figure 47-8 Structure of the cerebral cortex, showing I, molecular layer; II, external granular layer; III, layer of small pyramidal cells; IV, internal granular layer; V, large pyramidal cell layer; and VI, layer of fusiform or polymorphic cells. (From Ranson SW, Clark SL [after Brodmann]: Anatomy of the Nervous System. Philadelphia: WB Saunders, 1959.)

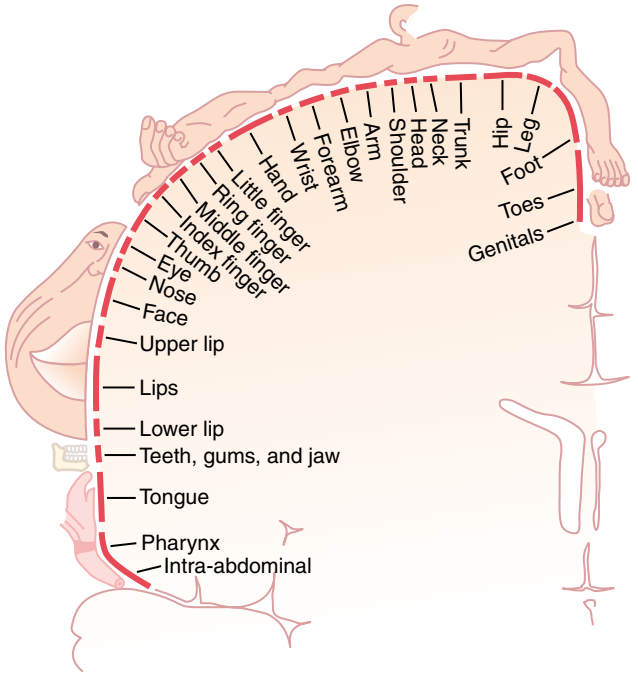


Figure 47-7 Representation of the different areas of the body in somatosensory area I of the cortex. (From Penfield W, Rasmussen T: Cerebral Cortex of Man: A Clinical Study of Localization of Function. New York: Hafner, 1968.)

As would be expected, the neurons in each layer perform functions different from those in other layers. Some of these functions are:

1. The incoming sensory signal excites neuronal layer IV first; then the signal spreads toward the surface of the cortex and also toward deeper layers.
2. Layers I and II receive diffuse, nonspecific input signals from lower brain centers that facilitate specific regions of the cortex; this system is described in Chapter 57. This input mainly controls the overall level of excitability of the respective regions stimulated.
3. The neurons in layers II and III send axons to related portions of the cerebral cortex on the opposite side of the brain through the *corpus callosum.*
4. The neurons in layers V and VI send axons to the deeper parts of the nervous system. Those in layer V are generally larger and project to more distant areas, such as to the basal ganglia, brain stem, and spinal cord, where they control signal transmission. From layer VI, especially large numbers of axons extend to the thalamus, providing signals from the cerebral cortex that interact with and help to control the excitatory levels of incoming sensory signals entering the thalamus.

The Sensory Cortex Is Organized in Vertical Columns of Neurons; Each Column Detects a Different Sensory Spot on the Body with a Specific Sensory Modality

Functionally, the neurons of the somatosensory cortex are arranged in vertical columns extending all the way through the six layers of the cortex, each column having a diameter of 0.3 to 0.5 millimeter and containing perhaps 10,000 neuronal cell bodies. Each of these columns serves a single specific sensory modality, some columns responding to stretch receptors around joints, some to stimulation of tactile hairs, others to discrete localized pressure points on the skin, and so forth. At layer IV, where the input sensory signals first enter the cortex, the columns of neurons function almost entirely separately from one another. At other levels of the columns, interactions occur that initiate analysis of the meanings of the sensory signals.

In the most anterior 5 to 10 millimeters of the postcentral gyrus, located deep in the central fissure in Brodmann's area 3a, an especially large share of the vertical columns respond to muscle, tendon, and joint stretch receptors. Many of the signals from these sensory columns then spread anteriorly, directly to the motor cortex located immediately forward of the central fissure. These signals play a major role in controlling the effluent motor signals that activate sequences of muscle contraction.

As one moves posteriorly in somatosensory area I, more and more of the vertical columns respond to slowly adapting cutaneous receptors, and then still farther posteriorly, greater numbers of the columns are sensitive to deep pressure.

In the most posterior portion of somatosensory area I, about 6 percent of the vertical columns respond only when a stimulus moves across the skin in a particular direction. Thus, this is a still higher order of interpretation of sensory signals; the process becomes even more complex as the signals spread farther backward from somatosensory area I into the parietal cortex, an area called the *somatosensory association area,* as we discuss subsequently.

Functions of Somatosensory Area I

Widespread bilateral excision of somatosensory area I causes loss of the following types of sensory judgment:

1. The person is unable to localize discretely the different sensations in the different parts of the body. However, he or she can localize these sensations crudely, such as to a particular hand, to a major level of the body trunk, or to one of the legs. Thus, it is clear that the brain stem, thalamus, or parts of the cerebral cortex not normally considered to be concerned with somatic sensations can perform some degree of localization.
2. The person is unable to judge critical degrees of pressure against the body.
3. The person is unable to judge the weights of objects.
4. The person is unable to judge shapes or forms of objects. This is called *astereognosis.*
5. The person is unable to judge texture of materials because this type of judgment depends on highly critical sensations caused by movement of the fingers over the surface to be judged.

Note that in the list nothing has been said about loss of pain and temperature sense. In specific absence of only somatosensory area I, appreciation of these sensory modalities is still preserved both in quality and intensity. But the sensations are poorly localized, indicating that pain and temperature *localization* depend greatly on the topographical map of the body in somatosensory area I to localize the source.

Somatosensory Association Areas

Brodmann's areas 5 and 7 of the cerebral cortex, located in the parietal cortex behind somatosensory area I (see Figure 47-5), play important roles in deciphering deeper meanings of the sensory information in the somatosensory areas. Therefore, these areas are called *somatosensory association areas.*

Electrical stimulation in a somatosensory association area can occasionally cause an awake person to experience a complex body sensation, sometimes even the "feeling" of an object such as a knife or a ball. Therefore, it seems clear that the somatosensory association area combines information arriving from multiple points in the primary somatosensory area to decipher its meaning. This also fits with the anatomical arrangement of the neuronal tracts that enter the somatosensory association area because it receives signals from (1) somatosensory area I, (2) the ventrobasal nuclei of the thalamus, (3) other areas of the thalamus, (4) the visual cortex, and (5) the auditory cortex.

Effect of Removing the Somatosensory Association Area—Amorphosynthesis. When the somatosensory association area is removed on one side of the brain, the person loses ability to recognize complex objects and complex forms felt on the opposite side of the body. In addition, he or she loses most of the sense of form of his or her own body or body parts on the opposite side. In fact, the person is mainly oblivious to the opposite side of the body—that is, forgets that it is there. Therefore, he or she also often forgets to use the other side for motor functions as well. Likewise, when feeling objects, the person tends to recognize only one side of the object and forgets that the other side even exists. This complex sensory deficit is called *amorphosynthesis.*

Overall Characteristics of Signal Transmission and Analysis in the Dorsal Column–Medial Lemniscal System

Basic Neuronal Circuit in the Dorsal Column–Medial Lemniscal System. The lower part of Figure 47-9 shows the basic organization of the neuronal circuit of the spinal cord dorsal column pathway, demonstrating that at each synaptic stage, divergence occurs. The upper

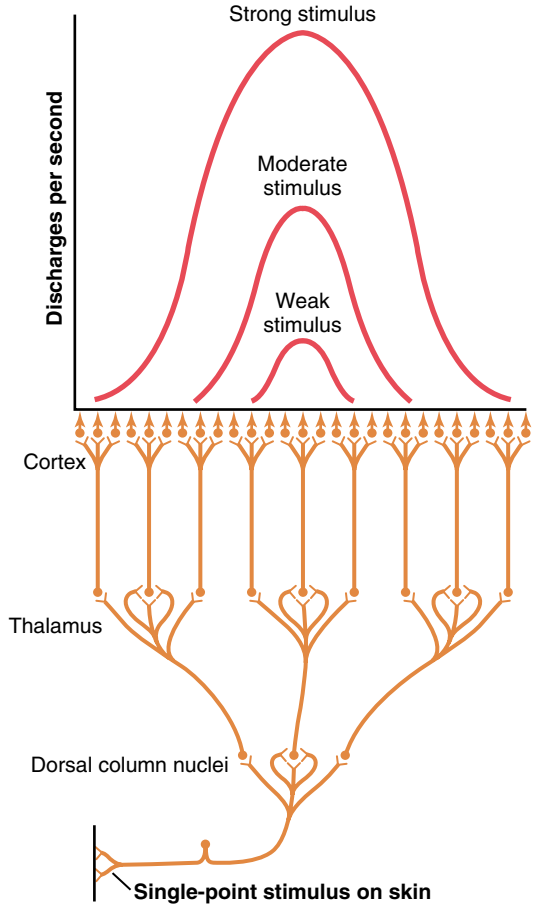


Figure 47-9 Transmission of a pinpoint stimulus signal to the cerebral cortex.

curves of the figure show that the cortical neurons that discharge to the greatest extent are those in a central part of the cortical "field" for each respective receptor. Thus, a weak stimulus causes only the centralmost neurons to fire. A stronger stimulus causes still more neurons to fire, but those in the center discharge at a considerably more rapid rate than do those farther away from the center.

Two-Point Discrimination. A method frequently used to test tactile discrimination is to determine a person's so-called "two-point" discriminatory ability. In this test, two needles are pressed lightly against the skin at the same time, and the person determines whether two points of stimulus are felt or one point. On the tips of the fingers, a person can normally distinguish two separate points even when the needles are as close together as 1 to 2 millimeters. However, on the person's back, the needles must usually be as far apart as 30 to 70 millimeters before two separate points can be detected. The reason for this difference is the different numbers of specialized tactile receptors in the two areas.

Figure 47-10 shows the mechanism by which the dorsal column pathway (as well as all other sensory pathways) transmits two-point discriminatory information. This figure shows two adjacent points on the skin that are strongly stimulated, as well as the areas of the somatosensory

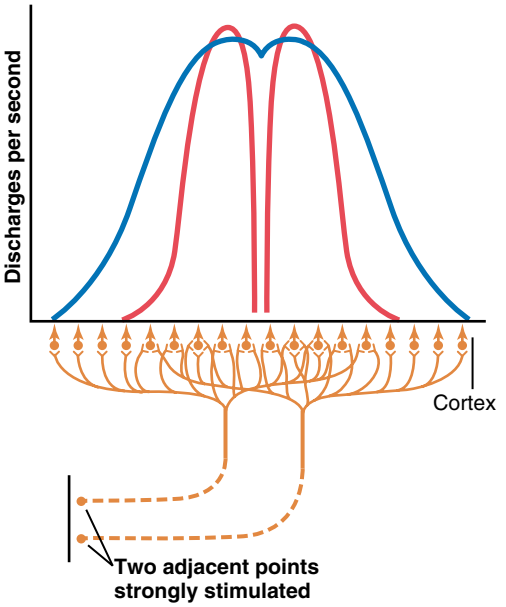


Figure 47-10 Transmission of signals to the cortex from two adjacent pinpoint stimuli. The blue curve represents the pattern of cortical stimulation without "surround" inhibition, and the two red curves represent the pattern when "surround" inhibition does occur.

cortex (greatly enlarged) that are excited by signals from the two stimulated points. The blue curve shows the spatial pattern of cortical excitation when both skin points are stimulated simultaneously. Note that the resultant zone of excitation has two separate peaks. These two peaks, separated by a valley, allow the sensory cortex to detect the presence of two stimulatory points, rather than a single point. The capability of the sensorium to distinguish this presence of two points of stimulation is strongly influenced by another mechanism, *lateral inhibition,* as explained in the next section.

Effect of Lateral Inhibition (Also Called *Surround Inhibition*) to Increase the Degree of Contrast in the Perceived Spatial Pattern. As pointed out in Chapter 46, virtually every sensory pathway, when excited, gives rise simultaneously to lateral *inhibitory* signals; these spread to the sides of the excitatory signal and inhibit adjacent neurons. For instance, consider an excited neuron in a dorsal column nucleus. Aside from the central excitatory signal, short lateral pathways transmit inhibitory signals to the surrounding neurons. That is, these signals pass through additional interneurons that secrete an inhibitory transmitter.

The importance of *lateral inhibition* is that it blocks lateral spread of the excitatory signals and, therefore, increases the degree of contrast in the sensory pattern perceived in the cerebral cortex.

In the case of the dorsal column system, lateral inhibitory signals occur at each synaptic level—for instance, in (1) the dorsal column nuclei of the medulla, (2) the ventrobasal nuclei of the thalamus, and (3) the cortex itself. At each of these levels, the lateral inhibition helps to block lateral spread of the excitatory signal. As a result, the peaks

of excitation stand out, and much of the surrounding diffuse stimulation is blocked. This effect is demonstrated by the two red curves in Figure 47-10, showing complete separation of the peaks when the intensity of lateral inhibition is great.

Transmission of Rapidly Changing and Repetitive Sensations. The dorsal column system is also of particular importance in apprising the sensorium of rapidly changing peripheral conditions. Based on recorded action potentials, this system can recognize changing stimuli that occur in as little as 1/400 of a second.

Vibratory Sensation. Vibratory signals are rapidly repetitive and can be detected as vibration up to 700 cycles per second. The higher-frequency vibratory signals originate from the pacinian corpuscles in the skin and deeper tissues, but lower-frequency signals (below about 200 per second) can originate from Meissner's corpuscles as well. These signals are transmitted only in the dorsal column pathway. For this reason, application of vibration (e.g., from a "tuning fork") to different peripheral parts of the body is an important tool used by neurologists for testing functional integrity of the dorsal columns.

Interpretation of Sensory Stimulus Intensity

The ultimate goal of most sensory stimulation is to apprise the psyche of the state of the body and its surroundings. Therefore, it is important that we discuss briefly some of the principles related to transmission of sensory *stimulus intensity* to the higher levels of the nervous system.

One question that comes to mind is, how is it possible for the sensory system to transmit sensory experiences of tremendously varying intensities? For instance, the auditory system can detect the weakest possible whisper but can also discern the meanings of an explosive sound, even though the sound intensities of these two experiences can vary more than 10 billion times; the eyes can see visual images with light intensities that vary as much as a half million times; and the skin can detect pressure differences of 10,000 to 100,000 times.

As a partial explanation of these effects, Figure 46-4 in the previous chapter shows the relation of the receptor potential produced by the pacinian corpuscle to the intensity of the sensory stimulus. At low stimulus intensity, slight changes in intensity increase the potential markedly, whereas at high levels of stimulus intensity, further increases in receptor potential are slight. Thus, the pacinian corpuscle is capable of accurately measuring extremely minute *changes* in stimulus at low-intensity levels, but at high-intensity levels, the change in stimulus must be much greater to cause the same amount of *change* in receptor potential.

The transduction mechanism for detecting sound by the cochlea of the ear demonstrates still another method for separating gradations of stimulus intensity. When sound stimulates a specific point on the basilar membrane, weak sound stimulates only those hair cells at the point of maximum sound vibration. But as the sound intensity increases, many more hair cells in each direction farther away from the maximum vibratory point also become stimulated. Thus, signals are transmitted over progressively increasing numbers of nerve fibers, which is another mechanism by which stimulus intensity is transmitted to the central nervous system. This mechanism, plus the direct effect of stimulus intensity on impulse rate in each nerve fiber, as well as several other mechanisms, makes it possible for some sensory systems to operate reasonably faithfully at stimulus intensity levels changing as much as millions of times.

Importance of the Tremendous Intensity Range of Sensory Reception. Were it not for the tremendous intensity range of sensory reception that we can experience, the various sensory systems would more often than not be operating in the wrong range. This is demonstrated by the attempts of most people, when taking photographs with a camera, to adjust the light exposure without using a light meter. Left to intuitive judgment of light intensity, a person almost always overexposes the film on bright days and greatly underexposes the film at twilight. Yet that person's own eyes are capable of discriminating with great detail visual objects in bright sunlight or at twilight; the camera cannot do this without very special manipulation because of the narrow critical range of light intensity required for proper exposure of film.

Judgment of Stimulus Intensity

Weber-Fechner Principle—Detection of "Ratio" of Stimulus Strength. In the mid-1800s, Weber first and Fechner later proposed the principle that *gradations of stimulus strength are discriminated approximately in proportion to the logarithm of stimulus strength.* That is, a person already holding 30 grams weight in his or her hand can barely detect an additional 1-gram increase in weight. And, when already holding 300 grams, he or she can barely detect a 10-gram increase in weight. Thus, in this instance, the *ratio* of the change in stimulus strength required for detection remains essentially constant, about 1 to 30, which is what the logarithmic principle means. To express this mathematically.

$$\text{Interpreted signal strength} = \text{Log (Stimulus)} + \text{Constant}$$

More recently, it has become evident that the Weber-Fechner principle is quantitatively accurate only for higher intensities of visual, auditory, and cutaneous sensory experience and applies only poorly to most other types of sensory experience. Yet the Weber-Fechner principle is still a good one to remember because it emphasizes that the greater the background sensory intensity, the greater an additional change must be for the psyche to detect the change.

Power Law. Another attempt by physiopsychologists to find a good mathematical relation is the following formula, known as the power law.

$$\text{Interpreted signal strength} = K \times (\text{Stimulus} - k)^{y}$$

In this formula, the exponent y and the constants K and k are different for each type of sensation.

When this power law relation is plotted on a graph using double logarithmic coordinates, as shown in Figure 47-11, and when appropriate quantitative values for the constants y, K, and k are found, a linear relation can be attained between interpreted stimulus strength and actual stimulus strength over a large range for almost any type of sensory perception.

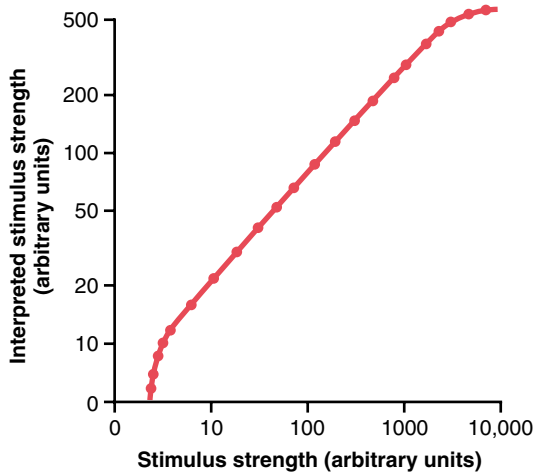


Figure 47-11 Graphical demonstration of the "power law" relation between actual stimulus strength and strength that the psyche interprets it to be. Note that the power law does not hold at either very weak or very strong stimulus strengths.

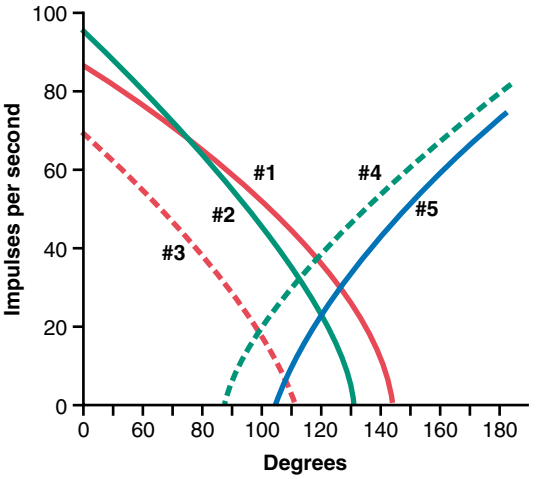


Figure 47-12 Typical responses of five different thalamic neurons in the thalamic ventrobasal complex when the knee joint is moved through its range of motion. (Data from Mountcastle VB, Poggie GF, Werner G: The relation of thalamic cell response to peripheral stimuli varied over an intensive continuum. J Neurophysiol 26:807, 1963.)

Position Senses

The *position senses* are frequently also called *proprioceptive senses*. They can be divided into two subtypes: (1) *static position sense,* which means conscious perception of the orientation of the different parts of the body with respect to one another, and (2) *rate of movement sense,* also called *kinesthesia* or *dynamic proprioception.*

Position Sensory Receptors. Knowledge of position, both static and dynamic, depends on knowing the degrees of angulation of all joints in all planes and their rates of change. Therefore, multiple different types of receptors help to determine joint angulation and are used together for position sense. Both skin tactile receptors and deep receptors near the joints are used. In the case of the fingers, where skin receptors are in great abundance, as much as half of position recognition is believed to be detected through the skin receptors. Conversely, for most of the larger joints of the body, deep receptors are more important.

For determining joint angulation in midranges of motion, among the most important receptors are the *muscle spindles.* They are also exceedingly important in helping to control muscle movement, as we shall see in Chapter 54. When the angle of a joint is changing, some muscles are being stretched while others are loosened, and the net stretch information from the spindles is transmitted into the computational system of the spinal cord and higher regions of the dorsal column system for deciphering joint angulations.

At the extremes of joint angulation, stretch of the ligaments and deep tissues around the joints is an additional important factor in determining position. Types of sensory endings used for this are the pacinian corpuscles, Ruffini's endings, and receptors similar to the Golgi tendon receptors found in muscle tendons.

The pacinian corpuscles and muscle spindles are especially adapted for detecting rapid rates of change. It is likely that these are the receptors most responsible for detecting rate of movement.

Processing of Position Sense Information in the Dorsal Column–Medial Lemniscal Pathway. Referring to Figure 47-12, one sees that *thalamic neurons* responding to joint rotation are of two categories: (1) those maximally stimulated when the joint is at full rotation and (2) those maximally stimulated when the joint is at minimal rotation. Thus, the signals from the individual joint receptors are used to tell the psyche how much each joint is rotated.

Transmission of Less Critical Sensory Signals in the Anterolateral Pathway

The anterolateral pathway for transmitting sensory signals up the spinal cord and into the brain, in contrast to the dorsal column pathway, transmits sensory signals that do not require highly discrete localization of the signal source and do not require discrimination of fine gradations of intensity. These types of signals include pain, heat, cold, crude tactile, tickle, itch, and sexual sensations. In Chapter 48, pain and temperature sensations are discussed specifically.

Anatomy of the Anterolateral Pathway

The *spinal cord anterolateral fibers* originate mainly in dorsal horn laminae I, IV, V, and VI (see Figure 47-2). These laminae are where many of the dorsal root sensory nerve fibers terminate after entering the cord.

As shown in Figure 47-13, the anterolateral fibers cross immediately in the *anterior commissure* of the cord to the opposite *anterior* and *lateral white columns,* where they turn upward toward the brain by way of the *anterior spinothalamic* and *lateral spinothalamic tracts.*

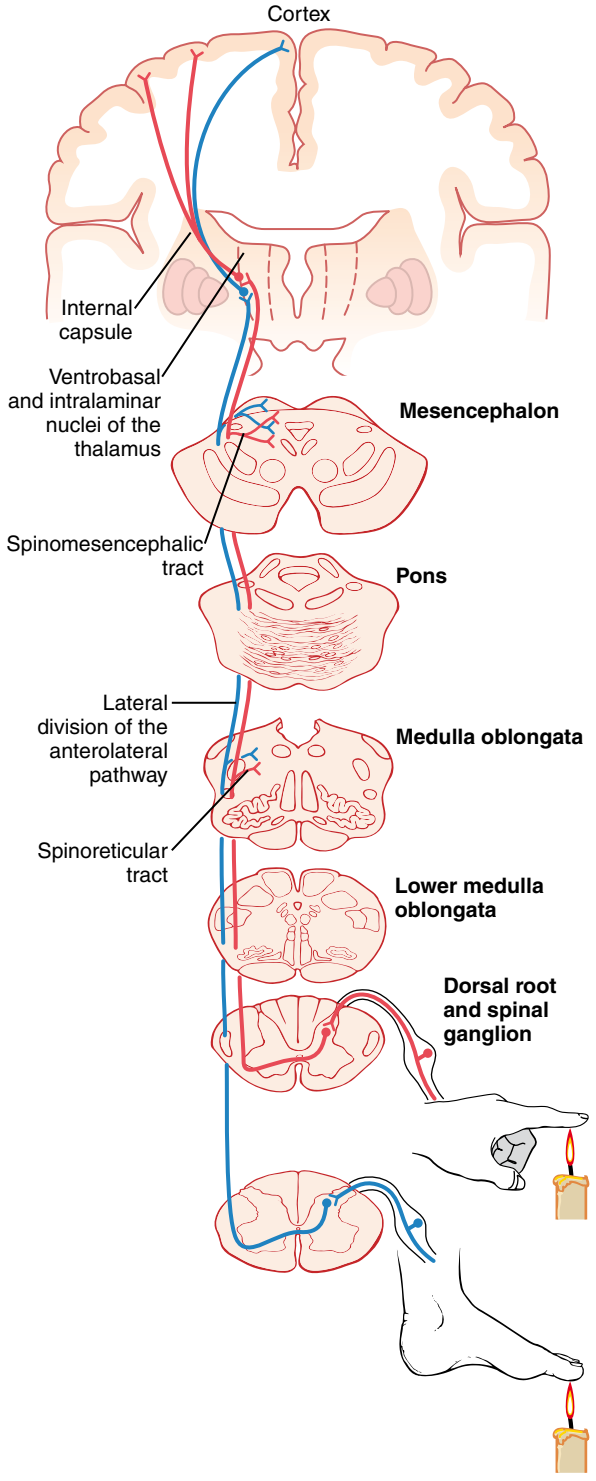


Figure 47-13 Anterior and lateral divisions of the anterolateral sensory pathway.

The upper terminus of the two spinothalamic tracts is mainly twofold: (1) throughout the *reticular nuclei of the brain stem* and (2) in two different nuclear complexes of the thalamus, the *ventrobasal complex* and the *intralaminar nuclei.* In general, the tactile signals are transmitted mainly into the ventrobasal complex, terminating in some of the same thalamic nuclei where the dorsal column tactile signals terminate. From here, the signals are transmitted to the somatosensory cortex along with the signals from the dorsal columns.

Conversely, only a small fraction of the pain signals project directly to the ventrobasal complex of the thalamus. Instead, most pain signals terminate in the reticular nuclei of the brain stem and from there are relayed to the intralaminar nuclei of the thalamus where the pain signals are further processed, as discussed in greater detail in Chapter 48.

Characteristics of Transmission in the Anterolateral Pathway. In general, the same principles apply to transmission in the anterolateral pathway as in the dorsal column–medial lemniscal system, except for the following differences: (1) the velocities of transmission are only one-third to one-half those in the dorsal column–medial lemniscal system, ranging between 8 and 40 m/sec; (2) the degree of spatial localization of signals is poor; (3) the gradations of intensities are also far less accurate, most of the sensations being recognized in 10 to 20 gradations of strength, rather than as many as 100 gradations for the dorsal column system; and (4) the ability to transmit rapidly changing or rapidly repetitive signals is poor.

Thus, it is evident that the anterolateral system is a cruder type of transmission system than the dorsal column–medial lemniscal system. Even so, certain modalities of sensation are transmitted only in this system and not at all in the dorsal column–medial lemniscal system. They are pain, temperature, tickle, itch, and sexual sensations, in addition to crude touch and pressure.

Some Special Aspects of Somatosensory Function

Function of the Thalamus in Somatic Sensation

When the somatosensory cortex of a human being is destroyed, that person loses most critical tactile sensibilities, but a slight degree of crude tactile sensibility does return. Therefore, it must be assumed that the thalamus (as well as other lower centers) has a slight ability to discriminate tactile sensation, even though the thalamus normally functions mainly to relay this type of information to the cortex.

Conversely, loss of the somatosensory cortex has little effect on one's perception of pain sensation and only a moderate effect on the perception of temperature. Therefore, there is much reason to believe that the lower brain stem, the thalamus, and other associated basal regions of the brain play dominant roles in discrimination of these sensibilities. It is interesting that these sensibilities appeared very early in the phylogenetic development of animals, whereas the critical tactile sensibilities and the somatosensory cortex were late developments.

Cortical Control of Sensory Sensitivity—"Corticofugal" Signals

In addition to somatosensory signals transmitted from the periphery to the brain, *corticofugal* signals are transmitted in the backward direction from the cerebral cortex to the lower sensory relay stations of the thalamus, medulla, and spinal cord; they control the intensity of sensitivity of the sensory input.

Corticofugal signals are almost entirely inhibitory, so when sensory input intensity becomes too great, the corticofugal signals automatically decrease transmission in

the relay nuclei. This does two things: First, it decreases lateral spread of the sensory signals into adjacent neurons and, therefore, increases the degree of sharpness in the signal pattern. Second, it keeps the sensory system operating in a range of sensitivity that is not so low that the signals are ineffectual nor so high that the system is swamped beyond its capacity to differentiate sensory patterns. This principle of corticofugal sensory control is used by all sensory systems, not only the somatic system, as explained in subsequent chapters.

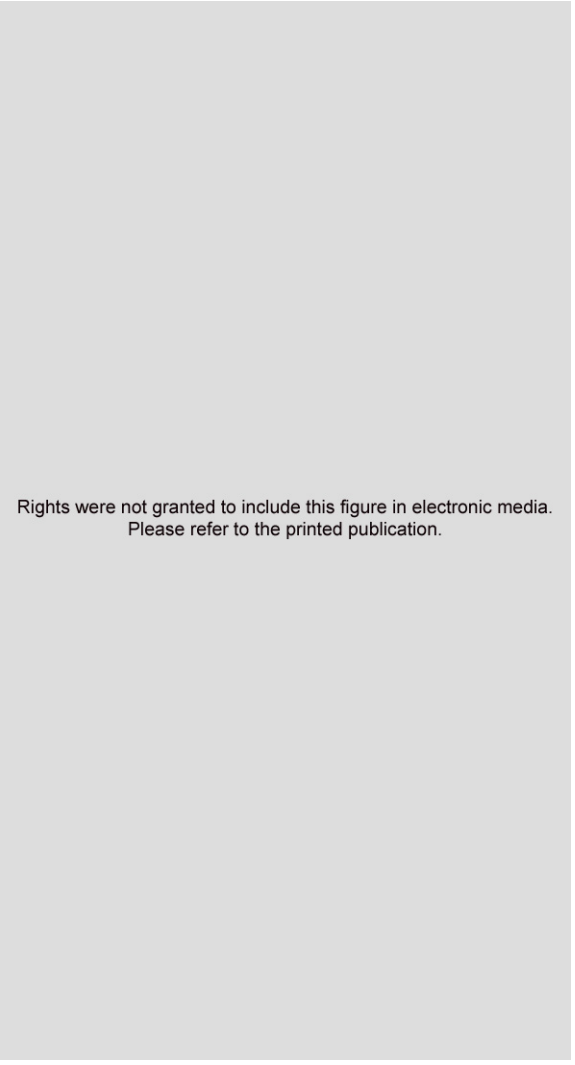


Figure 47-14 Dermatomes. (Modified from Grinker RR, Sahs AL: Neurology, 6th ed. Springfield, Ill: Charles C Thomas, 1966. Courtesy Charles C Thomas, Publisher, Ltd., Springfield, Ill.)

Segmental Fields of Sensation—Dermatomes

Each spinal nerve innervates a "segmental field" of the skin called a *dermatome.* The different dermatomes are shown in Figure 47-14. They are shown in the figure as if there were distinct borders between the adjacent dermatomes, which is far from true because much overlap exists from segment to segment.

The figure shows that the anal region of the body lies in the dermatome of the most distal cord segment, dermatome S5. In the embryo, this is the tail region and the most distal portion of the body. The legs originate embryologically from the lumbar and upper sacral segments (L2 to S3), rather than from the distal sacral segments, which is evident from the dermatomal map. One can use a dermatomal map as shown in Figure 47-14 to determine the level in the spinal cord at which a cord injury has occurred when the peripheral sensations are disturbed by the injury.

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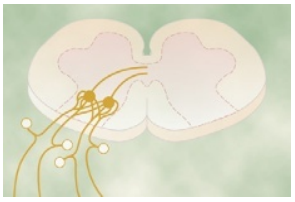
CHAPTER 48

Somatic Sensations: II. Pain, Headache, and Thermal Sensations



Many, if not most, ailments of the body cause pain. Furthermore, the ability to diagnose different diseases depends to a great extent on a physician's knowledge of the different qualities of pain. For these reasons, the first part of this chapter is devoted mainly to pain and to the physiologic bases of some associated clinical phenomena.

Pain Is a Protective Mechanism. Pain occurs whenever tissues are being damaged, and it causes the individual to react to remove the pain stimulus. Even such simple activities as sitting for a long time on the ischia can cause tissue destruction because of lack of blood flow to the skin where it is compressed by the weight of the body. When the skin becomes painful as a result of the ischemia, the person normally shifts weight subconsciously. But a person who has lost the pain sense, as after spinal cord injury, fails to feel the pain and, therefore, fails to shift. This soon results in total breakdown and desquamation of the skin at the areas of pressure.

Types of Pain and Their Qualities—Fast Pain and Slow Pain

Pain has been classified into two major types: *fast pain* and *slow pain.* Fast pain is felt within about 0.1 second after a pain stimulus is applied, whereas slow pain begins only after 1 second or more and then increases slowly over many seconds and sometimes even minutes. During the course of this chapter, we shall see that the conduction pathways for these two types of pain are different and that each of them has specific qualities.

Fast pain is also described by many alternative names, such as *sharp pain, pricking pain, acute pain,* and *electric pain.* This type of pain is felt when a needle is stuck into the skin, when the skin is cut with a knife, or when the skin is acutely burned. It is also felt when the skin is subjected to electric shock. Fast-sharp pain is not felt in most deeper tissues of the body.

Slow pain also goes by many names, such as *slow burning pain, aching pain, throbbing pain, nauseous pain,* and *chronic pain.* This type of pain is usually associated with *tissue destruction.* It can lead to prolonged, almost unbearable suffering. It can occur both in the skin and in almost any deep tissue or organ.

Pain Receptors and Their Stimulation

Pain Receptors Are Free Nerve Endings. The pain receptors in the skin and other tissues are all free nerve endings. They are widespread in the superficial layers of the *skin,* as well as in certain internal tissues, such as the *periosteum,* the *arterial walls,* the *joint surfaces,* and the *falx* and *tentorium* in the cranial vault. Most other deep tissues are only sparsely supplied with pain endings; nevertheless, any widespread tissue damage can summate to cause the slow-chronic-aching type of pain in most of these areas.

Three Types of Stimuli Excite Pain Receptors—Mechanical, Thermal, and Chemical. Pain can be elicited by multiple types of stimuli. They are classified as *mechanical, thermal,* and *chemical pain stimuli.* In general, fast pain is elicited by the mechanical and thermal types of stimuli, whereas slow pain can be elicited by all three types.

Some of the chemicals that excite the chemical type of pain are *bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine,* and *proteolytic enzymes.* In addition, *prostaglandins* and *substance P* enhance the sensitivity of pain endings but do not directly excite them. The chemical substances are especially important in stimulating the slow, suffering type of pain that occurs after tissue injury.

Nonadapting Nature of Pain Receptors. In contrast to most other sensory receptors of the body, pain receptors adapt very little and sometimes not at all. In fact, under some conditions, excitation of pain fibers becomes progressively greater, especially so for slow-aching-nauseous pain, as the pain stimulus continues. This increase in sensitivity of the pain receptors is called *hyperalgesia.*

One can readily understand the importance of this failure of pain receptors to adapt because it allows the pain to keep the person apprised of a tissue-damaging stimulus as long as it persists.

Rate of Tissue Damage as a Stimulus for Pain

The average person begins to perceive pain when the skin is heated above 45°C, as shown in Figure 48-1. This is also the temperature at which the tissues begin to be damaged by heat; indeed, the tissues are eventually destroyed if the temperature remains above this level indefinitely. Therefore, it is immediately apparent that pain resulting from heat is closely correlated with the *rate at which damage to the tissues is occurring* and not with the total damage that has already occurred.

The intensity of pain is also closely correlated with the *rate of tissue damage* from causes other than heat, such as bacterial infection, tissue ischemia, tissue contusion, and so forth.

Special Importance of Chemical Pain Stimuli During Tissue Damage. Extracts from damaged tissue cause intense pain when injected beneath the normal skin. Most of the chemicals listed earlier that excite the chemical pain receptors can be found in these extracts. One chemical that seems to be more painful than others is *bradykinin.* Many researchers have suggested that bradykinin might be the agent most responsible for causing pain following tissue damage. Also, the intensity of the pain felt correlates with the local increase in potassium ion concentration or the increase in proteolytic enzymes that directly attack the nerve endings and excite pain by making the nerve membranes more permeable to ions.

Tissue Ischemia as a Cause of Pain. When blood flow to a tissue is blocked, the tissue often becomes very painful within a few minutes. The greater the rate of metabolism of the tissue, the more rapidly the pain appears. For instance, if a blood pressure cuff is placed around the upper arm and inflated until the arterial blood flow ceases, exercise of the forearm muscles sometimes can cause muscle pain within 15 to 20 seconds. In the absence of muscle exercise, the pain may not appear for 3 to 4 minutes even though the muscle blood flow remains zero.

One of the suggested causes of pain during ischemia is accumulation of large amounts of lactic acid in the tissues, formed as a consequence of anaerobic metabolism (metabolism without oxygen). It is also probable that other chemical agents, such as bradykinin and proteolytic enzymes, are formed in the tissues because of cell damage and that these, in addition to lactic acid, stimulate the pain nerve endings.

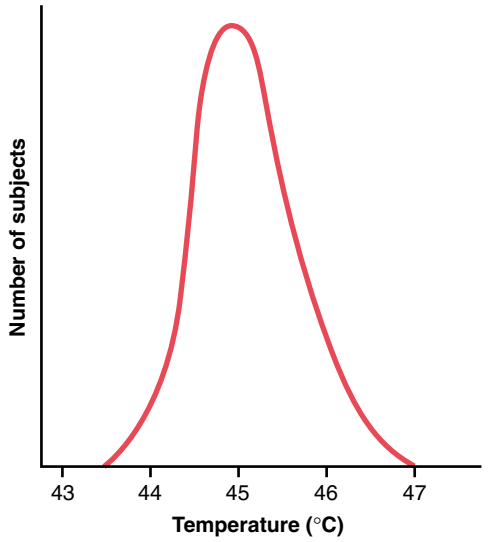


Figure 48-1 Distribution curve obtained from a large number of persons showing the minimal skin temperature that will cause pain. (Modified from Hardy DJ: Nature of pain. J Clin Epidemiol 4:22, 1956.)

Muscle Spasm as a Cause of Pain. Muscle spasm is also a common cause of pain, and it is the basis of many clinical pain syndromes. This pain probably results partially from the direct effect of muscle spasm in stimulating mechanosensitive pain receptors, but it might also result from the indirect effect of muscle spasm to compress the blood vessels and cause ischemia. Also, the spasm increases the rate of metabolism in the muscle tissue, thus making the relative ischemia even greater, creating ideal conditions for the release of chemical pain-inducing substances.

Dual Pathways for Transmission of Pain Signals into the Central Nervous System

Even though all pain receptors are free nerve endings, these endings use two separate pathways for transmitting pain signals into the central nervous system. The two pathways mainly correspond to the two types of pain—a *fast-sharp pain pathway* and a *slow-chronic pain pathway.*

Peripheral Pain Fibers—"Fast" and "Slow" Fibers. The fast-sharp pain signals are elicited by either mechanical or thermal pain stimuli; they are transmitted in the peripheral nerves to the spinal cord by small type Aδ fibers at velocities between 6 and 30 m/sec. Conversely, the slow-chronic type of pain is elicited mostly by chemical types of pain stimuli but sometimes by persisting mechanical or thermal stimuli. This slow-chronic pain is transmitted to the spinal cord by type C fibers at velocities between 0.5 and 2 m/sec.

Because of this double system of pain innervation, a sudden painful stimulus often gives a "double" pain sensation: a fast-sharp pain that is transmitted to the brain by the Aδ fiber pathway, followed a second or so later by a slow pain that is transmitted by the C fiber pathway. The sharp pain apprises the person rapidly of a damaging influence and, therefore, plays an important role in making the person react immediately to remove himself or herself from the stimulus. The slow pain tends to become greater over time. This sensation eventually produces intolerable

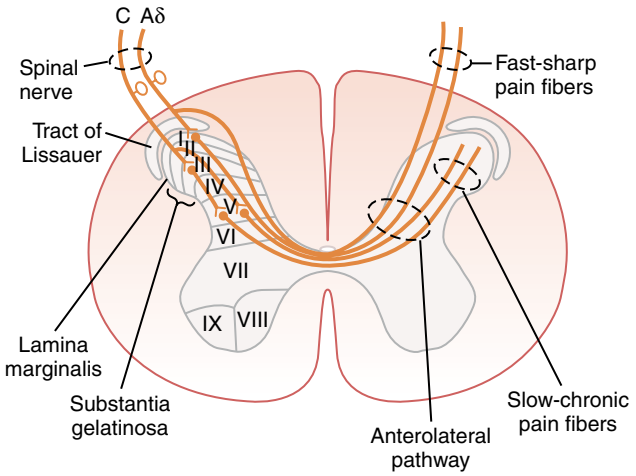


Figure 48-2 Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain.

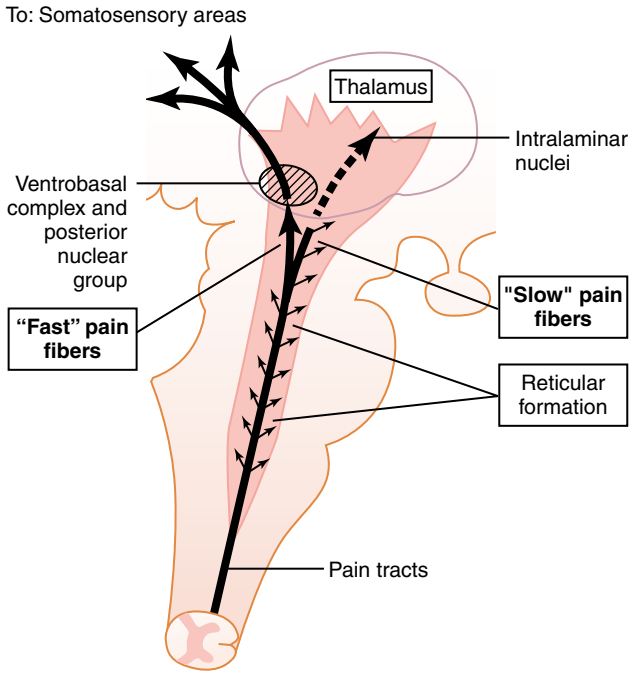


Figure 48-3 Transmission of pain signals into the brain stem, thalamus, and cerebral cortex by way of the *fast pricking pain pathway* and the *slow burning pain pathway.*

pain and makes the person keep trying to relieve the cause of the pain.

On entering the spinal cord from the dorsal spinal roots, the pain fibers terminate on relay neurons in the dorsal horns. Here again, there are two systems for processing the pain signals on their way to the brain, as shown in Figures 48-2 and 48-3.

Dual Pain Pathways in the Cord and Brain Stem—The Neospinothalamic Tract and the Paleospinothalamic Tract

On entering the spinal cord, the pain signals take two pathways to the brain, through (1) the *neospinothalamic tract* and (2) the *paleospinothalamic tract.*

Neospinothalamic Tract for Fast Pain. The fast type Aδ pain fibers transmit mainly mechanical and acute thermal pain. They terminate mainly in lamina I (lamina marginalis) of the dorsal horns, as shown in Figure 48-2, and there excite second-order neurons of the neospinothalamic tract. These give rise to long fibers that cross immediately to the opposite side of the cord through the anterior commissure and then turn upward, passing to the brain in the anterolateral columns.

Termination of the Neospinothalamic Tract in the Brain Stem and Thalamus. A few fibers of the neospinothalamic tract terminate in the reticular areas of the brain stem, but most pass all the way to the thalamus without interruption, terminating in the *ventrobasal complex* along with the dorsal column–medial lemniscal tract for tactile sensations, as was discussed in Chapter 47. A few fibers also terminate in the posterior nuclear group of the thalamus. From these thalamic areas, the signals are transmitted to other basal areas of the brain, as well as to the somatosensory cortex.

Capability of the Nervous System to Localize Fast Pain in the Body. The fast-sharp type of pain can be localized much more exactly in the different parts of the body than can slow-chronic pain. However, when only pain receptors are stimulated, without the simultaneous stimulation of tactile receptors, even fast pain may be poorly localized, often only within 10 centimeters or so of the stimulated area. Yet when tactile receptors that excite the dorsal column–medial lemniscal system are simultaneously stimulated, the localization can be nearly exact.

Glutamate, the Probable Neurotransmitter of the Type Aδ Fast Pain Fibers. It is believed that *glutamate* is the neurotransmitter substance secreted in the spinal cord at the type Aδ pain nerve fiber endings. This is one of the most widely used excitatory transmitters in the central nervous system, usually having a duration of action lasting for only a few milliseconds.

Paleospinothalamic Pathway for Transmitting Slow-Chronic Pain. The paleospinothalamic pathway is a much older system and transmits pain mainly from the peripheral slow-chronic type C pain fibers, although it does transmit some signals from type Aδ fibers as well. In this pathway, the peripheral fibers terminate in the spinal cord almost entirely in laminae II and III of the dorsal horns, which together are called the *substantia gelatinosa,* as shown by the lateral most dorsal root type C fiber in Figure 48-2. Most of the signals then pass through one or more additional short fiber neurons within the dorsal horns themselves before entering mainly lamina V, also in the dorsal horn. Here the last neurons in the series give rise to long axons that mostly join the fibers from the fast pain pathway, passing first through the anterior commissure to the opposite side of the cord, then upward to the brain in the anterolateral pathway.

Substance P, the Probable Slow-Chronic Neurotransmitter of Type C Nerve Endings. Research suggests that type C pain fiber terminals entering the spinal cord release both glutamate transmitter and substance P transmitter. The glutamate transmitter acts instantaneously and lasts for only a few milliseconds. Substance P is released much more slowly, building up in concentration over a period of seconds or even minutes. In fact, it has been suggested that the "double" pain sensation one feels after a pinprick might result partly from the fact that the glutamate transmitter gives a faster pain sensation, whereas the substance P transmitter gives a more lagging sensation. Regardless of the yet unknown details, it seems clear that glutamate is the neurotransmitter most involved in transmitting fast pain into the central nervous system, and substance P is concerned with slow-chronic pain.

Projection of the Paleospinothalamic Pathway (Slow-Chronic Pain Signals) into the Brain Stem and Thalamus. The slow-chronic paleospinothalamic pathway terminates widely in the brain stem, in the large shaded area shown in Figure 48-3. Only one tenth to one fourth of the fibers pass all the way to the thalamus. Instead, most terminate in one of three areas: (1) the *reticular nuclei* of the medulla, pons, and mesencephalon; (2) the *tectal area* of the mesencephalon deep to the superior and inferior colliculi; or (3) the *periaqueductal gray region* surrounding the aqueduct of Sylvius. These lower regions of the brain appear to be important for feeling the suffering types of pain, because animals whose brains have been sectioned above the mesencephalon to block pain signals from reaching the cerebrum still evince undeniable evidence of suffering when any part of the body is traumatized. From the brain stem pain areas, multiple short-fiber neurons relay the pain signals upward into the intralaminar and ventrolateral nuclei of the thalamus and into certain portions of the hypothalamus and other basal regions of the brain.

Very Poor Capability of the Nervous System to Localize Precisely the Source of Pain Transmitted in the Slow-Chronic Pathway. Localization of pain transmitted by way of the paleospinothalamic pathway is imprecise. For instance, slow-chronic pain can usually be localized only to a major part of the body, such as to one arm or leg but not to a specific point on the arm or leg. This is in keeping with the multisynaptic, diffuse connectivity of this pathway. It explains why patients often have serious difficulty in localizing the source of some chronic types of pain.

Function of the Reticular Formation, Thalamus, and Cerebral Cortex in the Appreciation of Pain. Complete removal of the somatic sensory areas of the cerebral cortex does not destroy an animal's ability to perceive pain. Therefore, it is likely that pain impulses entering the brain stem reticular formation, the thalamus, and other lower brain centers cause conscious perception of pain. This does not mean that the cerebral cortex has nothing to do with normal pain appreciation; electrical stimulation of cortical somatosensory areas does cause a human being to perceive mild pain from about 3 percent of the points stimulated. However, it is believed that the cortex plays an especially important role in interpreting pain quality, even though pain perception might be principally the function of lower centers.

Special Capability of Pain Signals to Arouse Overall Brain Excitability. Electrical stimulation in the *reticular areas of the brain stem* and in the *intralaminar nuclei of the thalamus,* the areas where the slow-suffering type of pain terminates, has a strong arousal effect on nervous activity throughout the entire brain. In fact, these two areas constitute part of the brain's principal "arousal system," which is discussed in Chapter 59. This explains why it is almost impossible for a person to sleep when he or she is in severe pain.

Surgical Interruption of Pain Pathways. When a person has severe and intractable pain (sometimes resulting from rapidly spreading cancer), it is necessary to relieve the pain. To do this, the pain nervous pathways can be cut at any one of several points. If the pain is in the lower part of the body, a *cordotomy* in the thoracic region of the spinal cord often relieves the pain for a few weeks to a few months. To do this, the spinal cord on the side opposite to the pain is partially cut in its *anterolateral quadrant* to interrupt the anterolateral sensory pathway.

A cordotomy, however, is not always successful in relieving pain, for two reasons. First, many pain fibers from the upper part of the body do not cross to the opposite side of the spinal cord until they have reached the brain, so the cordotomy does not transect these fibers. Second, pain frequently returns several months later, partly as a result of sensitization of other pathways that normally are too weak to be effectual (e.g., sparse pathways in the dorsolateral cord). Another experimental operative procedure to relieve pain has been to cauterize specific pain areas in the intralaminar nuclei in the thalamus, which often relieves suffering types of pain while leaving intact one's appreciation of "acute" pain, an important protective mechanism.

Pain Suppression ("Analgesia") System in the Brain and Spinal Cord

The degree to which a person reacts to pain varies tremendously. This results partly from a capability of the brain itself to suppress input of pain signals to the nervous system by activating a pain control system, called an *analgesia system.*

The analgesia system is shown in Figure 48-4. It consists of three major components: (1) The *periaqueductal gray* and *periventricular areas* of the mesencephalon and upper pons surround the aqueduct of Sylvius and

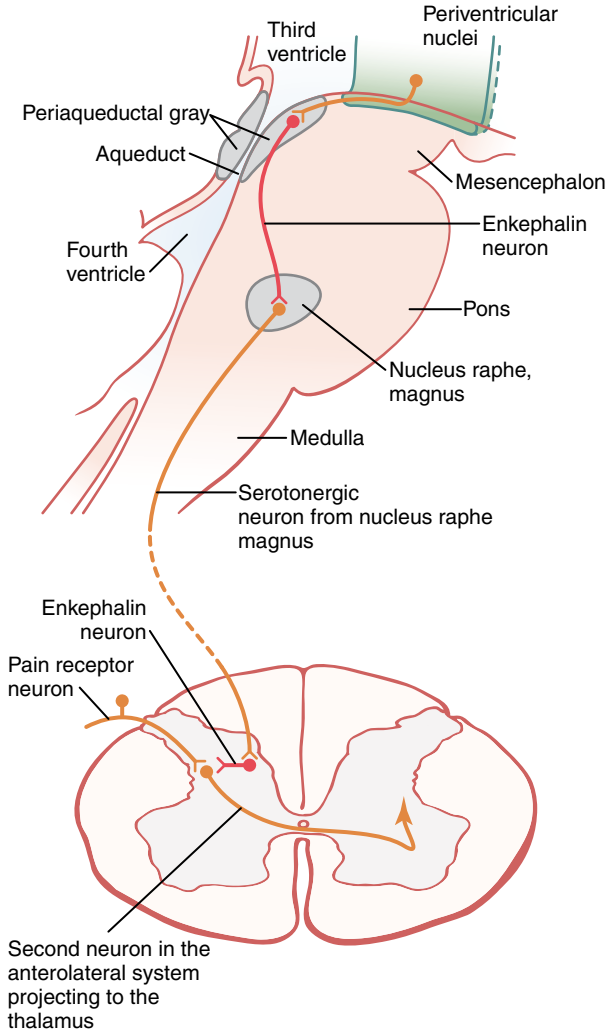


Figure 48-4 Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of *enkephalin-secreting neurons* that suppress pain signals in both the cord and the brain stem.

portions of the third and fourth ventricles. Neurons from these areas send signals to (2) the *raphe magnus nucleus,* a thin midline nucleus located in the lower pons and upper medulla, and the *nucleus reticularis paragigantocellularis,* located laterally in the medulla. From these nuclei, second-order signals are transmitted down the dorsolateral columns in the spinal cord to (3) a *pain inhibitory complex located in the dorsal horns of the spinal cord.* At this point, the analgesia signals can block the pain before it is relayed to the brain.

Electrical stimulation either in the periaqueductal gray area or in the raphe magnus nucleus can suppress many strong pain signals entering by way of the dorsal spinal roots. Also, stimulation of areas at still higher levels of the brain that excite the periaqueductal gray area can also suppress pain. Some of these areas are (1) the *periventricular nuclei in the hypothalamus,* lying adjacent to the third ventricle, and (2) to a lesser extent, the *medial forebrain bundle,* also in the hypothalamus.

Several transmitter substances are involved in the analgesia system; especially involved are *enkephalin* and *serotonin.* Many nerve fibers derived from the periventricular nuclei and from the periaqueductal gray area secrete enkephalin at their endings. Thus, as shown in Figure 48-4, the endings of many fibers in the raphe magnus nucleus release enkephalin when stimulated.

Fibers originating in this area send signals to the dorsal horns of the spinal cord to secrete serotonin at their endings. The serotonin causes local cord neurons to secrete enkephalin as well. The enkephalin is believed to cause both *presynaptic* and *postsynaptic inhibition* of incoming type C and type Aδ pain fibers where they synapse in the dorsal horns.

Thus, the analgesia system can block pain signals at the initial entry point to the spinal cord. In fact, it can also block many local cord reflexes that result from pain signals, especially withdrawal reflexes described in Chapter 54.

Brain's Opiate System—Endorphins and Enkephalins

More than 40 years ago it was discovered that injection of minute quantities of morphine either into the periventricular nucleus around the third ventricle or into the periaqueductal gray area of the brain stem causes an extreme degree of analgesia. In subsequent studies, it has been found that morphine-like agents, mainly the opiates, also act at many other points in the analgesia system, including the dorsal horns of the spinal cord. Because most drugs that alter excitability of neurons do so by acting on synaptic receptors, it was assumed that the "morphine receptors" of the analgesia system must be receptors for some morphine-like neurotransmitter that is naturally secreted in the brain. Therefore, an extensive search was undertaken for the natural opiate of the brain. About a dozen such opiate-like substances have now been found at different points of the nervous system; all are breakdown products of three large protein molecules: *pro-opiomelanocortin, proenkephalin,* and *prodynorphin.* Among the more important of these opiate-like substances are *β-endorphin, met-enkephalin, leu-enkephalin*, and *dynorphin.*

The two enkephalins are found in the brain stem and spinal cord, in the portions of the analgesia system described earlier, and β-endorphin is present in both the hypothalamus and the pituitary gland. Dynorphin is found mainly in the same areas as the enkephalins, but in much lower quantities.

Thus, although the fine details of the brain's opiate system are not understood, *activation of the analgesia system* by nervous signals entering the periaqueductal gray and periventricular areas, or *inactivation of pain pathways* by morphine-like drugs, can almost totally suppress many pain signals entering through the peripheral nerves.

Inhibition of Pain Transmission by Simultaneous Tactile Sensory Signals

Another important event in the saga of pain control was the discovery that stimulation of large-type Aβ sensory fibers from peripheral tactile receptors can depress transmission

of pain signals from the same body area. This presumably results from local lateral inhibition in the spinal cord. It explains why such simple maneuvers as rubbing the skin near painful areas is often effective in relieving pain. And it probably also explains why liniments are often useful for pain relief.

This mechanism and the simultaneous psychogenic excitation of the central analgesia system are probably also the basis of pain relief by *acupuncture.*

Treatment of Pain by Electrical Stimulation

Several clinical procedures have been developed for suppressing pain by electrical stimulation. Stimulating electrodes are placed on selected areas of the skin or, on occasion, implanted over the spinal cord, supposedly to stimulate the dorsal sensory columns.

In some patients, electrodes have been placed stereotaxically in appropriate intralaminar nuclei of the thalamus or in the periventricular or periaqueductal area of the diencephalon. The patient can then personally control the degree of stimulation. Dramatic relief has been reported in some instances. Also, pain relief has been reported to last for as long as 24 hours after only a few minutes of stimulation.

Referred Pain

Often a person feels pain in a part of the body that is fairly remote from the tissue causing the pain. This is called *referred pain.* For instance, pain in one of the visceral organs often is referred to an area on the body surface. Knowledge of the different types of referred pain is important in clinical diagnosis because in many visceral ailments the only clinical sign is referred pain.

Mechanism of Referred Pain. Figure 48-5 shows the probable mechanism by which most pain is referred. In the figure, branches of visceral pain fibers are shown to synapse in the spinal cord on the same second-order neurons (1 and 2) that receive pain signals from the skin. When the visceral pain fibers are stimulated, pain signals from the viscera are conducted through at least some of the same neurons that conduct pain signals from the skin, and the person has the feeling that the sensations originate in the skin itself.

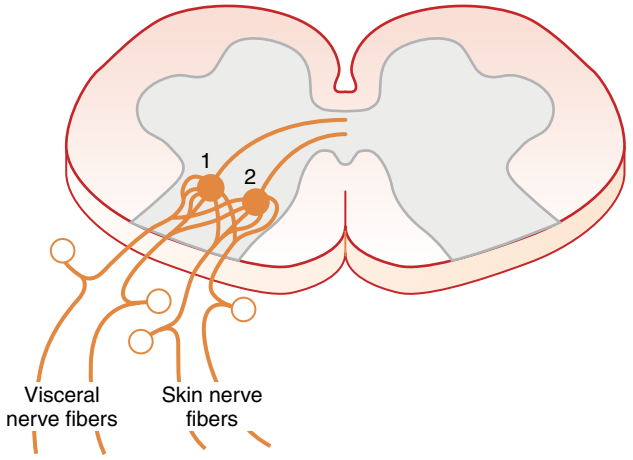


Figure 48-5 Mechanism of referred pain and referred hyperalgesia.

Visceral Pain

Pain from the different viscera of the abdomen and chest is one of the few criteria that can be used for diagnosing visceral inflammation, visceral infectious disease, and other visceral ailments. Often, the viscera have sensory receptors for no other modalities of sensation besides pain. Also, visceral pain differs from surface pain in several important aspects.

One of the most important differences between surface pain and visceral pain is that highly localized types of damage to the viscera seldom cause severe pain. For instance, a surgeon can cut the gut entirely in two in a patient who is awake without causing significant pain. Conversely, any stimulus that causes *diffuse stimulation of pain nerve endings* throughout a viscus causes pain that can be severe. For instance, ischemia caused by occluding the blood supply to a large area of gut stimulates many diffuse pain fibers at the same time and can result in extreme pain.

Causes of True Visceral Pain

Any stimulus that excites pain nerve endings in diffuse areas of the viscera can cause visceral pain. Such stimuli include ischemia of visceral tissue, chemical damage to the surfaces of the viscera, spasm of the smooth muscle of a hollow viscus, excess distention of a hollow viscus, and stretching of the connective tissue surrounding or within the viscus. Essentially all visceral pain that originates in the thoracic and abdominal cavities is transmitted through small type C pain fibers and, therefore, can transmit only the chronic-aching-suffering type of pain.

Ischemia. Ischemia causes visceral pain in the same way that it does in other tissues, presumably because of the formation of acidic metabolic end products or tissue-degenerative products such as bradykinin, proteolytic enzymes, or others that stimulate pain nerve endings.

Chemical Stimuli. On occasion, damaging substances leak from the gastrointestinal tract into the peritoneal cavity. For instance, proteolytic acidic gastric juice may leak through a ruptured gastric or duodenal ulcer. This juice causes widespread digestion of the visceral peritoneum, thus stimulating broad areas of pain fibers. The pain is usually excruciatingly severe.

Spasm of a Hollow Viscus. Spasm of a portion of the gut, the gallbladder, a bile duct, a ureter, or any other hollow viscus can cause pain, possibly by mechanical stimulation of the pain nerve endings. Or the spasm might cause diminished blood flow to the muscle, combined with the muscle's increased metabolic need for nutrients, thus causing severe pain.

Often pain from a spastic viscus occurs in the form of *cramps,* with the pain increasing to a high degree of severity and then subsiding. This process continues intermittently, once every few minutes. The intermittent cycles result from periods of contraction of smooth muscle. For instance, each time a peristaltic wave travels along an overly excitable spastic gut, a cramp occurs. The cramping type of pain frequently occurs in appendicitis, gastroenteritis, constipation,

menstruation, parturition, gallbladder disease, or ureteral obstruction.

Overdistention of a Hollow Viscus. Extreme overfilling of a hollow viscus also can result in pain, presumably because of overstretch of the tissues themselves. Overdistention can also collapse the blood vessels that encircle the viscus or that pass into its wall, thus perhaps promoting ischemic pain.

Insensitive Viscera. A few visceral areas are almost completely insensitive to pain of any type. These include the parenchyma of the liver and the alveoli of the lungs. Yet the liver *capsule* is extremely sensitive to both direct trauma and stretch, and the *bile ducts* are also sensitive to pain. In the lungs, even though the alveoli are insensitive, both the *bronchi* and the *parietal pleura* are very sensitive to pain.

"Parietal Pain" Caused by Visceral Disease

When a disease affects a viscus, the disease process often spreads to the parietal peritoneum, pleura, or pericardium. These parietal surfaces, like the skin, are supplied with extensive pain innervation from the peripheral spinal nerves. Therefore, pain from the parietal wall overlying a viscus is frequently sharp. An example can emphasize the difference between this pain and true visceral pain: a knife incision through the *parietal* peritoneum is very painful, whereas a similar cut through the visceral peritoneum or through a gut wall is not very painful, if painful at all.

Localization of Visceral Pain—"Visceral" and the "Parietal" Pain Transmission Pathways

Pain from the different viscera is frequently difficult to localize, for a number of reasons. First, the patient's brain does not know from firsthand experience that the different internal organs exist; therefore, any pain that originates internally can be localized only generally. Second, sensations from the abdomen and thorax are transmitted through two pathways to the central nervous system—the *true visceral pathway* and the *parietal pathway.* True visceral pain is transmitted via pain sensory fibers within the autonomic nerve bundles, and the sensations are *referred* to surface areas of the body often far from the painful organ. Conversely, parietal sensations are conducted *directly* into local spinal nerves from the parietal peritoneum, pleura, or pericardium, and these sensations are usually *localized directly over the painful area.*

Localization of Referred Pain Transmitted via Visceral Pathways. When visceral pain is referred to the surface of the body, the person generally localizes it in the dermatomal segment from which the visceral organ originated in the embryo, not necessarily where the visceral organ now lies. For instance, the heart originated in the neck and upper thorax, so the heart's visceral pain fibers pass upward along the sympathetic sensory nerves and enter the spinal cord between segments C-3 and T-5. Therefore, as shown in Figure 48-6, pain from the heart is referred to the side of the neck, over the shoulder, over the pectoral muscles, down the arm, and into the substernal area of the upper chest. These are the areas of the body surface that send their own somatosensory nerve fibers into the C-3 to T-5 cord segments. Most frequently, the pain is on the left side rather than on the right because the left side of the heart is much more frequently involved in coronary disease than the right.

The stomach originated approximately from the seventh to ninth thoracic segments of the embryo. Therefore, stomach pain is referred to the anterior epigastrium above the umbilicus, which is the surface area of the body subserved by the seventh through ninth thoracic segments. Figure 48-6 shows several other surface areas to which visceral pain is referred from other organs, representing in general the areas in the embryo from which the respective organs originated.

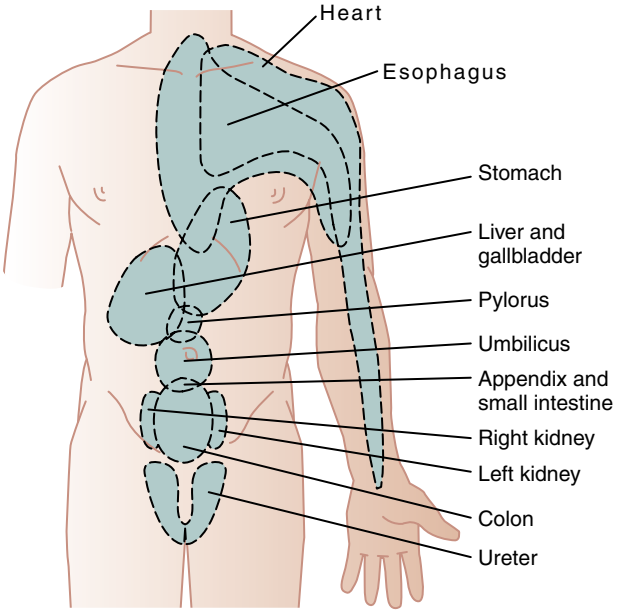


Figure 48-6 Surface areas of referred pain from different visceral organs.

Parietal Pathway for Transmission of Abdominal and Thoracic Pain. Pain from the viscera is frequently localized to two surface areas of the body at the same time because of the dual transmission of pain through the referred visceral pathway and the direct parietal pathway. Thus, Figure 48-7 shows dual transmission from an inflamed appendix. Pain impulses pass first from the appendix through visceral

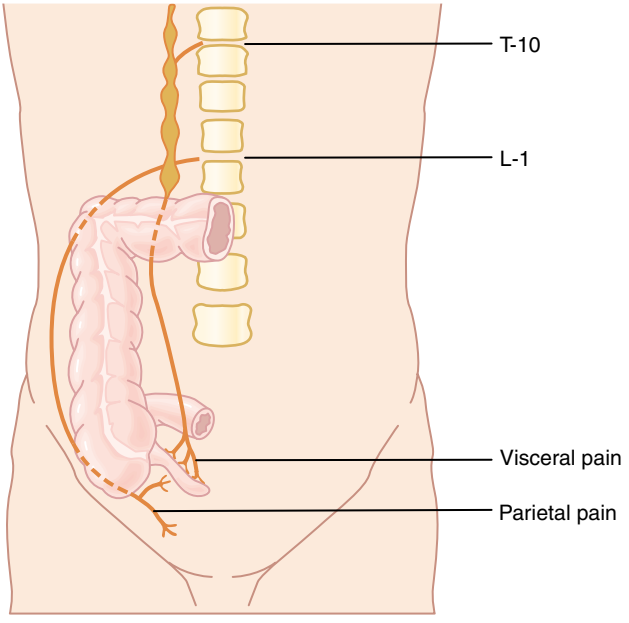


Figure 48-7 Visceral and parietal transmission of pain signals from the appendix.

pain fibers located within sympathetic nerve bundles, and then into the spinal cord at about T-10 or T-11; this pain is referred to an area around the umbilicus and is of the aching, cramping type. Pain impulses also often originate in the parietal peritoneum where the inflamed appendix touches or is adherent to the abdominal wall. These cause pain of the sharp type directly over the irritated peritoneum in the right lower quadrant of the abdomen.

Some Clinical Abnormalities of Pain and Other Somatic Sensations

Hyperalgesia

A pain nervous pathway sometimes becomes excessively excitable; this gives rise to *hyperalgesia,* which means hypersensitivity to pain. Possible causes of hyperalgesia are (1) excessive sensitivity of the pain receptors themselves, which is called *primary hyperalgesia,* and (2) facilitation of sensory transmission, which is called *secondary hyperalgesia.*

An example of primary hyperalgesia is the extreme sensitivity of sunburned skin, which results from sensitization of the skin pain endings by local tissue products from the burn—perhaps histamine, and prostaglandins, and others. Secondary hyperalgesia frequently results from lesions in the spinal cord or the thalamus. Several of these lesions are discussed in subsequent sections.

Herpes Zoster (Shingles)

Occasionally *herpesvirus* infects a dorsal root ganglion. This causes severe pain in the dermatomal segment subserved by the ganglion, thus eliciting a segmental type of pain that circles halfway around the body. The disease is called *herpes zoster,* or "shingles," because of a skin eruption that often ensues.

The cause of the pain is presumably infection of the pain neuronal cells in the dorsal root ganglion by the virus. In addition to causing pain, the virus is carried by neuronal cytoplasmic flow outward through the neuronal peripheral axons to their cutaneous origins. Here the virus causes a rash that vesiculates within a few days and then crusts over within another few days, all of this occurring within the dermatomal area served by the infected dorsal root.

Tic Douloureux

Lancinating pain occasionally occurs in some people over one side of the face in the sensory distribution area (or part of the area) of the fifth or ninth nerves; this phenomenon is called *tic douloureux* (or *trigeminal neuralgia* or *glossopharyngeal neuralgia*). The pain feels like sudden electrical shocks, and it may appear for only a few seconds at a time or may be almost continuous. Often it is set off by exceedingly sensitive trigger areas on the surface of the face, in the mouth, or inside the throat—almost always by a mechanoreceptive stimulus rather than a pain stimulus. For instance, when the patient swallows a bolus of food, as the food touches a tonsil, it might set off a severe lancinating pain in the mandibular portion of the fifth nerve.

The pain of tic douloureux can usually be blocked by surgically cutting the peripheral nerve from the hypersensitive area. The sensory portion of the fifth nerve is often sectioned immediately inside the cranium, where the motor and sensory roots of the fifth nerve separate from each other, so that the motor portions, which are necessary for many jaw movements, can be spared while the sensory elements are destroyed. This operation leaves the side of the face anesthetic, which in itself may be annoying. Furthermore, sometimes the operation is unsuccessful, indicating that the lesion that causes the pain might be in the sensory nucleus in the brain stem and not in the peripheral nerves.

Brown-Séquard Syndrome

If the spinal cord is transected entirely, all sensations and motor functions distal to the segment of transection are blocked, but if the spinal cord is transected on only one side, the *Brown-Séquard syndrome* occurs. The effects of such transection can be predicted from knowledge of the cord fiber tracts shown in Figure 48-8. All motor functions are blocked on the side of the transection in all segments below the level of the transection. Yet only some of the modalities of sensation are lost on the transected side, and others are lost on the opposite side. The sensations of pain, heat, and cold—sensations served by the spinothalamic pathway—are lost *on the opposite side of the body* in all dermatomes two to six segments below the level of the transection. By contrast, the sensations that are transmitted only in the dorsal and dorsolateral columns—kinesthetic and position sensations, vibration sensation, discrete localization, and two-point discrimination—are lost *on the side of the transection* in all dermatomes below the level of the transection. Discrete "light touch" is impaired on the side of the transection because the principal pathway for the transmission of light touch, the dorsal column, is transected. That is, the fibers in this column do not cross to the opposite side until they reach the medulla of the brain. "Crude touch," which is poorly localized, still persists because of partial transmission in the opposite spinothalamic tract.

Headache

Headaches are a type of pain referred to the surface of the head from deep head structures. Some headaches result from pain stimuli arising inside the cranium, but others result from pain arising outside the cranium, such as from the nasal sinuses.

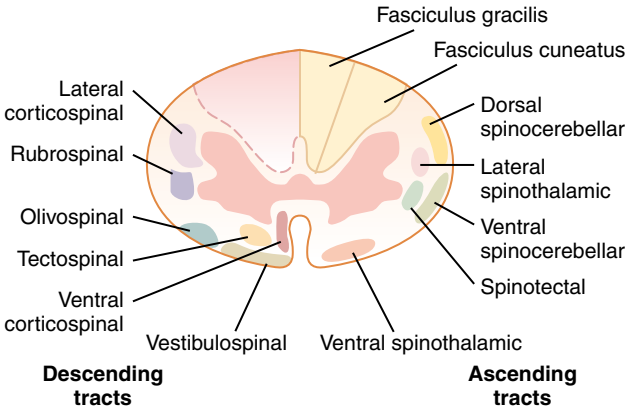


Figure 48-8 Cross section of the spinal cord, showing principal ascending tracts on the right and principal descending tracts on the left.

Headache of Intracranial Origin

Pain-Sensitive Areas in the Cranial Vault. The brain tissues themselves are almost totally insensitive to pain. Even cutting or electrically stimulating the sensory areas of the cerebral cortex only occasionally causes pain; instead, it causes prickly types of paresthesias on the area of the body represented by the portion of the sensory cortex stimulated. Therefore, it is likely that much or most of the pain of headache is not caused by damage within the brain itself.

Conversely, *tugging on the venous sinuses around the brain, damaging the tentorium,* or *stretching the dura at the base of the brain* can cause intense pain that is recognized as headache. Also, almost any type of traumatizing, crushing, or stretching stimulus to the *blood vessels of the meninges* can cause headache. An especially sensitive structure is the middle meningeal artery, and neurosurgeons are careful to anesthetize this artery specifically when performing brain operations under local anesthesia.

Areas of the Head to Which Intracranial Headache Is Referred. Stimulation of pain receptors in the cerebral vault above the tentorium, including the upper surface of the tentorium itself, initiates pain impulses in the cerebral portion of the fifth nerve and, therefore, causes referred headache to the front half of the head in the surface areas supplied by this somatosensory portion of the fifth cranial nerve, as shown in Figure 48-9.

Conversely, pain impulses from beneath the tentorium enter the central nervous system mainly through the glossopharyngeal, vagal, and second cervical nerves, which also supply the scalp above, behind, and slightly below the ear. Subtentorial pain stimuli cause "occipital headache" referred to the posterior part of the head.

Types of Intracranial Headache

Headache of Meningitis. One of the most severe headaches of all is that resulting from meningitis, which causes inflammation of all the meninges, including the sensitive areas of the dura and the sensitive areas around the venous sinuses. Such intense damage can cause extreme headache pain referred over the entire head.

Headache Caused by Low Cerebrospinal Fluid Pressure. Removing as little as 20 milliliters of fluid from the spinal canal, particularly if the person remains in an upright position, often causes intense intracranial headache. Removing this quantity of fluid removes part of the flotation for the brain that is normally provided by the cerebrospinal fluid. The weight of the brain stretches and otherwise distorts the various dural surfaces and thereby elicits the pain that causes the headache.

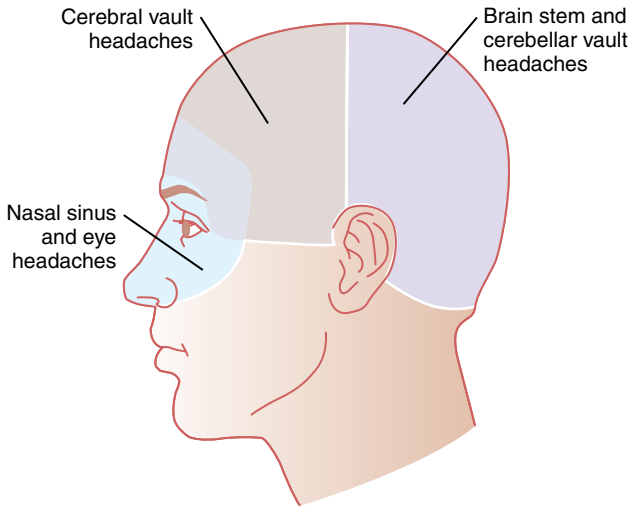


Figure 48-9 Areas of headache resulting from different causes.

Migraine Headache. Migraine headache is a special type of headache that may result from abnormal vascular phenomena, although the exact mechanism is unknown. Migraine headaches often begin with various prodromal sensations, such as nausea, loss of vision in part of the field of vision, visual aura, and other types of sensory hallucinations. Ordinarily, the prodromal symptoms begin 30 minutes to 1 hour before the beginning of the headache. Any theory that explains migraine headache must also explain the prodromal symptoms.

One theory of migraine headaches is that prolonged emotion or tension causes reflex vasospasm of some of the arteries of the head, including arteries that supply the brain. The vasospasm theoretically produces ischemia of portions of the brain, and this is responsible for the prodromal symptoms. Then, as a result of the intense ischemia, something happens to the vascular walls, perhaps exhaustion of smooth muscle contraction, to allow the blood vessels to become flaccid and incapable of maintaining normal vascular tone for 24 to 48 hours. The blood pressure in the vessels causes them to dilate and pulsate intensely, and it is postulated that the excessive stretching of the walls of the arteries—including some extracranial arteries, such as the temporal artery—causes the actual pain of migraine headaches. Other theories of the cause of migraine headaches include spreading cortical depression, psychological abnormalities, and vasospasm caused by excess local potassium in the cerebral extracellular fluid.

There may be a genetic predisposition to migraine headaches because a positive family history for migraine has been reported in 65 to 90 percent of cases. Migraine headaches also occur about twice as frequently in women as in men.

Alcoholic Headache.. As many people have experienced, a headache often follows excessive alcohol consumption. It is likely that alcohol, because it is toxic to tissues, directly irritates the meninges and causes the intracranial pain. Dehydration may also play a role in the "hangover" that follows an alcoholic binge; hydration usually attenuates but does not abolish headache and other symptoms of hangover.

Extracranial Types of Headache

Headache Resulting from Muscle Spasm. Emotional tension often causes many of the muscles of the head, especially those muscles attached to the scalp and the neck muscles attached to the occiput, to become spastic, and it is postulated that this is one of the common causes of headache. The pain of the spastic head muscles supposedly is referred to the overlying areas of the head and gives one the same type of headache as intracranial lesions do.

Headache Caused by Irritation of Nasal and Accessory Nasal Structures. The mucous membranes of the nose and nasal sinuses are sensitive to pain, but not intensely so. Nevertheless, infection or other irritative processes in widespread areas of the nasal structures often summate and cause headache that is referred behind the eyes or, in the case of

frontal sinus infection, to the frontal surfaces of the forehead and scalp, as shown in Figure 48-9. Also, pain from the lower sinuses, such as from the maxillary sinuses, can be felt in the face.

Headache Caused by Eye Disorders. Difficulty in focusing one's eyes clearly may cause excessive contraction of the eye ciliary muscles in an attempt to gain clear vision. Even though these muscles are extremely small, it is believed that tonic contraction of them can cause retro-orbital headache. Also, excessive attempts to focus the eyes can result in reflex spasm in various facial and extraocular muscles, which is a possible cause of headache.

A second type of headache that originates in the eyes occurs when the eyes are exposed to excessive irradiation by light rays, especially ultraviolet light. Looking at the sun or the arc of an arc-welder for even a few seconds may result in headache that lasts from 24 to 48 hours. The headache sometimes results from "actinic" irritation of the conjunctivae, and the pain is referred to the surface of the head or retro-orbitally. However, focusing intense light from an arc or the sun on the retina can also burn the retina, and this could be the cause of the headache.

Thermal Sensations

Thermal Receptors and Their Excitation

The human being can perceive different gradations of cold and heat, from *freezing cold* to *cold* to *cool* to *indifferent* to *warm* to *hot* to *burning hot.*

Thermal gradations are discriminated by at least three types of sensory receptors: cold receptors, warmth receptors, and pain receptors. The pain receptors are stimulated only by extreme degrees of heat or cold and, therefore, are responsible, along with the cold and warmth receptors, for "freezing cold" and "burning hot" sensations.

The cold and warmth receptors are located immediately under the skin at discrete separated *spots.* In most areas of the body, there are 3 to 10 times as many cold spots as warmth spots, and the number in different areas of the body varies from 15 to 25 cold spots per square centimeter in the lips to 3 to 5 cold spots per square centimeter in the finger to less than 1 cold spot per square centimeter in some broad surface areas of the trunk.

Although the existence of distinctive warmth nerve endings is quite certain, on the basis of psychological tests, they have not been identified histologically. They are presumed to be free nerve endings because warmth signals are transmitted mainly over type C nerve fibers at transmission velocities of only 0.4 to 2 m/sec.

A definitive cold receptor, however, has been identified. It is a special, small type Aδ myelinated nerve ending that branches several times, the tips of which protrude into the bottom surfaces of basal epidermal cells. Signals are transmitted from these receptors via type Aδ nerve fibers at velocities of about 20 m/sec. Some cold sensations are believed to be transmitted in type C nerve fibers as well, which suggests that some free nerve endings also might function as cold receptors.

Stimulation of Thermal Receptors—Sensations of Cold, Cool, Indifferent, Warm, and Hot. Figure 48-10 shows the effects of different temperatures on the responses of four types of nerve fibers: (1) a pain fiber stimulated by cold, (2) a cold fiber, (3) a warmth fiber, and (4) a pain fiber stimulated by heat. Note especially that these fibers respond differently at different levels of temperature. For instance, in the *very* cold region, only the cold-pain fibers are stimulated (if the skin becomes even colder so that it nearly freezes or actually does freeze, these fibers cannot be stimulated). As the temperature rises to +10° to 15°C, the cold-pain impulses cease, but the cold receptors begin to be stimulated, reaching peak stimulation at about 24°C and fading out slightly above 40°C. Above about 30°C, the warmth receptors begin to be stimulated, but these also fade out at about 49°C. Finally, at around 45°C, the heat-pain fibers begin to be stimulated by heat and, paradoxically, some of the cold fibers begin to be stimulated again, possibly because of damage to the cold endings caused by the excessive heat.

One can understand from Figure 48-10 that a person determines the different gradations of thermal sensations by the relative degrees of stimulation of the different types of endings. One can also understand why extreme degrees of both cold and heat can be painful and why both these sensations, when intense enough, may give almost the same quality of sensation—that is, freezing cold and burning hot sensations feel almost alike.

Stimulatory Effects of Rising and Falling Temperature—Adaptation of Thermal Receptors. When a cold receptor is suddenly subjected to an abrupt fall in temperature, it becomes strongly stimulated at first, but this stimulation fades rapidly during the first few seconds and progressively more slowly during the next 30 minutes or more. In other words, the receptor "adapts" to a great extent, but never 100 percent.

Thus, it is evident that the thermal senses respond markedly to *changes in temperature,* in addition to being able to respond to steady states of temperature. This means that when the temperature of the skin is actively

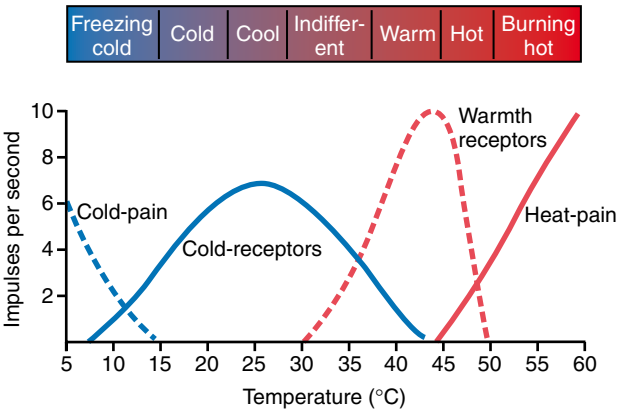


Figure 48-10 Discharge frequencies at different skin temperatures of a *cold-pain fiber,* a *cold fiber,* a *warmth fiber,* and a *heat-pain fiber.*

falling, a person feels much colder than when the temperature remains cold at the same level. Conversely, if the temperature is actively rising, the person feels much warmer than he or she would at the same temperature if it were constant. The response to changes in temperature explains the extreme degree of heat one feels on first entering a tub of hot water and the extreme degree of cold felt on going from a heated room to the out-of-doors on a cold day.

Mechanism of Stimulation of Thermal Receptors

It is believed that the cold and warmth receptors are stimulated by changes in their metabolic rates, and that these changes result from the fact that temperature alters the rate of intracellular chemical reactions more than twofold for each 10°C change. In other words, thermal detection probably results not from direct physical effects of heat or cold on the nerve endings but from chemical stimulation of the endings as modified by temperature.

Spatial Summation of Thermal Sensations. Because the number of cold or warm endings in any one surface area of the body is slight, it is difficult to judge gradations of temperature when small skin areas are stimulated. However, when a large skin area is stimulated all at once, the thermal signals from the entire area summate. For instance, rapid changes in temperature as little as 0.01°C can be detected if this change affects the entire surface of the body simultaneously. Conversely, temperature changes 100 times as great often will not be detected when the affected skin area is only 1 square centimeter in size.

Transmission of Thermal Signals in the Nervous System

In general, thermal signals are transmitted in pathways parallel to those for pain signals. On entering the spinal cord, the signals travel for a few segments upward or downward in the *tract of Lissauer* and then terminate mainly in laminae I, II, and III of the dorsal horns—the same as for pain. After a small amount of processing by one or more cord neurons, the signals enter long, ascending thermal fibers that cross to the opposite anterolateral sensory tract and terminate in both (1) the reticular areas of the brain stem and (2) the ventrobasal complex of the thalamus.

A few thermal signals are also relayed to the cerebral somatic sensory cortex from the ventrobasal complex. Occasionally a neuron in cortical somatic sensory area I has been found by microelectrode studies to be directly responsive to either cold or warm stimuli on a specific area of the skin. However, removal of the entire cortical postcentral gyrus in the human being reduces but does not abolish the ability to distinguish gradations of temperature.

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