The neuron

Neurons typically have two structures: the cell body and his extensions: dendrites, axon and axon terminals. Dendrites are elaborate branching processes that arise from the cell body and they are pathways for incoming signals from other neurons to the cell body. Integration of incoming signals occurs mainly in the axon hillock. This is the part of the cell body, which gives rise to an elongated tube called an axon, a fiber that can be up to 1.2 m long.

![Figure 2.1 The neuron with cell body, dendrites, axon and axon terminals.](http://www.zuniv.net/physiology/book/images/)

Near its termination each axon divides into fine branches, each of which ends in an axon terminal (i.e., synaptic button or button terminal). The axon terminals contain mitochondria and synaptic vesicles filled with neurotransmitter. These presynaptic structures are the sites where electrical signals are converted into chemical messages for transmission to nearby neurons. Unipolar neurons only have a single major process extending from the cell body. Bipolar and multipolar neurons have two or more major processes arising from the cell body. Most neurons have only one axon, a few more than one and some neurons function without an axon. Their location, structure and functional properties classify neurons. Communication from an axon to a dendrite is called ax dendritic, from a dendrite to another is termed dendro-dendritic, from a dendrite to an axon is called dendro-axonal, from a dendrite to the soma is called dendro-somatic and between two axons is referred to as axo-axonal.

Neurons properties

Neurons are able to receive changes in the environment that are transmitted by the nerve pathways to central control organs and then command to the effectors (muscles, glands).

Neurons properties are:
- excitability
- conduction
- degeneration and regeneration
Excitability

All cells respond to stimuli by membrane depolarization (on the action of the stimulus). Stimulus represents any sudden change energy in the environment that alters the permeability of the membrane. Stimulus must respect the following conditions to produce an excitation:
- Intensity; the lowest intensity that produces the response is the threshold intensity. Stimulus with same/above intensity threshold produce excitation and the stimuli under threshold cannot produce excitation;
- Suddenness
- Density per unit area
- Act a certain period of time.

Types of stimuli: electrical, mechanical, chemical, thermal. Excitation is accompanied by changes membrane potential.

Neuronal membranes are composed of lipid bilayers stabilized by hydrophobic interactions and thus function as barriers to free diffusion for water-soluble molecules. The ability of the neuronal membrane to control the movement and concentration of charged particles generates ion gradients with a charge difference across the membrane. The potential difference across the resting membrane is called the resting membrane potential (RMP). NaCl is found in high concentration outside the neurons, whereas [K⁺] are high inside the cell. These ion gradients maintain a constant leakage of NaCl into the cell and a leakage of K⁺ out. The gradients are maintained by the Na⁺-K⁺-pump, which is thus controlling the resting membrane potential. Cl⁻ ions distribute passively across most neuronal membranes and contribute little to the resting membrane potential, but they are important for the modulation of incoming signals. At rest, many K⁺-channels are open and K⁺ moves down its concentration gradient out of the cell, whereby the inside becomes negatively charged (until it is difficult for K⁺ to leave the cell, and the K⁺-out flux slows down). The RMP approaches the equilibrium potential for K⁺.

The following formula, called the Goldman equation, or the Goldman-Hodgkin-Katz equation, gives the calculated membrane potential on the inside of the membrane when two univalent positive ions, sodium (Na⁺) and potassium (K⁺), and one univalent negative ion, chloride (Cl⁻), are involved.

$$MP = \frac{RT}{F} \ln \left( \frac{P_{Na^+}[Na^+]_{out} + P_{K^+}[K^+]_{out} + P_{Cl^-}[Cl^-]_{in}}{P_{Na^+}[Na^+]_{in} + P_{K^+}[K^+]_{in} + P_{Cl^-}[Cl^-]_{out}} \right)$$

[Na⁺]=concentration  P=permeability.

The following equation, called the Nernst equation, can be used to calculate the Nernst potential for any univalent ion at normal body temperature of 98.6°F (37°C):

$$\frac{MP}{(Na^+)} = \frac{RT}{F} \ln \left( \frac{P_{Na^+}[Na^+]_{out}}{P_{Na^+}[Na^+]_{in}} \right) = \frac{RT}{F} \ln \left( \frac{[Na^+]_{out}}{[Na^+]_{in}} \right)$$

When using this formula, it is usually assumed that the potential in the extracellular fluid outside the membrane remains at zero potential, and the Nernst potential is the potential inside the membrane. Also, the sign of the potential is positive (+) if the ion diffusing from inside to outside is a negative ion, and it is negative (−) if the ion is positive. Thus, when the concentration
of positive potassium ions on the inside is 10 times that on the outside, the log of 10 is 1, so that the Nernst potential calculates to be –61 millivolts inside the membrane.

**Figure 2.2** Establishment of resting membrane potentials in nerve fibers under three conditions:
A, when the membrane potential is caused entirely by potassium diffusion alone;
B, when the membrane potential is caused by diffusion of both sodium and potassium ions; and
C, when the membrane potential is caused by diffusion of both sodium and potassium ions plus pumping of both these ions by the Na+-K+ pump.

Factors participating in the RMP:
- Na-K-ATPase in the cell expels three Na\(^+\) and introduce 2K\(^+\) - present in almost all cells, 30% of cell energy is used for its operation;
- diffusion of ions through the membrane due to unequal permeability for ions, K easily crosses the cell membrane but is retained in cells by negative charge given by intracellular proteins (negative) whereas membrane permeability for Na is lower.
- Donnan membrane-equilibrium - the presence of intracellular proteins makes the surface negatively charged cell membrane positive (K) to be retained and anions to be rejected.

Excitation is a RMP change and is expressed electrophysiologically by the appearance of action potential (response to action of the stimulus).

**Measuring the Membrane Potential**
The method for measuring the membrane potential is simple in theory but often difficult in practice because of the small size of most of the fibers. Figure shows a small pipette filled with an electrolyte solution. The pipette is impaled through the cell membrane to the interior of the fiber. Then another electrode, called the "indifferent electrode," is placed in the extracellular fluid, and the potential difference between the inside and outside of the fiber is measured using an appropriate voltmeter.
The action potential

Neurons can carry electrical signals along their whole length without any loss of signal strength. This electrical signal is an all-or-none phenomenon or law termed the action potential. The incoming signals to dendrites and cell bodies consist of small, graded changes (i.e., small synaptic potentials) in the resting membrane potential caused by the actions of neurotransmitters and modulators.

Resting Stage. This is the resting membrane potential before the action potential begins. The membrane is said to be “polarized” during this stage because of the –90 mV negative membrane potential that is present.

Depolarization Stage. At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon. The normal “polarized” state of –90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called depolarization. In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually “overshoot” beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.

Repolarization Stage. Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called repolarization of the membrane.

The action potential is an all-or-none electrical signal, which appears as a positive wave when recording internally. The action potential is conducted with the same shape and size along the whole length of a muscle cell or a nerve fiber.

During the early part of the action potential the cell membrane is completely refractory. A new stimulus, regardless of its size, cannot evoke an action potential. Almost all Na⁺-channels are inactivated, and will not reopen until the cell membrane is repolarized. This is the absolute
refractory period covering most of the peak and lasting until well into the repolarizing phase (ARP).

During the hyperpolarizing after potential, a suprathreshold stimulus is able to trigger a new AP, albeit of smaller amplitude than the first action potential. This period is called the relative refractory period (RRP). The cell membrane is relatively refractory, because some Na⁺-channels are voltage-inactivated and at the same time K⁺-conductance is increased. To explain more fully the factors that cause both depolarization and repolarization, we need to describe the special characteristics of two other types of transport channels through the nerve membrane: the voltage-gated sodium and potassium channels.

**Voltage-Gated Sodium and Potassium Channels**
The necessary actor in causing both depolarization and repolarization of the nerve membrane during the action potential is the voltage-gated sodium channel. A voltage-gated potassium channel also plays an important role in increasing the rapidity of repolarization of the membrane. These two voltage-gated channels are in addition to the Na⁺-K⁺ pump and the K⁺-Na⁺ leak channels.

**Voltage-Gated Sodium Channel—Activation and Inactivation of the Channel**
The upper panel of Figure shows the voltage-gated sodium channel in three separate states. This channel has two gates—one near the outside of the channel called the activation gate, and another near the inside called the inactivation gate. The upper left of the figure depicts the state of these two gates in the normal resting membrane when the membrane potential is –90 millivolts. In this state, the activation gate is closed, which prevents any entry of sodium ions to the interior of the fiber through these sodium channels.

**Activation of the Sodium Channel**. When the membrane potential becomes less negative than during the resting state, rising from –90 millivolts toward zero, it finally reaches a voltage—usually somewhere between –70 and –50 millivolts—that causes a sudden conformational change in the
activation gate, flipping it all the way to the open position. This is called the activated state; during this state, sodium ions can pour inward through the channel, increasing the sodium permeability of the membrane as much as 500- to 5000-fold.

Inactivation of the Sodium Channel. The upper right panel of Figure shows a third state of the sodium channel. The same increase in voltage that opens the activation gate also closes the inactivation gate. The inactivation gate, however, closes a few 10,000ths of a second after the activation gate opens. That is, the conformational change that flips the inactivation gate to the closed state is a slower process than the conformational change that opens the activation gate. Therefore, after the sodium channel has remained open for a few 10,000ths of a second, the inactivation gate closes, and sodium ions no longer can pour to the inside of the membrane. At this point, the membrane potential begins to recover back toward the resting membrane state, which is the repolarization process. Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to or near the original resting membrane potential level. Therefore, it usually is not possible for the sodium channels to open again without the nerve fiber’s first repolarizing.

Voltage-Gated Potassium Channel and Its Activation
The lower panel of Figure shows the voltage-gated potassium channel in two states: during the resting state (left) and toward the end of the action potential (right). During the resting state, the gate of the potassium channel is closed, and potassium ions are prevented from passing through this channel to the exterior. When the membrane potential rises from –90 millivolts toward zero, this voltage change causes a conformational opening of the gate and allows increased potassium diffusion outward through the channel. However, because of the slight delay in opening of the potassium channels, for the most part, they open just at the same time that the sodium channels are beginning to close because of inactivation. Thus, the decrease in sodium entry to the cell and the simultaneous increase in potassium exit from the cell combine to speed the repolarization process, leading to full recovery of the resting membrane potential within another few 10,000ths of a second.

Nerve conduction

The lipophilic core of the cell membrane is an electrical insulator, but the salt solutions of the cytoplasm and the extracellular fluid act as conductors of electrical current. Opening of many voltage-gated Na⁺-channels, whereby the Na⁺-conductance is increased about 104-fold, so the membrane is instantly depolarized, causes the action potential. The action potential essentially spread by alterations of the voltage-gated Na⁺-channels.

Depolarization spreads along the membrane of excitable cells by local currents flowing to the adjacent segments of the membrane. The phenomenon is called the local response or electrotonic conduction. The depolarization decreases mono-exponentially from the excitation site. Na⁺-channels will be recruited in all areas of the membrane, where the threshold potential is exceeded. The Na⁺-channels behind the peak of the action potential are refractory. This explains why an action potential travels in both directions, when it is evoked in the middle of a nerve.

All-or-Nothing Principle. Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, or it does not travel at all if conditions are not right. This is called the all-or-nothing principle, and it applies to all normal excitable tissues. Occasionally, the action potential
reaches a point on the membrane at which it does not generate sufficient voltage to stimulate the next area of the membrane. When this occurs, the spread of depolarization stops. Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than 1. This “greater than 1” requirement is called the safety factor for propagation.

Special characteristics of signal transmission in (myelinated and unmyelinated) nerve fibers

The large fibers are myelinated, and the small ones are unmyelinated. The average nerve trunk contains about twice as many unmyelinated fibers as myelinated fibers. The central core of the fiber is the axon, and the membrane of the axon is the membrane that actually conducts the action potential. The axon is filled in its center with axoplasm, which is a viscid intracellular fluid. Surrounding the axon is a myelin sheath that is often much thicker than the axon itself. About once every 1 to 3 millimeters along the length of the myelin sheath is a node of Ranvier.

Figure 2.4 Function of the Schwann cell to insulate nerve fibers. A, Wrapping of a Schwann cell membrane around a large axon to form the myelin sheath of the myelinated nerve fiber. B, Partial wrapping of the membrane and cytoplasm of a Schwann cell around multiple unmyelinated nerve fibers (shown in cross section).

The myelin sheath is deposited around the axon by Schwann cells in the following manner: the membrane of a Schwann cell first envelops the axon. Then the Schwann cell rotates around the axon many times, laying down multiple layers of Schwann cell membrane containing the lipid substance sphingomyelin. This substance is an excellent electrical insulator that decreases ion flow through the membrane about 5000-fold. At the juncture between each two successive Schwann cells along the axon, a small uninsulated area only 2 to 3 micrometers in length remains where ions still can flow with ease through the axon membrane between the extracellular fluid and the intracellular fluid inside the axon. This area is called the node of Ranvier.

“Saltatory” conduction in myelinated fibers from node to node

Even though almost no ions can flow through the thick myelin sheaths of myelinated nerves, they can flow with ease through the nodes of Ranvier. Therefore, action potentials occur only at the nodes. Yet the action potentials are conducted from node to node, as shown in figure; this is called saltatory conduction. That is, electrical current flows through the surrounding extracellular fluid outside the myelin sheath as well as through the axoplasm inside the axon from node to node, exciting successive nodes one after another. Thus, the nerve impulse jumps down the fiber, which is the origin of the term “saltatory.” Saltatory conduction is of value for two reasons. First, by causing the depolarization process to jump long intervals along the axis of the nerve fiber, this mechanism increases the velocity of nerve transmission in myelinated fibers as much as 5- to 50-fold. Second, saltatory conduction conserves energy for the axon because
only the nodes depolarize, allowing perhaps 100 times less loss of ions than would otherwise be necessary, and therefore requiring little metabolism for reestablishing the sodium and potassium concentration differences across the membrane after a series of nerve impulses.

![Saltatory conduction along a myelinated axon](image)

**Figure 2.5** Saltatory conduction along a myelinated axon

---

Due to: trauma, acute compression
Signs and symptoms: loss of motor function, loss of sensory function.

**Degenerative changes**

1. Axonal injury: degenerative changes at proximal and distal end, anterograde degeneration (Wallerian Degeneration) and retrograde degeneration (extends up to the first node of Ranvier proximal to the injury, changes in the dendritic tree, the parent cell body and the part of the axon still attached to the cell body);
2. cell body injury: chromatolytic changes; swelling of the cell; displacement of the nucleus to periphery, sometimes extruded out; fragmentation and reduction of Golgi apparatus; disappearance of neurofibrils.

**Chromatolysis**

Disintegration of the Nissl substance: begins within 24 – 48 hours, near the axon hillock and spreads to other parts occurs in certain infectious or degenerative diseases of the nervous system: poliomyelitis, progressive muscular atrophy degree of chromatolysis depends on proximity of the site of injury to the nerve cell more in motor neurons.

**Wallerian degeneration:**
- in less than 24 hours: neurofilaments break up; axons break up into short lengths
- within 10 days: myelin sheaths break down into lipid droplets around the axon
- within a month: myelin gets denatured chemically
- within three months: macrophages from the endoneurium invade the degenerating myelin sheaths and axis cylinder and phagocytose the debris.

**Regeneration of nervous tissue**

Severe injury to nervous tissue causes cell death. Neurons are post mitotic cells. For this reason lost neurons cannot be replaced. There is, however, considerable capacity for regeneration of axons in the peripheral nervous system. Both growth and maintenance of axons require the nerve growth factors (NGF). NGF is an essential survival factor for neurons outside the CNS - in particular sensory neurons. NFG binds to receptors belonging to the insulin receptor family (tyrosine kinase family).

When a motor axon has been severed, the cell body undergoes chromatolysis. This is a neuronal reaction, where the rough endoplasmic reticulum (the Nissl bodies) becomes active. The Nissl bodies accumulate proteins required for repair of the axon. The axonal reaction is an attempt to repair the fiber by production of new protein structures that are transported along the axon. Therefore, proteins distend the rough endoplasmic reticulum. The axon and the myelin sheath distal to the injury die and are phagocytized. The neuroglia Schwann cells that had formed the myelin remains alive. This is the so-called wallerian degeneration named after Waller. The Schwann cells proliferate and form long rows along the pathway previously occupied by the dead axon. The severed axon regenerates along this pathway, and growth cones may eventually reinnervate the target organ.

Fast axonal transport of organelles in the cytosol occurs as rapidly as 0.4 m per day. At this rate synaptic vesicles can travel along the motor axon from the spinal cord to a patient's foot within three days. Fast axonal transport of enzymes and organelles occurs on microtubule in the axons, and is not interrupted by resting periods in cell compartments outside the transport system. Oxidation of glucose in the mitochondria provides ATP for the Na⁺-K⁺-pump and for transport filaments and microtubules embedded in the axonal cytoplasm.
Slow axonal transport occurs as diffusion of cytosolic proteins and organelles such as mitochondria. This transport occurs at a rate 100 times more slowly than fast axonal transport. Organelles or enzymes are stored in different cell compartments on their way or their direction of transport reverses. Axonal transport can be anterograde, when it occurs in the direction from the soma to the axonal terminals. Axonal transport can also be retrograde, when it occurs in the opposite direction. Here vesicles are degraded by lysosomes, when returned to the soma. A typical example of slow transport is the transfer of the many mitochondria towards the terminal of an axon.

In the CNS, fast neurotransmission is inhibitory or excitatory. In the neuromuscular junction, each signal is always excitatory and sufficient to trigger a muscular contraction. In the neuromuscular junction, acetylcholine is the only neurotransmitter, whereas in the CNS there are a large variety of neurotransmitters.

The sensory system transmits signals from sensory nerve receptors in the body. The nerve receptors are located in the skin, muscles, tendons, joints and viscera. The signals are transferred to the CNS by a pathway of first, second, third, and higher-order neurons. The third and higher order neurons are located in the thalamus and the cortex. The cell body of the first order afferent neuron is located in the dorsal root or in the cranial nerve ganglia. The signals pass through the spinal cord, the brain stem, and the thalamus before reaching the cerebral cortex.

The reflex arc

A reflex is an automatic response to a stimulus. Humans use reflex actions in only some of their behavior, for example controlling the eye's pupil size. Simple reflexes produce rapid involuntary responses to a stimulus. Reflex reactions in humans are controlled by the reflex arc. When the safety of an organism demands a very quick response, the signals may be passed directly from a sensory neuron, via a relay neuron, to a motor neuron for instant, unthinking action. This is a reflex action.

A reflex arc is the nerve pathway which makes such a fast, automatic response possible. It does not matter how brainy you are - you will always pull your hand away from a flame without
thinking about it. A particular pathway by which the impulses can travel from the receptor to the effector is known as a reflex arc. A reflex arc consists of the following:

- A receptor or sense organ,
- A sensory neuron,
- A reflex centre (spinal cord or brain)
- A motor neuron, and
- an effector (muscle or gland).

A somatic reflex arc is one in which there is the simplest possible arrangement of elements to permit a response to stimuli, and in which the final element in the chain is skeletal muscle. The first is some sensory transducer in the periphery, for example, a Pacinian corpuscle or other tactile sensor in the skin. Next is the pseudo-unipolar sensory neuron in the circuit. Its soma is physically located in a craniospinal ganglion (pictured here as a dorsal root ganglion, but it could also be on a cranial nerve). Then is an interconnector neuron, whose soma is found in the CNS followed by the motor neuron whose soma is in the ventral horn of the gray H of the spinal cord. The last element involved is the effector organ, which in the case of this type of arc, will always be skeletal muscle. Notice that this loop is completely independent; it's not necessary to have CNS involvement beyond the "relay" at the interconnector neuron. Let's say you inadvertently put your hand on a hot stove burner. You will of course immediately remove it, and in doing so you are making use of this type of arc, bypassing conscious thought. In fact, the sensation of uncomfortable heat makes it to the CNS after the motor response to withdraw your hand is initiated. In other words, you move your hand away before you "know why" you're doing it.

**Sensory receptors and nerve fibers**

Sensory receptors are either neurons in the case of vision, smell and cutaneous senses, or modified epithelial cells in the case of vision, auditory, vestibular, smell and taste senses (the special sensory receptors). Some sensory receptors have characteristics similar to the well-known plasma membrane receptors. Plasma membrane receptors consist of a protein or glycoprotein molecule, an ion channel or a specific enzyme (G-protein).
The stimulation of a receptor elicits a receptor potential (generator potential) that is graded continuously with stimulus intensity. When the stimulus is strong enough to reach the threshold, action potentials (APs) are fired. In neurons the stimulus intensity is coded by the frequency of action potentials. Sensory receptor systems are biological transducers. The depolarization generates a graded receptor potential forcing a current towards the first node of Ranvier with maintained stimulus. The receptor potential rapidly decreases (rapid adaptation), because the adequate stimulus is alterations in the deformity rate (vibrations in the range 150-300 Hz). At the first node of Ranvier, a propagating action potential along the axon is released, provided the generator potential is sufficiently large.

Some signals need to be transmitted to or from the central nervous system extremely rapidly; otherwise, the information would be useless. As shown in the next table, 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. Both conduction velocity and size is used in classification of nerve fibers. The fibers are divided into types A, B and C, based on the three main conduction velocities shown in the record of the compound action potential from a mixed nerve.

Type A fibers are the fast conducting myelinated fibers (thick fibers subdivided into α, β, γ, and δ), type B are preganglionic sympathetic fibers, and type C are the small, unmyelinated fibers. Another classification is based on the thickness of the axons (I-IV). The size classification became necessary, when Aα - fibers were separated into two subgroups: Ia and Ib.

The Aα (I) fibers are motor α-fibers and proprioceptors from the annulospiral endings of muscle spindles (Ia) and from Golgi tendon organs (Ib).

The Aβ (II) fibers conduct discrete touch and fine pressure signals from cutaneous tactile receptors.

The Aγ (II) fibers are motor fibers to muscle spindles. They have their origin in the spinal cord.

The Aδ (III) fibers transfer pain sensations, decline in skin temperature as well as crude, passive touch and deep pressure.

- The B fibers (III) are autonomic preganglionic fibers.
- The C fibers (IV) are unmyelinated and lead pain, touch and signals from heat receptors from the skin. The C fibers have no myelin sheath.

Sensory receptors in the nervous system are classified as exteroceptors (located on the body surface), proprioceptors (located in muscles, tendons and joint capsules), interoceptors (located in the viscera), and telereceptors (stimulated by events far from the person).

Cutaneous receptors are exteroceptors. Pacinian and Meissner corpuscles are rapidly adapting (dynamic) touch velocity detectors in glabrous skin. In hairy skin, hair-follicle receptors are velocity detectors (they adapt rapidly). Meissner corpuscles are in the papillae of the hairless skin such as fingertips, lips and clitoris. Merkels discs and Ruffini-end organs are slowly adapting (static) touch intensity detectors both in hairless and hairy skin. Merkels discs are found in elevated dome corpuscles in hairy skin (up to 50 Merkel discs in a corpuscle of 0.5 mm in diameter).

Thermoreceptors are also exteroceptors and react to temperature changes. We have cold-receptors just below the skin surface (200 nm deep). Cold receptors respond to changes in temperature. Heat receptors are also located in the skin. The location of certain heat and cold points in the skin is determined by bringing a thin hot or cold object in contact with the skin. Cold receptors and heat receptors in the skin are located close to the surface. Both types of
receptors are also located in the deep tissue and in the CNS. Proprioceptors, located in muscles, joints and joint capsules, are mechanoreceptors (muscle spindles, Golgi-receptors, Pacinian and Ruffini corpuscles, and free nerve endings). The Ruffini mechanoreceptors are also called joint receptors, because they are located in ligaments, tendons and articular capsules. They provide information for the CNS concerning articular movements, movement velocity and joint position. Joint receptors of the proximal joints are particularly sensitive. The static and dynamic receptors inform the CNS about the position and movement of the joint, respectively.

Nociceptors or nocireceptors (pain receptors) are responsive to stimuli that potentially cause injury. Nociceptors are free nerve endings of two types. The fast adapting Aδ fiber mechanical nociceptors (group III) are high-threshold, finely myelinated afferents that originate superficially in the skin. The slowly adapting C-polymodal nociceptors (group IV) are unmyelinated afferent fibers that originate in the deeper cutaneous tissue, and respond to various mechanical, thermal and chemical stimuli. In the spinal cord nociceptive afferents synapse with secondary neurons in lamina I and II.

**Classification of Sensory Receptors**

<table>
<thead>
<tr>
<th>I. Mechanoreceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin tactile sensibilities (epidermis and dermis)</td>
</tr>
<tr>
<td>Free nerve endings</td>
</tr>
<tr>
<td>Expanded tip endings</td>
</tr>
<tr>
<td>Merkel’s disks</td>
</tr>
<tr>
<td>Plus several other variants</td>
</tr>
<tr>
<td>Spray endings</td>
</tr>
<tr>
<td>Ruffini’s endings</td>
</tr>
<tr>
<td>Encapsulated endings</td>
</tr>
<tr>
<td>Meissner’s corpuscles</td>
</tr>
<tr>
<td>Krause’s corpuscles</td>
</tr>
<tr>
<td>Hair end-organs</td>
</tr>
<tr>
<td>Deep tissue sensibilities</td>
</tr>
<tr>
<td>Free nerve endings</td>
</tr>
<tr>
<td>Expanded tip endings</td>
</tr>
<tr>
<td>Spray endings</td>
</tr>
<tr>
<td>Ruffini’s endings</td>
</tr>
<tr>
<td>Encapsulated endings</td>
</tr>
<tr>
<td>Pacinian corpuscles</td>
</tr>
<tr>
<td>Plus a few other variants</td>
</tr>
<tr>
<td>Muscle endings</td>
</tr>
<tr>
<td>Muscle spindles</td>
</tr>
<tr>
<td>Golgi tendon receptors</td>
</tr>
<tr>
<td>Hearing</td>
</tr>
<tr>
<td>Sound receptors of cochlea</td>
</tr>
<tr>
<td>Equilibrium</td>
</tr>
<tr>
<td>Vestibular receptors</td>
</tr>
<tr>
<td>Arterial pressure</td>
</tr>
<tr>
<td>Baroreceptors of carotid sinuses and aorta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Thermoreceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold</td>
</tr>
<tr>
<td>Cold receptors</td>
</tr>
<tr>
<td>Warmth</td>
</tr>
<tr>
<td>Warm receptors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Nociceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Free nerve endings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Electromagnetic receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision</td>
</tr>
<tr>
<td>Rods</td>
</tr>
<tr>
<td>Cones</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V. Chemoreceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste</td>
</tr>
<tr>
<td>Receptors of taste buds</td>
</tr>
<tr>
<td>Smell</td>
</tr>
<tr>
<td>Receptors of olfactory epithelium</td>
</tr>
<tr>
<td>Arterial oxygen</td>
</tr>
<tr>
<td>Receptors of aortic and carotid bodies</td>
</tr>
<tr>
<td>Osmolality</td>
</tr>
<tr>
<td>Neurons in or near supraoptic nuclei</td>
</tr>
<tr>
<td>Blood CO₂</td>
</tr>
<tr>
<td>Receptors in or on surface of medulla and in aortic and carotid bodies</td>
</tr>
<tr>
<td>Blood glucose, amino acids, fatty acids</td>
</tr>
<tr>
<td>Receptors in hypothalamus</td>
</tr>
</tbody>
</table>
Accommodation of sensory receptors or adaptation is a progressive decrease in firing frequency despite maintained depolarization. The frequency of action potentials from stimulated receptors falls, although the stimulus is maintained at constant strength. Accommodation or adaptation occurs, when a proportion of the voltage-gated Na\(^+\)-channels is rapidly inactivated by depolarization, which also opens K\(^+\)-channels. This makes the cell more refractory to stimulation. Accommodation can also be caused by a hyperpolarization induced by gradual activation of Ca\(^{2+}\)-dependent K\(^+\)-channels.

Pain- and cold-receptors, Merkel discs and Ruffini-end organs adapt extremely slowly and incompletely. Joint receptors, smell-taste-receptors, muscle spindles, carotid sinus- and pulmonary stretch receptors, and the optic nerve, all adapt somewhat better.

The adequate stimulus is the stimulus, for which the receptor has a lower energy threshold than for other stimuli (ie, the stimulus to which the receptor is most sensitive). The adequate stimulus for pain receptors is mechanical deformation, extreme temperature or tissue damage. The sense impression depends on the site in the brain which receives the sensory signal (ie, central analysis) and on the receptor localization (i.e., peripheral analysis). This is how different neurons transmit different types of sensations, even though they may transmit the same electrical signals.

**Synapse**

In the nervous system, a synapse is a structure that permits a neuron to pass an electrical or chemical signal to another cell (neural or otherwise). 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.
Chemical substances that function as synaptic transmitters:
I. Small molecule, rapidly acting transmitters:
   Class I: acetylcholine
   Class II: the amines: norepinephrine, epinephrine, dopamine, serotonin, histamine
   Class III: aminoacids: gamma-aminobutyric acid (GABA), glycine, glutamate, aspartate
   Class IV: nitric oxide (NO)
II. Neuropeptide, slowly acting transmitters or growth factors:
   1. Hypothalamic-releasing hormones: thyrotropin-releasing hormone, somatostatin
   2. Pituitary peptides: ACTH, beta Endorphin, prolactin, vasopresin
   3. Peptides that acts on gut and brain: gastrin, cholecystokinin, vasoactive intestinal polypeptide, insulin, glucagon
   4. From other tissues: angiotensin II, bradykinin, calcitonin.

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 (in visceral smooth muscle, cardiac muscle).

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

The membrane of the postsynaptic neuron contains large numbers of receptor proteins, also shown in Figure. 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.

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

Figure 2.10 Anatomy of the synapse (after Guyton)
the channels and on through to the opposite side, whereas sodium, potassium, and calcium cations are blocked, mainly because their hydrated ions are too large to pass. We will learn later that when cation channels open and allow positively charged sodium ions to enter, the positive electrical charges of the sodium ions will in turn excite this neuron. Therefore, a transmitter substance that opens cation channels is called an excitatory transmitter. Conversely, opening anion channels allows negative electrical charges to enter, which inhibits the neuron. Therefore, transmitter substances that open these channels are called inhibitory transmitters. When a transmitter substance activates an ion channel, the channel usually opens within a fraction of a millisecond; when the transmitter substance is no longer present, the channel closes equally rapidly. The opening and closing of ion channels provide a means for very rapid control of postsynaptic neurons.

"Second Messenger" system in the postsynaptic neuron.

Many functions of the nervous system—for instance, the process of memory—require prolonged changes in neurons for seconds to months after the initial transmitter substance is gone. The ion channels are not suitable for causing prolonged postsynaptic neuronal changes because these channels close within milliseconds after the transmitter substance is no longer present. However, in many instances, prolonged postsynaptic neuronal excitation or inhibition is achieved by activating a “second messenger” chemical system inside the postsynaptic neuronal cell itself, and then it is the second messenger that causes the prolonged effect. There are several types of second messenger systems. One of the most common types uses a group of proteins called G-proteins. Figure 45–7 shows in the upper left corner a membrane receptor protein. A G-protein is attached to the portion of the receptor that protrudes into the interior of the cell. The G-protein in turn consists of three components: an alpha (α) component that is the activator portion of the G-protein, and beta (β) and gamma (γ) components that are attached to the alpha component and also to the inside of the cell membrane adjacent to the receptor protein. On activation by a nerve impulse, the alpha portion of the G-protein separates from the beta and gamma portions and then is free to move within the cytoplasm of the cell. Inside the cytoplasm, the separated alpha component performs one or more of multiple functions, depending on the specific characteristic of each type of neuron. Shown in Figure 2.11 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.

Excitatory or inhibitory receptors in the postsynaptic membrane

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

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

Inhibition
1. Opening of chloride ion channels through the postsynaptic neuronal membrane. This allows rapid diffusion of negatively charged chloride ions from outside the postsynaptic neuron to the
inside, thereby carrying negative charges inward and increasing the negativity inside, which is inhibitory.

2. Increase in conductance of potassium ions out of the neuron. This allows positive ions to diffuse to the exterior, which causes increased negativity inside the neuron; this is inhibitory.

3. Activation of receptor enzymes that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

Special characteristics of synaptic transmission

1. “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.

2. Fatigue of synaptic transmission. When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the postsynaptic neuron is at first very great, but the firing rate becomes progressively less in succeeding milliseconds or seconds. This is called fatigue of synaptic transmission. Fatigue is an exceedingly important characteristic of synaptic function because when areas of the nervous system become overexcited, fatigue causes them to lose this excess excitability after awhile. For example, fatigue is probably the most important means by which the excess excitability of the brain during an epileptic seizure is finally subdued so that the seizure ceases. Thus, the development of fatigue is a protective mechanism against excess neuronal activity.

3. 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.

4. 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.

5. 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 lipidsoluble, it has been reasoned that some of them might change the physical characteristics of the neuronal membranes, making them less responsive to excitatory agents.

6. 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.