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Neurotransmission

Learning Objectives: To acquaint the students about:

1. The structure of a typical neuron and the function of each of its parts
2. Explain how the neuron develops and maintains a resting potential.
3. Compare a graded potential with an action potential, describing the production and transmission of each.
4. Contrast continuous conduction with saltatory conduction
5. Describe the actions of the various neurotransmitters.
6. Trace the events that take place in synaptic transmission and draw diagrams to support your description.

Most animals have *nervous system* that takes in information, transmits it to the spinal cord and brain where it is integrated, and then responds. In most animals, responses to stimuli depend on **neural signaling,** information transfer by networks of nerve cells, called **neurons,** that are connected to thousands of other neurons.

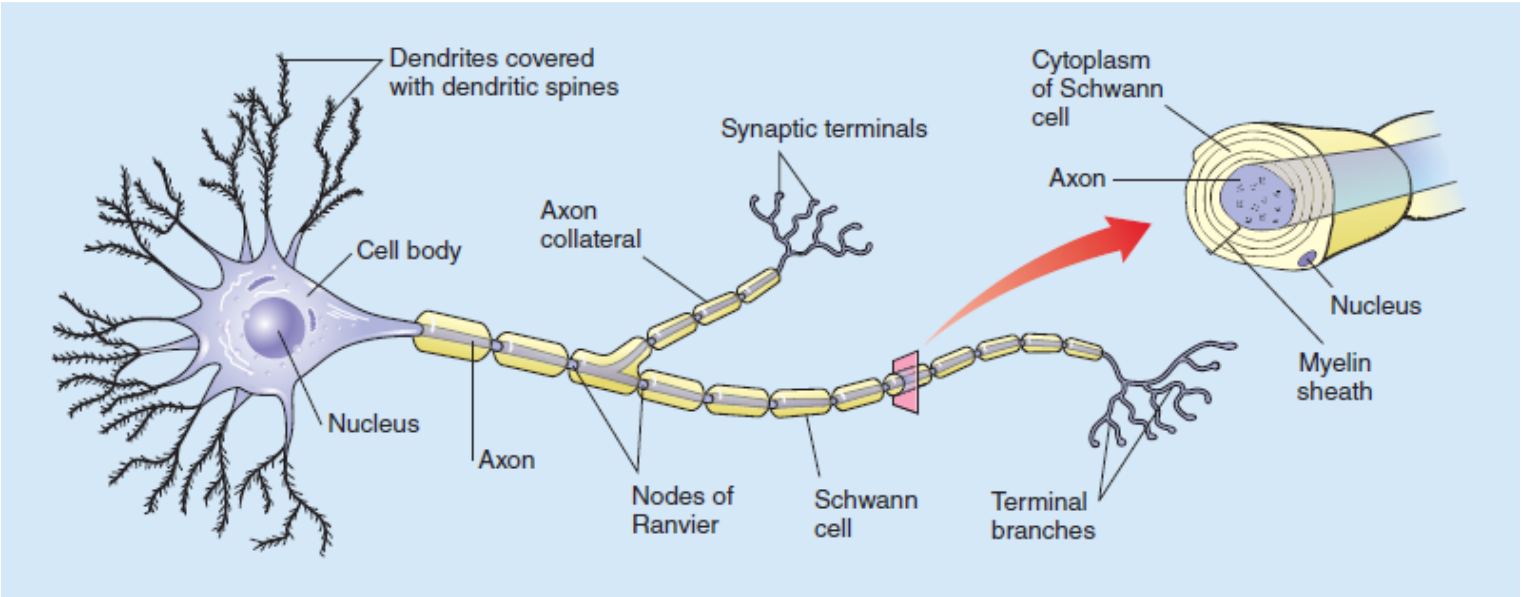
Neurons receive stimuli and transmit neural signals

The neuron is highly specialized to receive and transmit information. Neurons produce and transmit electrical signals called **nerve impulses,** or *action potentials.* The neuron is distinguished from all other cells by its long **processes** (cytoplasmic extensions). A neuron has four parts—dendrites, cell body, axon, and presynaptic terminals.

•The largest portion of neuron, the **cell body,** contains nucleus, cytoplasm, and most of the organelles. Typically, two types of processes project from the cell body of a multipolar neuron. Numerous dendrites extend from one end, and a long, single axon projects from the opposite end. **Dendrites** are typically short, highly branched processes specialized to receive stimuli and send signals to the cell body. The cell body integrates incoming signals. The axon conducts nerve impulses away from the cell body to another neuron or to a muscle or gland. At its end the axon divides, forming many **terminal branches** that end in **synaptic terminals.** The synaptic terminals release **neurotransmitters,** chemicals that transmit signals from one neuron to another or from a neuron to an effector. The junction between a synaptic terminal and other neuron is called a **synapse.**

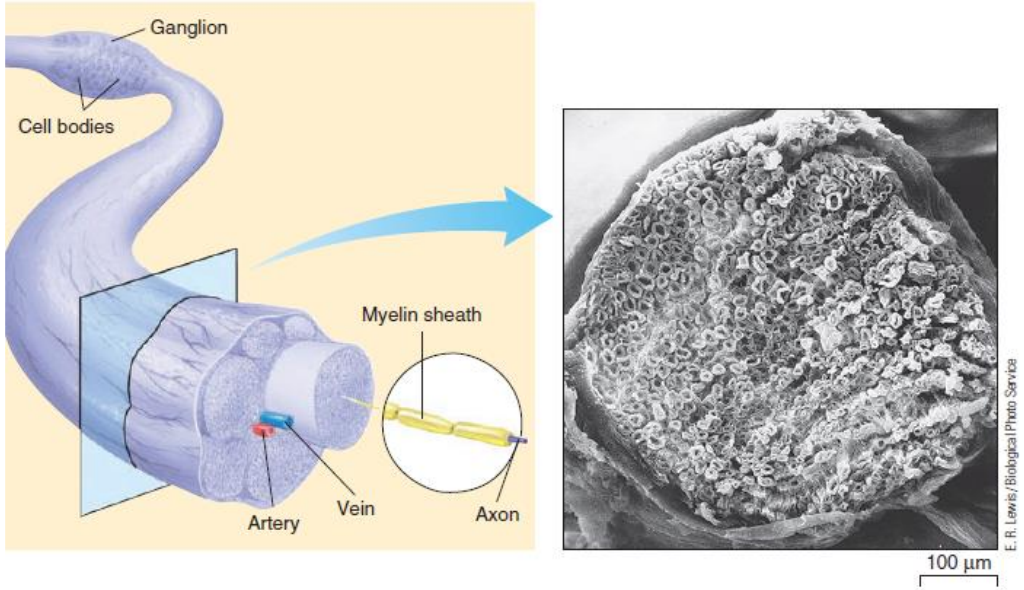
•In vertebrates, the axons of many neurons outside the CNS are surrounded by a series of **Schwann cells.** The PM of these glial cells contain **myelin,** a white, fatty material. Schwann cells wrap their PM around the axon, forming an insulating covering called the **myelin sheath.**

•Gaps in the myelin sheath, called **nodes of Ranvier,** occur between successive Schwann cells. At these points the axon is not insulated with myelin. Axons >2 μm in diameter have myelin sheaths and are described as *myelinated.*



Axons aggregate to form nerves and tracts

A **nerve** consists of hundreds or even thousands of axons wrapped together in connective tissue. We can compare a nerve to a telephone cable. The individual axons correspond to the wires that run through the cable, and the sheaths and connective tissue coverings correspond to the insulation.



TRANSMITTING INFORMATION ALONG THE NEURON

- Most animal cells have a difference in electric charge across the PM—the electric charge ***inside the cell is more negative*** than the electric charge of the extracellular fluid. The PM is said to be electrically **polarized,** meaning that one side, has a different charge than the other side.

- When electric charges are separated in this way, a potential energy difference exists across the membrane. The difference in electric charge across the PM gives rise to an *electrical gradient.* Voltage is the force that causes charged particles to flow between 2 points. The voltage measured across PM is called **membrane potential.**

- If the charges are permitted to come together, they have the ability to do work. Thus, the cell can be thought of as a biological battery. In excitable cells, such as neurons and muscle cells, the membrane potential can change rapidly. Such changes can transmit signals to other cells.

The relation between the concentration difference of a permeating ion across a membrane and the membrane potential at equilibrium is given by the **Nernst equation**:

$$E = \frac{RT}{zF} \ln \frac{C_{out}}{C_{in}}$$

in which E is the membrane potential (E stands for *electromotive force*, an older term for voltage), R is the gas constant, T is absolute temperature, z is the valence of the ion species (charge for the kind of ion), F is Faraday's constant (charge per mole of ions), and C_{out} and C_{in} are the ion concentrations on the two sides of the membrane.

Notice that *the larger the concentration difference across the membrane, the larger the membrane potential* at which the ion species is in equilibrium. The reason for this relation is that increasing the concentration difference increases the concentration gradient of the ion species and thus increases the electrical force necessary to oppose it.

RESTING MEMBRANE POTENTIAL

Ion channels and pumps maintain the resting potential of the neuron

The membrane potential in a resting (not excited) neuron or muscle cell is its **resting potential.** The resting potential is generally expressed in units called *millivolts* (mV). Like other cells that can produce electrical signals, the neuron has a resting potential of about -70 mV, because the cytosol close to PM is negatively charged relative to the extracellular fluid (ecf) .

Two main factors determine the magnitude of the membrane potential: (1) differences in the concentrations between specific ions inside the cell and those in the extracellular fluid and (2) selective permeability of PM to these ions.

The distribution of ions inside neurons and in extracellular fluid surrounding them is like most other cells in the body.

The resting membrane potential of large nerve fibers when they are not transmitting nerve signals is about ***−90 millivolts***, indicating that, the potential *inside the fiber* is 90 millivolts more negative than the potential in e.c.f. on the outside of the fiber.

NERNST EQUATION

$$E_{ion} = 61 \times \log \frac{[ion]_o}{[ion]_i}$$

	Outside $[ion]_o$	Inside $[ion]_i$	Ratio outside:inside	E_{ion} (37°C)
K+	5mM	150mM	1:30	-91mV
Na+	150mM	15mM	10:1	62mV

Hint: log (1) = 0, log (<1) = -ve, log (>1) = +ve

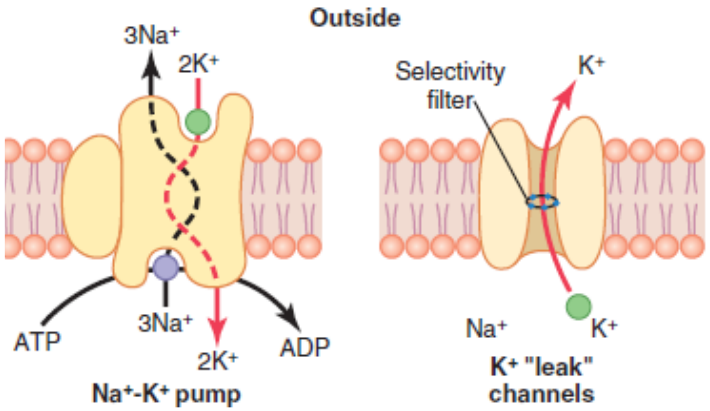
Ion concentration: $[ion]_o > [ion]_i$ then E_{ion} = +ve
$[ion]_o < [ion]_i$ then E_{ion} = -ve

*at room temperature (25°C) the constant is 58

The equilibrium can be calculated for any ion (eg Na+ or K+) using the Nernst equation
- At body temperature (37.C), can be influenced by temperature (it will change how ionic species move)
- 61 is a constant (includes factors like temperature and other constants)
- This equation allows you to make predictions and operation alise things such as equilibrium potential
- The bigger the concentration difference, the bigger the equilibrium potential (bigger for potassium than sodium because of this)

Active Transport of Sodium and Potassium Ions through the Membrane—The Sodium-Potassium (Na_+-K_+) Pump.

All cell membranes of the body have a powerful Na^+-K^+ pump that continually transports sodium ions to the outside of the cell and potassium ions to the inside.



This is an *electrogenic pump* because more positive charges are pumped to the outside than to the inside (three Na_+ ions to the outside for each two K_+ ions to the inside), leaving a net deficit of positive ions on the inside and causing a negative potential inside the cell membrane.

The Na_+-K_+ pump also causes large concentration gradients for sodium and potassium across the resting nerve membrane. These gradients are as follows:

Na_+ (outside):142mEq/L
Na_+ (inside):14mEq/L
K^+ (outside): 4mEq/L
K_+ (inside):140mEq/L

So, Na^+ inside /Na^+ outside $= 0.1$
K^+ inside /K^+ outside $= 35.0$

Leakage of Potassium Through the Nerve Cell Membrane.

A *potassium channel*, or *potassium [K_+] "leak" channel*) exists in the nerve membrane through which potassium can leak even in a resting cell. These K+ leak channels may also leak sodium ions slightly but are far more permeable to potassium than to sodium—normally about 100 times as permeable.

ORIGIN OF THE NORMAL RESTING MEMBRANE POTENTIAL

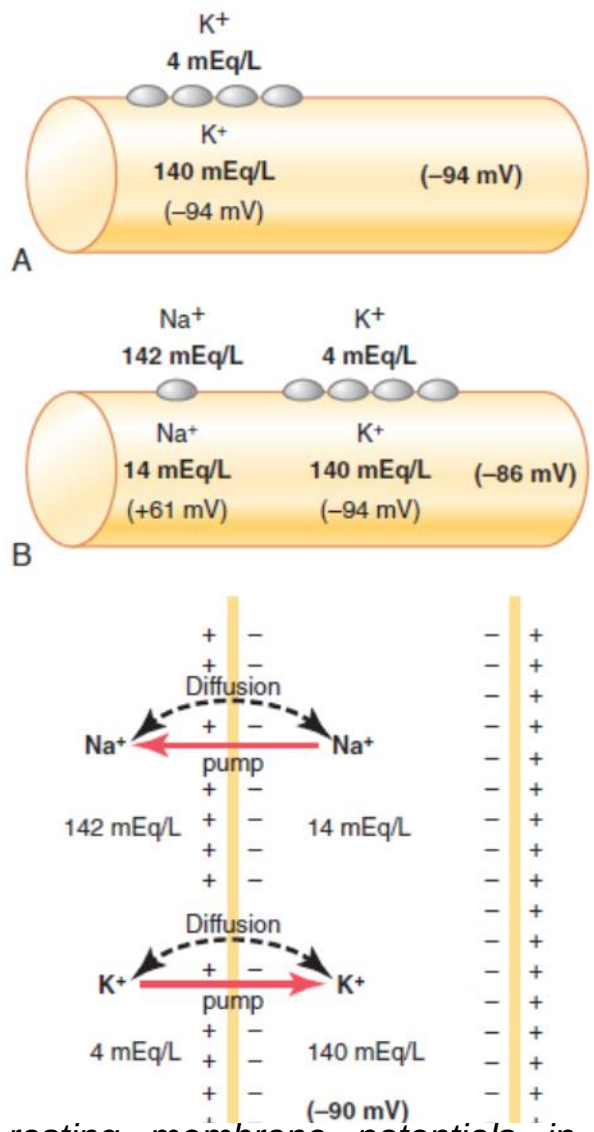
important factors in establishment of normal resting membrane potential (−90 mV) are:

Contribution of the Potassium Diffusion Potential: Because of the high ratio of K+ ions inside to outside, 35 : 1, the Nernst potential corresponding to this ratio is −94 mV. Thus, if K+ were the only factor causing resting potential, it would be equal to −94 mV.

Contribution of Sodium Diffusion Through the Nerve Membrane Addition of slight permeability of the nerve membrane to Na+, caused by minute diffusion of Na+ through the K+-Na+ leak channels. The ratio of Na+ from inside to outside membrane is 0.1, which gives a Nernst potential for inside of membrane of +61 mV. Also the Nernst potential for K diffusion of −94 mV. If the membrane is highly permeable to K but only slightly permeable to Na+, it is logical that K diffusion of potassium contributes far more to the membrane potential. In the normal nerve fiber, the permeability of membrane to K is ~ 100 x as great as its permeability to Na+. Using this value gives a summated potential inside the membrane of −86 mV.

Contribution of the Na+-K+ Pump. Continuous pumping of 3 Na+ to outside occurs for each 2K+ pumped to inside of the membrane. The pumping of more Na+ to outside than K+ being pumped to inside causes continual loss of +ve charges from inside the membrane, creating an additional degree of negativity (~ −4 mV additional) on inside beyond that which can be accounted for by diffusion alone. Thus, the net membrane potential when all these factors are operative at the same time is ~ −90mV.

In summary, ***diffusion potentials alone*** caused by K and Na diffusion would give a ***membrane potential of about −86 millivolts***, with almost all of this being determined by K+ diffusion. An additional −4 millivolts is then contributed to membrane potential by the continuously acting electrogenic Na+-K+ pump, giving a net membrane potential of −90 millivolts



Establishment of resting membrane potentials in nerve fibers under 3 conditions: ***A,*** *when membrane potential is caused entirely by K+ diffusion alone;* ***B,*** *when the membrane potential is caused by diffusion of both Na+ and K+ ions; and* ***C,*** *when the membrane potential is caused by diffusion of both Na+ and K+ plus pumping of both these ions by the Na+-K+ pump.*

Graded local signals vary in magnitude

Neurons are excitable cells. They respond to stimuli and can convert stimuli into nerve impulses. An electrical, chemical, or mechanical stimulus may alter the resting potential by increasing the membrane's permeability to sodium ions.

When a stimulus causes the membrane potential to become less -ve (closer to zero) than the resting potential, that region of the membrane is **depolarized.** Because depolarization brings a neuron closer to transmitting a neural impulse, it is described as *excitatory.* In contrast, when the membrane potential becomes more negative than the resting potential, the membrane is **hyperpolarized.** Hyperpolarization is *inhibitory;* it decreases the ability of neuron to generate a neural impulse.

A stimulus may change potential in a relatively small region of PM. Such a **graded potential** is a local response. It functions as a signal only over a very short distance because it fades out within a few millimeters of its point of origin. A graded potential varies in magnitude; that is, the potential charge varies depending on the strength of the stimulus applied. The larger the stimulus is, the larger the change in permeability and the greater the change in membrane potential.

Axons transmit signals called action potentials

When a stimulus is strong enough, a rapid, large change in membrane potential occurs, depolarizing the membrane to a critical point known as the **threshold level.** At that point, the neuron fires a nerve impulse, or **action potential,** an electrical signal that travels rapidly down the axon into the synaptic terminals. All cells can generate graded potentials, but only neurons, muscle cells, and a few cells of the endocrine and immune systems can generate action potentials.

Changes in voltage regulate specific **voltage activated ion channels** (also called **voltage-gated ion channels**) in the plasma membrane of the axon and cell body.

An action potential is generated when the voltage reaches threshold level

The membrane of most neurons can depolarize by about 15 mV, that is, to a potential of about −55 mV, without initiating an action potential. However, when depolarization is greater than −55 mV, the threshold level is reached and an action potential is generated. The neuron membrane quickly reaches zero potential and even **overshoots** to +35 mV or more as a momentary reversal in polarity takes place. Th e sharp rise and fall of the action potential is called a *spike.*

NEURON ACTION POTENTIAL

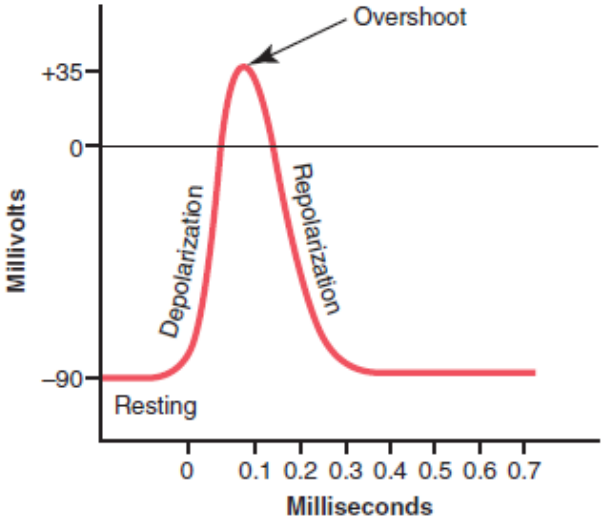
Nerve signals are transmitted by *action potentials,* which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and ends with an almost equally rapid change back to the negative potential. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.

The successive stages of the action potential are as follows.

Resting Stage. The resting stage is the resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage because of the −90 millivolts negative membrane potential that is present.

Depolarization Stage. At this time, the membrane suddenly becomes permeable to Na+ ions, allowing tremendous numbers of positively charged Na+ to diffuse to the interior of the axon. The normal "polarized" state of −90 mV is immediately neutralized by the inflowing +ve charged Na+, with the potential rising rapidly in the positive direction—a process called *depolarization.* In large nerve fibers, the great excess of positive Na+ moving to the inside causes the membrane potential to actually "overshoot" beyond the zero level and to become somewhat positive.

Repolarization Stage. Within a few 10,000ths of a second after the membrane becomes highly permeable to Na+, the Na channels begin to close and the K channels open to a greater degree than normal. Then, rapid diffusion of K+ ions to the exterior re-establishes the normal negative resting membrane potential, called *repolarization* of the membrane.



Typical action potential

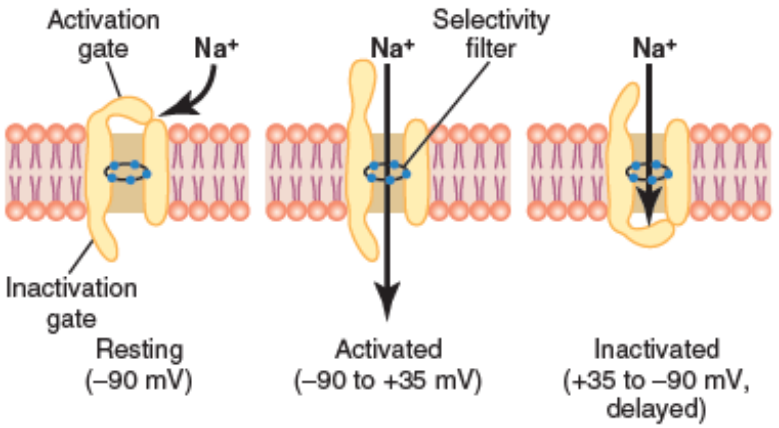
Activation and Inactivation of the Voltage-Gated Sodium Channel

The voltage-gated Na channel exists in 3 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.* In the normal resting membrane when the membrane potential is −90 mV, the activation gate is closed, which prevents any entry of Na+ ions to the interior of the fiber through these Na 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—between −70 and −50 millivolts—that causes a sudden conformational change in the activation gate, flipping it all the way to the open position. During this *activated state,* Na ions can pour inward through channel, increasing the Na permeability of membrane 500- to 5000-fold.

Inactivation 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. Thus, after the Na channel has remained open for a few 10,000ths of a second, the inactivation gate closes and Na ions no longer can pour to inside of the membrane. At this point, membrane potential begins to return toward resting membrane state, the **repolarization** process.

Another important characteristic of the Na 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 is usually not possible for the Na channels to open again without first repolarizing the nerve fiber.

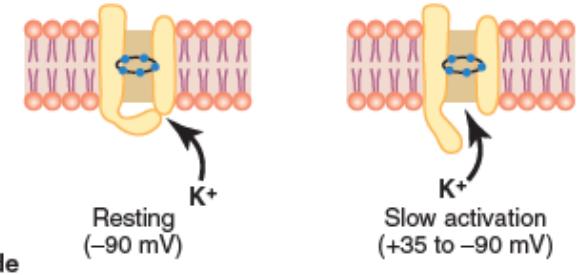


Characteristics of the voltage-gated Na channels, showing successive activation and inactivation of Na channels when the membrane potential is changed from the normal resting -ve value to a +ve value.

Voltage-Gated Potassium Channel and Its Activation

The voltage-gated potassium channel exists 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.

Voltage-gated potassium channels, showing delayed activation when the membrane potential is changed from the normal resting negative value to a positive value.



Typical changes in conductance of the voltage-gated Na and Kc channels when membrane potential is suddenly changed from −90 millivolts to +10 millivolts and then, 2 milliseconds later, back to −90 millivolts. *Note the sudden opening of the sodium channels (the activation stage) within a small fraction of a millisecond after the membrane potential is increased to the positive value. However, during the next millisecond, the Na channels automatically close (inactivation stage).*

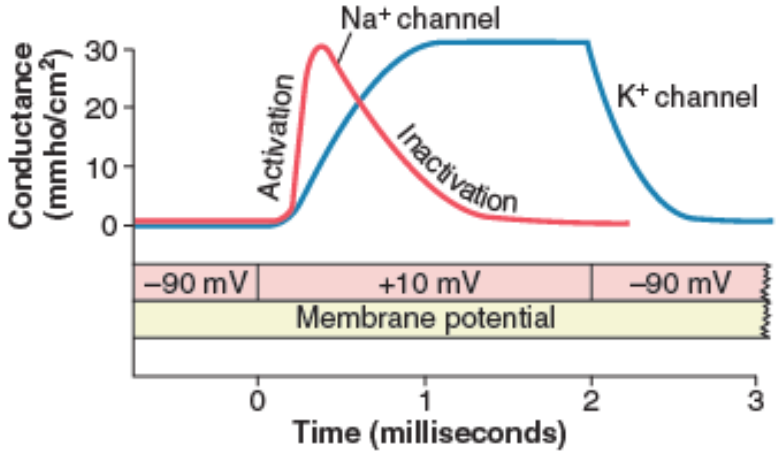
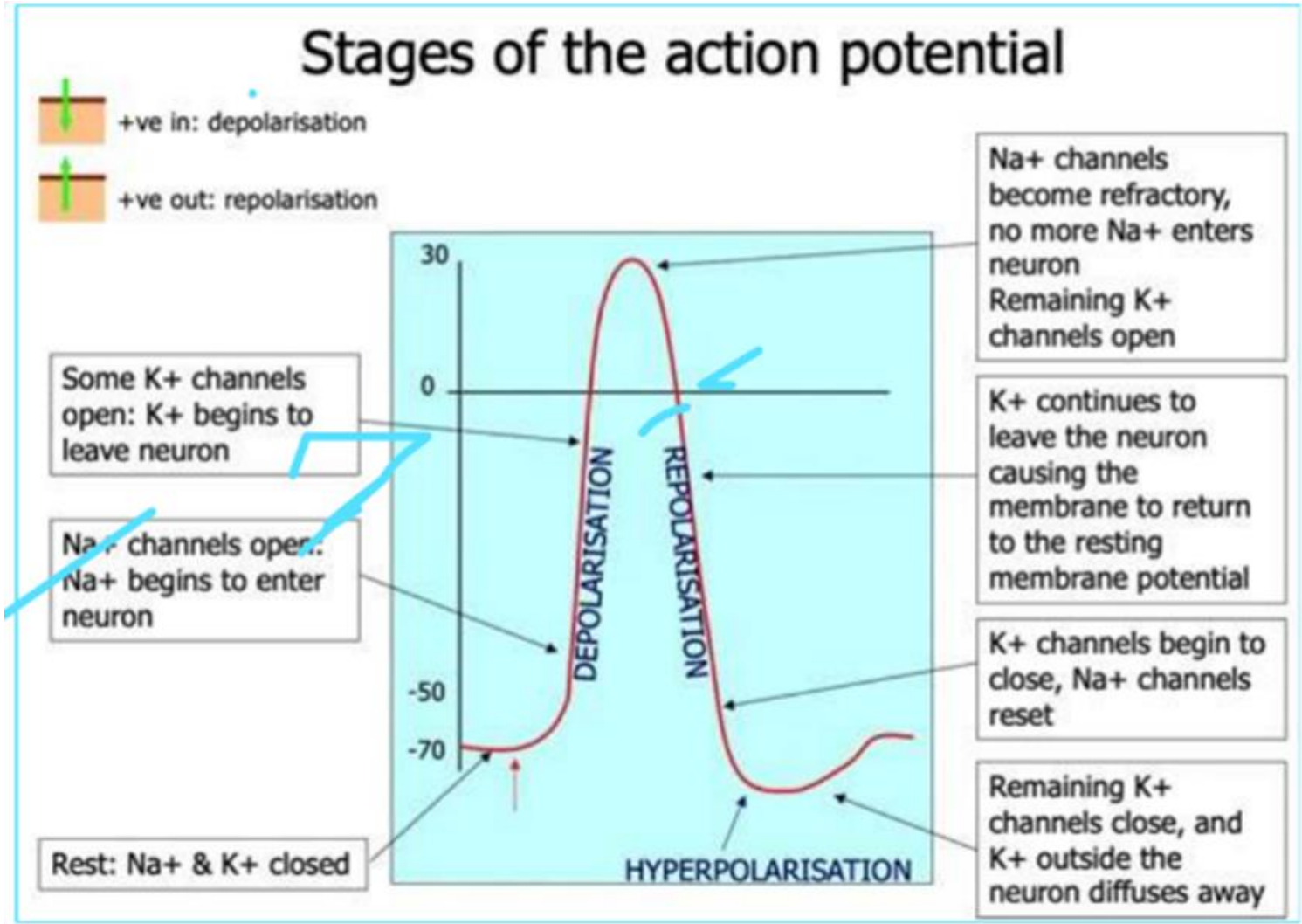


Figure 5-9. Typical changes in conductance of sodium and potassium ion channels when the membrane potential is suddenly increased from the normal resting value of –90 millivolts to a positive value of +10 millivolts for 2 milliseconds. This figure shows that the sodium channels open (activate) and then close (inactivate) before the end of the 2 milliseconds, whereas the potassium channels only open (activate), and the rate of opening is much slower than that of the sodium channels.

Stages of the action potential



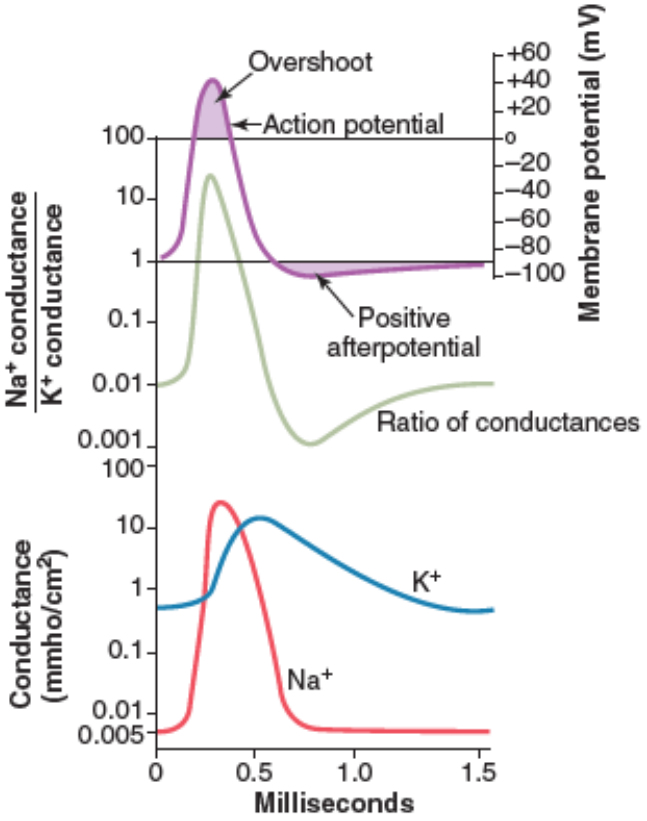
SUMMARY OF THE EVENTS THAT CAUSE THE ACTION POTENTIAL

Sequential events that occur during and shortly after the action potential and changes in membrane conductance for sodium and potassium ions.

During the resting state, before the action potential begins, the conductance for K+ ions is 50 to 100 times as great as the conductance for Na+ ions. This disparity is caused by much greater leakage of K+ ions than Na+ ions through the leak channels. However, at the onset of the action potential, the Na channels instantaneously become activated and allow up to a 5000-fold increase in Na conductance. The inactivation process then closes the Na channels within another fraction of a millisecond.

The onset of the action potential also causes voltage gating of the K channels, causing them to begin opening more slowly a fraction of a millisecond after the Na channels open. At the end of the action potential, the return of the membrane potential to the -ve state causes the K channels to close back to original status, but, only after an additional millisec or more delay.

The ratio of Na to K conductance at each instant during the action potential, and above this depiction is the action potential itself. During the early portion of the action potential, the ratio of Na to K conductance increases >1000-fold. Therefore, far more Na ions flow to the interior of the fiber than do K+ ions to the exterior. This is what causes the membrane potential to become positive at the action potential onset. Then the Na channels begin to close and the K channels begin to open, and thus the ratio of conductance shifts far in favor of high K conductance but low Na conductance. This shift allows very rapid loss of K+ ions to the exterior but virtually zero flow of sodium ions to the interior. Consequently, the action potential quickly returns to its baseline level.



Changes in Na and K conductance during the course of action potential. Na conductance increases several thousand–fold during early stages of action potential, whereas K conductance increases only ~ 30-fold during latter stages of action potential and for a short period thereafter.

INITIATION OF THE ACTION POTENTIAL

Up to this point, we have explained the changing sodium and potassium permeability of the membrane, as well as the development of the action potential, but we have not explained what initiates the action potential.

A Positive-Feedback Cycle Opens the Sodium Channels.

First, as long as the membrane of the nerve fiber remains undisturbed, no action potential occurs in the normal nerve. However, if any event causes enough initial rise in the membrane potential from −90 millivolts toward the zero level, the rising voltage will cause many voltage gated sodium channels to begin opening. This occurrence allows rapid inflow of sodium ions, which causes a further rise in the membrane potential, thus opening still more voltage-gated sodium channels and allowing more streaming of sodium ions to the interior of the fiber. This process is a positive-feedback cycle that, once the feedback is strong enough, continues until all the voltage gated sodium channels have become activated (opened).

Then, within another fraction of a millisecond, the rising membrane potential causes closure of the sodium channels and opening of potassium channels, and the action potential soon terminates.

Threshold for Initiation of the Action Potential.

An action potential will not occur until the initial rise in membrane potential is great enough to create the positive feedback described in the preceding paragraph. This occurs when the number of sodium ions entering the fiber becomes greater than the number of potassium ions leaving the fiber. A sudden rise in membrane potential of 15 to 30 millivolts is usually required. Therefore, a sudden increase in the membrane potential in a large nerve fiber from −90 millivolts up to about −65 millivolts usually causes the explosive development of an action potential. This level of −65 mV is said to be the *threshold* for stimulation.

PROPAGATION OF THE ACTION POTENTIAL

An action potential elicited at any one point on an excitable membrane usually excites adjacent portions of the membrane, resulting in propagation of the action potential along the membrane.

Fig 5-11*A* shows a normal resting nerve fiber, and **Fig 5-11*B*** shows a nerve fiber that has been excited in its midportion—that is, the midportion suddenly develops increased permeability to sodium. The *arrows* show a "local circuit" of current flow from the depolarized areas of the membrane to the adjacent resting membrane areas. That is, positive electrical charges are carried by the inward-diffusing sodium ions through the depolarized membrane and then for several millimeters in both directions along the core of the axon. These positive charges increase the voltage for a distance of 1 to 3 millimeters inside the large myelinated fiber to above the threshold voltage value for initiating an action potential. Therefore, the sodium channels in these new areas immediately open, as shown in **Fig 5-11*C*** and ***D,*** and the explosive action potential spreads. These newly depolarized areas produce still more local circuits of current flow farther along the membrane, causing progressively more and more depolarization. Thus, the depolarization process travels along the entire length of the fiber. This transmission of the depolarization process along a nerve or muscle fiber is called a *nerve* or *muscle impulse.*

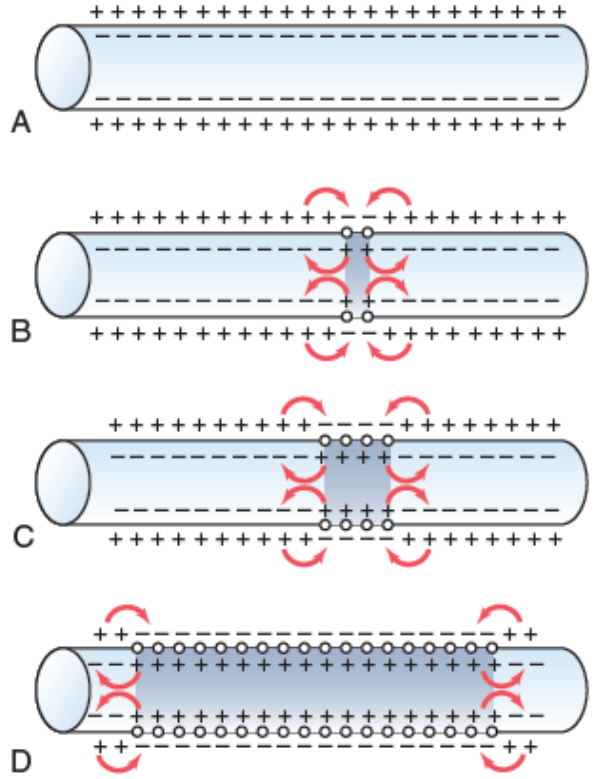


Figure 5-11. Propagation of action potentials in both directions along a conductive fiber.

Direction of Propagation. An excitable membrane has no single direction of propagation, but the action potential travels in all directions away from the stimulus—until the entire membrane has become depolarized.

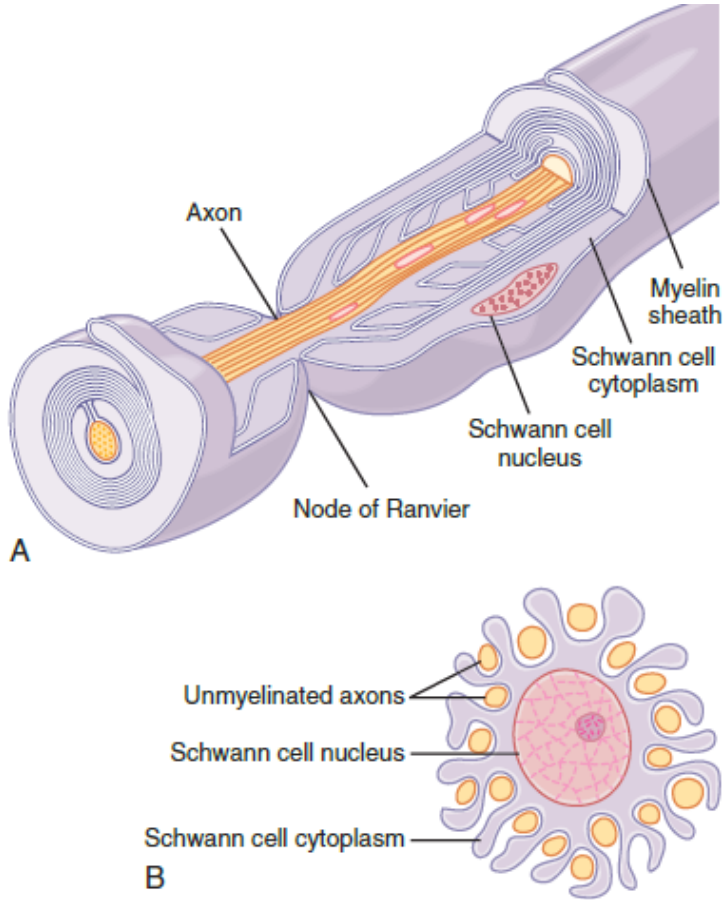
All-or-Nothing Principle. Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, but it does not travel at all if conditions are not right. This is the *all-or-nothing principle,* 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. Under this situation, the spread of depolarization stops. Thus, for continued propagation of an impulse, the ratio of action potential to threshold for excitation must at all times be >1. This "greater than 1" requirement is called the *safety factor* for propagation.

Myelinated and Unmyelinated Nerve Fibers. The large fibers are *myelinated,* and the small ones are *unmyelinated.* In a typical myelinated fiber, 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.*

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. The Schwann cell

then 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 *micro*meters 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*



Function of 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 aroundmultiple unmyelinated nerve fibers

"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, 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 along the fiber, which is the origin of the term "saltatory."

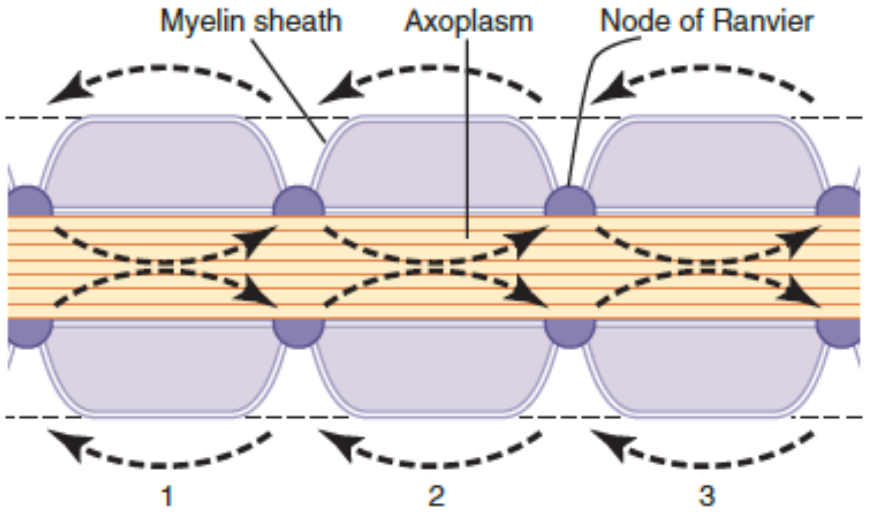
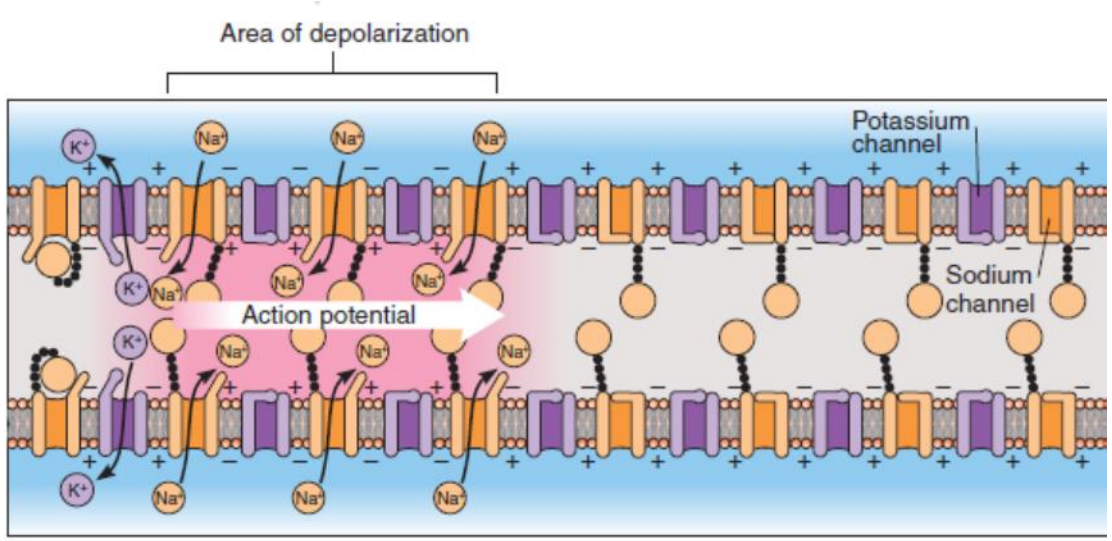


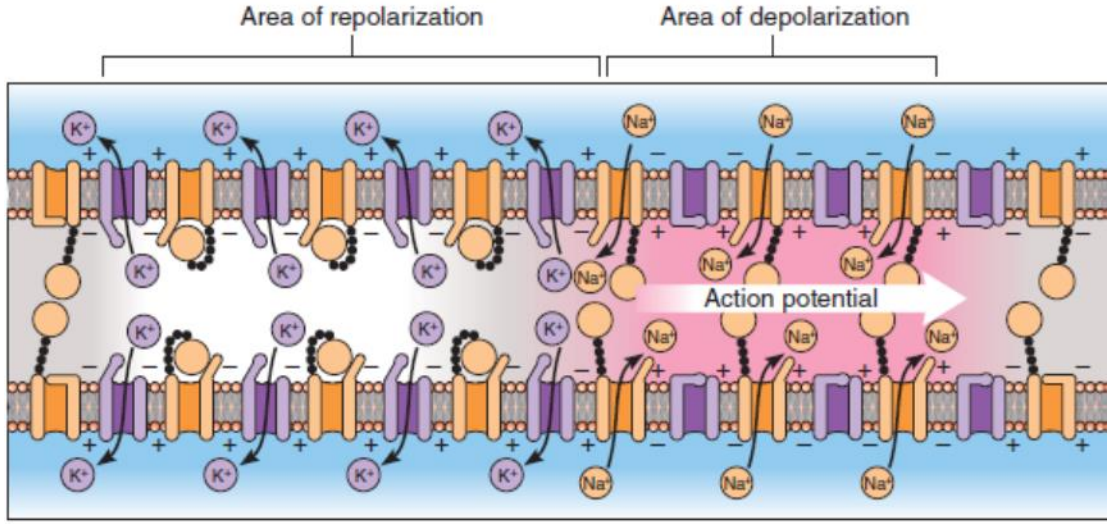
Figure 5-17. Saltatory conduction along a myelinated axon. The flow of electrical current from node to node is illustrated by the arrows.

Saltatory conduction has advantages over continuous conduction 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 less energy*** expenditure for re-establishing the Na and K concentration differences across the membrane after a series of nerve impulses. (***Ions move across PM only at the nodes, so fewer Na+ and K+ are displaced. As a result, the Na-K pumps do not expend as much ATP to re-establish resting conditions each time an impulse is conducted.***)

The excellent insulation afforded by myelin membrane and 50-fold decrease in membrane capacitance also allow repolarization with little transfer of ions.



1 Action potential is transmitted as wave of depolarization that travels down axon. At region of depolarization, Na^+ diffuse into cell.

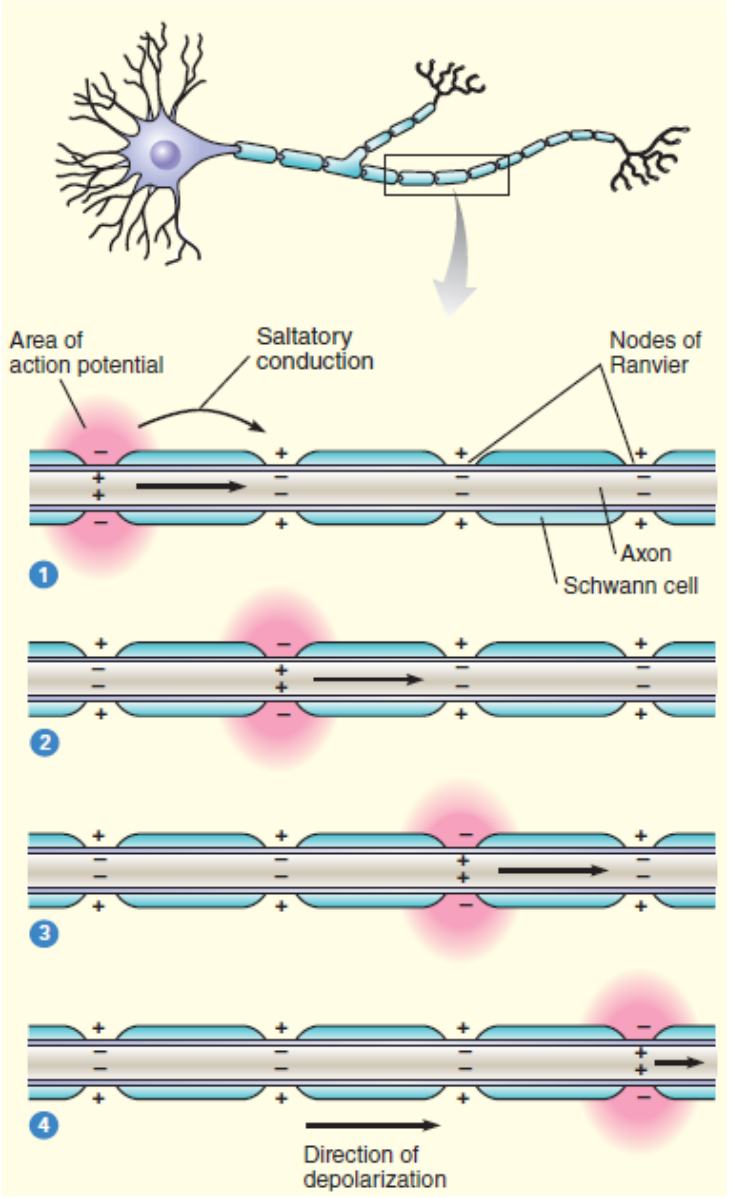


2 As action potential progresses along axon, repolarization occurs quickly behind it.

Transmission of an action potential along axon. When the dendrites of a neuron are stimulated sufficiently to depolarize membrane to its threshold level, a strong pulse of voltage change travels down the axon. This pulse is an action potential.

The ion activity at an active node results in diffusion of ions along the axon that depolarize the next node. The action potential appears to jump from one node of Ranvier to the next.

When nodes are farther apart, less of the axon must depolarize and the axon conducts the impulse faster. Using saltatory conduction, a myelinated axon can conduct an impulse up to 50 times faster than the fastest unmyelinated axon.



In saltatory conduction, Na^+ rapidly diffuse from one node of Ranvier to the next in a myelinated neuron. Action potentials appear to leap from node to node.

EXCITATION—THE PROCESS OF ELICITING THE ACTION POTENTIAL

Basically, any factor that causes sodium ions to begin to diffuse inward through the membrane in sufficient numbers can set off automatic regenerative opening of the sodium channels. This automatic regenerative opening can result from *mechanical* disturbance of the membrane, *chemical* effects on the membrane, or passage of *electricity* through the membrane. All these approaches are used at different points in the body to elicit nerve or muscle action potentials: mechanical pressure to excite sensory nerve endings in the skin, chemical neurotransmitters to transmit signals from one neuron to the next in the brain, and electrical current to transmit signals between successive muscle cells in the heart and intestine

"REFRACTORY PERIOD" AFTER AN ACTION POTENTIAL, DURING WHICH A NEW STIMULUS CANNOT BE ELICITED

A new action potential cannot occur in an excitable fiber as long as the membrane is still depolarized from the preceding action potential. The reason for this restriction is that shortly after the action potential is initiated, the sodium channels (or calcium channels, or both) become inactivated and no amount of excitatory signal applied to these channels at this point will open the inactivation gates. The only condition that will allow them to reopen is for the membrane potential to return to or near the original resting membrane potential level. Then, within another small fraction of a second, the inactivation gates of the channels open and a new action potential can be initiated.

The period during which a second action potential cannot be elicited, even with a strong stimulus, is called the *absolute refractory period.* This period for large myelinated nerve fibers is about 1/2500 second. Therefore, one can readily calculate that such a fiber can transmit a maximum of about 2500 impulses per second.

TRANSMITTING INFORMATION ACROSS SYNAPSES

A **synapse** is a junction between two neurons or between a neuron and an eff ector, such as between a neuron and a muscle cell. A neuron that *terminates* at a specific synapse is called a **presynaptic neuron,** whereas a neuron that *begins* at that synapse is a **postsynaptic neuron.**

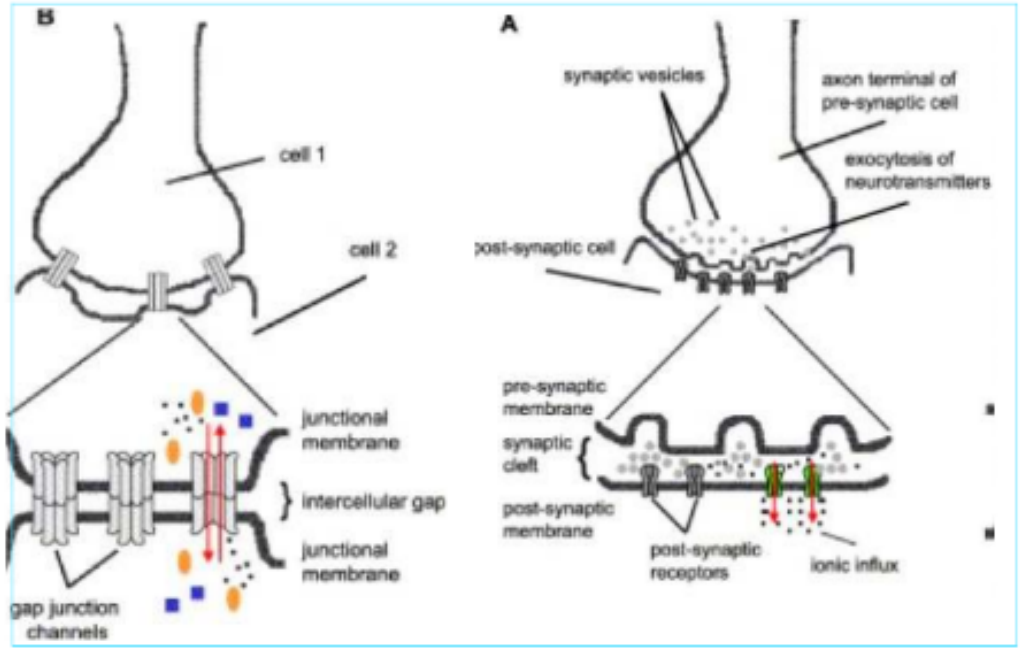
Two types of synapses have been identified: electrical synapses and chemical synapses. In **electrical synapses,** the presynaptic and postsynaptic neurons occur very close together (within 2 nm of one another) and form *gap junctions*. Th e interiors
of the two cells are physically connected by a protein channel.

Electrical synapses let ions pass from one cell to another, permitting an impulse to be directly and rapidly transmitt ed from a presynaptic to a postsynaptic neuron Th e majority of synapses are **chemical synapses.** Presynaptic and postsynaptic neurons are separated by a space, the **synaptic cleft ,** about 20 nm wide (less than one-millionth of an inch). Because
depolarization is a property of the plasma membrane, when an action potential reaches the end of the axon, it cannot jump the gap. Th e electrical signal must be converted into a chemical one.

Neurotransmitters are the chemical messengers that conduct the neural signal across the synapse and bind to chemically activated ion channels in the membrane of the postsynaptic neuron. This binding triggers specific gated ion channels to open (or close), resulting in changes in permeability of the postsynaptic membrane. When a postsynaptic neuron reaches its threshold level of depolarization, it transmits an action potential.

Neurons use neurotransmitters to signal other cells

Many chemical compounds are now known or suspected to function as neurotransmitters, chemical messengers used by neurons to signal other neurons or to signal muscle or gland cells. Neurotransmitters are categorized into several chemical groups, including acetylcholine, biogenic amines, amino acids, neuropeptides, and gaseous neurotransmitters.

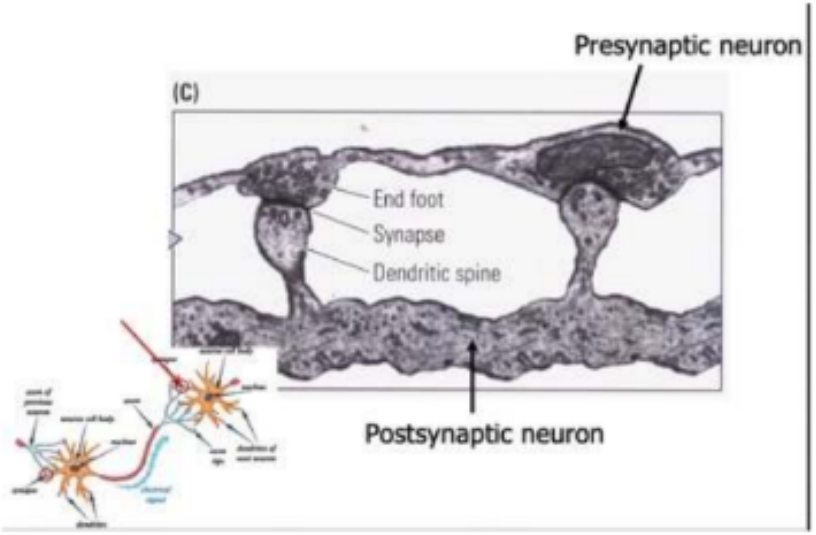


The Synapse

Types of Synapses

1) Electrical Synapses
- very rare in adult mammalian neurons
- Junction between the neurons s very small (3nm gap junction)
- gap is spanned by proteins (connexins) which are used to communicate between the neurons (ions move freely)

2) Chemical Synapses
- common in adult mammalian neurons
- Junctions between the neurons 20-50nm (synaptic cleft)
- chemicals (neurotransmitters) are released from the presynaptic neuron to communicate with the postsynaptic neurons



- End foot is where the vesicles are
- Dendritic spine is where signals are being received

Neurotransmitters are **endogenous chemicals** that enable communication within the nervous system and between the nervous system and the rest of the body. They relay information between individual neurons, and ultimately regulate a wide range of bodily functions.
There are various classes of neurotransmitters, with different functions and mechanisms of action. Neurotransmitter levels and function are crucial to maintaining homeostasis, and if altered can lead to diseases.

Mechanism of Action
Neurotransmitters transmit signals across a synapse at various locations, such as:
•From one neuron to another target neuron
•At the neuromuscular junction **(NMJ),** that is from a neuron to a target muscle cell
•From a neuron to a target gland.
A **synapse** is a junction through which a neuron relays information to another neuron; it has three main components:
•The axon terminal, or pre-synaptic side where information is transmitted from
•The synaptic cleft
•The dendrite, or post-synaptic side, receiving the information.
There is generally a low level baseline level of neurotransmitter release that occurs without any need for stimulation. However, the amount released is increased in response to threshold **action potentials.** Binding of neurotransmitters to the post-synaptic neuron then results in either excitation or inhibition depending on which is released and the receptor it binds to.

Neurotransmitters - Classes of Neurotransmitter

There are hundreds of neurotransmitters, but they can be grouped into classes depending on their structure, or function. Focusing on **structure**, neurotransmitters can be classed as:

•Monoamines – such as dopamine, noradrenaline, adrenaline, histamine, serotonin

•Amino acids – such as glutamate, GABA (gamma-aminobutyric acid), glycine, aspartate, D-serine

•Peptides – such as opioids, endorphins, somatostatin, oxytocin, vasopressin

•Other – such as acetylcholine (ACh), adenosine, nitric oxide

Often, it is more useful to classify neurotransmitters based on their **function**:

•**Excitatory** neurotransmitters increase electrical excitability on the post-synaptic side through modulation of the trans-membrane ion flow to facilitate transmission of an action potential.

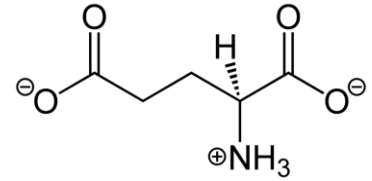
•**Inhibitory** neurotransmitters decrease electrical excitability on postsynaptic side to prevent propagation of action potential.

•**Neuromodulators** function to alter the strength of transmission between neurons by affecting the amount of neurotransmitter that is produced and released.

Specific Neurotransmitter Examples

Glutamate

Glutamate is typically synthesised within neurons from **glutamine** and is the most abundant neurotransmitter in the brain. It is an excitatory neurotransmitter and binds to four different receptors:



•**NMDA** receptors – an ionotropic receptor permeable to sodium, potassium and calcium ions

•**AMPA** receptors – an iontropic receptor permeable to sodium and potassium ions

•**Kainate** receptors – an iontropic receptor permeable to sodium and potassium ions, these are similar to AMPA receptors but much less common

•Metabotropic G-protein coupled receptors It is thought to have an essential role in learning and memory, particularly in the process of **long-term potentiation.**

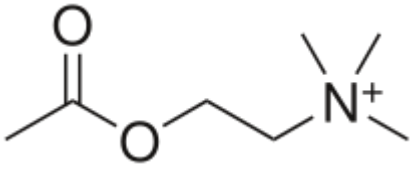
Acetylcholine (ACh)

ACh is used both in the central and peripheral nervous system, in particular at the NMJ. It is synthesised in neurons from **choline** and **acetyl-CoA.** ACh is an excitatory neurotransmitter and binds to two different receptor types:

•**Nicotinic** ACh receptors (nAChRs) – iontropic receptors found at the NMJ, within the CNS and the sympathetic and parasympathetic nervous system. They are also found pre-synaptically in the brain and are thought to have a neuromodulatory effect

•**Muscarinic** ACh receptors (mAChRs) – G protein coupled receptors found in the CNS and within post-ganglionic parasympathetic neurons

Because it is present in so many different areas of the body ACh plays a role in many different processes, including stimulation of muscles at the NMJ; arousal; **attention;** digestion and salivation.



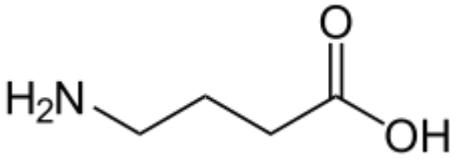
ACh

GABA is synthesised from **glutamate** and is an inhibitory neurotransmitter within the CNS. It binds to two different receptors:

•GABA A receptors – **ionotropic** receptors permeable to chloride and bicarbonate ions

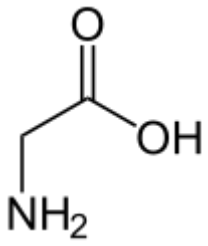
•GABA B receptors – **metabotropic** G protein coupled receptors

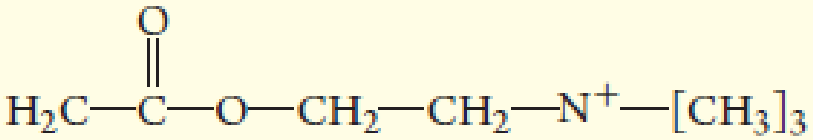
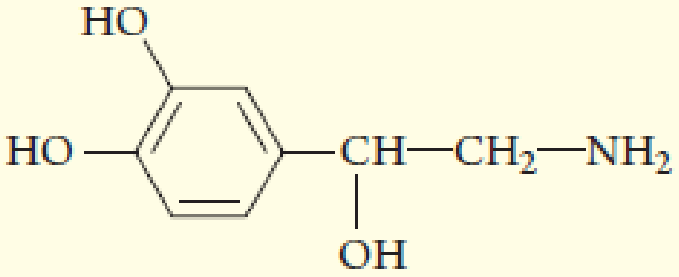
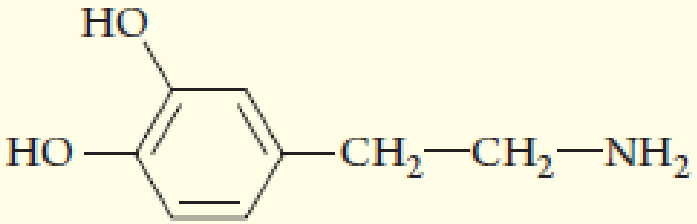
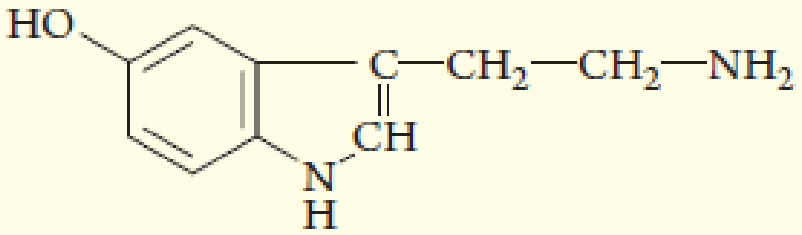
GABA has both rapid inhibitory effects when binding to post-synaptic receptors and slower inhibition via **neuromodulation** at pre-synaptic receptors. It is involved in many different processes in the brain, such as regulating neuronal activity; anxiety and sleep.

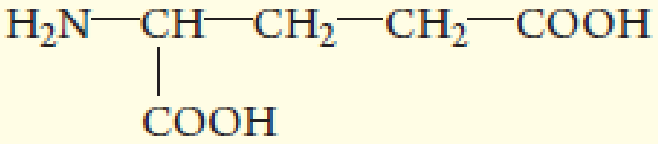
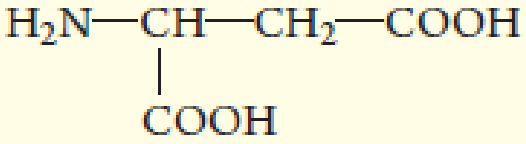
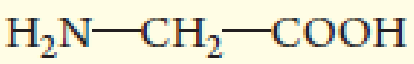


Glycine is an amino acid which is used at the majority of inhibitory synapses in the spinal cord and brainstem. It binds to **ionotropic** receptors which are permeable to chloride and bicarbonate ions.

As an inhibitory neurotransmitter glycine is important in many motor and sensory functions, such as reciprocal inhibition of antagonistic muscles in spinal reflexes. Glycine also has an excitatory role within the CNS as it is a **co-agonist** at glutamatergic NMDA receptors.



Neurotransmitter	Structure	Site of Action	Action
Acetylcholine		CNS, neuromuscular junctions	Excitatory effect on skeletal muscle; inhibitory effect on cardiac muscle; excitatory or inhibitory at other sites; acetylcholine concentration in the brain decreases during the progression of Alzheimer's disease
Biogenic Amines			
Norepinephrine		CNS, PNS	Excitatory or inhibitory; concentration in brain affects mood, sleep, wakefulness, attention
Dopamine		CNS	Helps maintain balance between excitation and inhibition of neurons; important in motor functions; concentration in brain affects mood; also involved in motivation and reward
Serotonin (5-hydroxytryptamine, 5-HT)		CNS	Excitatory effect on pathways that control muscle action; inhibitory effect on sensory pathways; helps regulate food intake, sleep, and wakefulness; affects mood

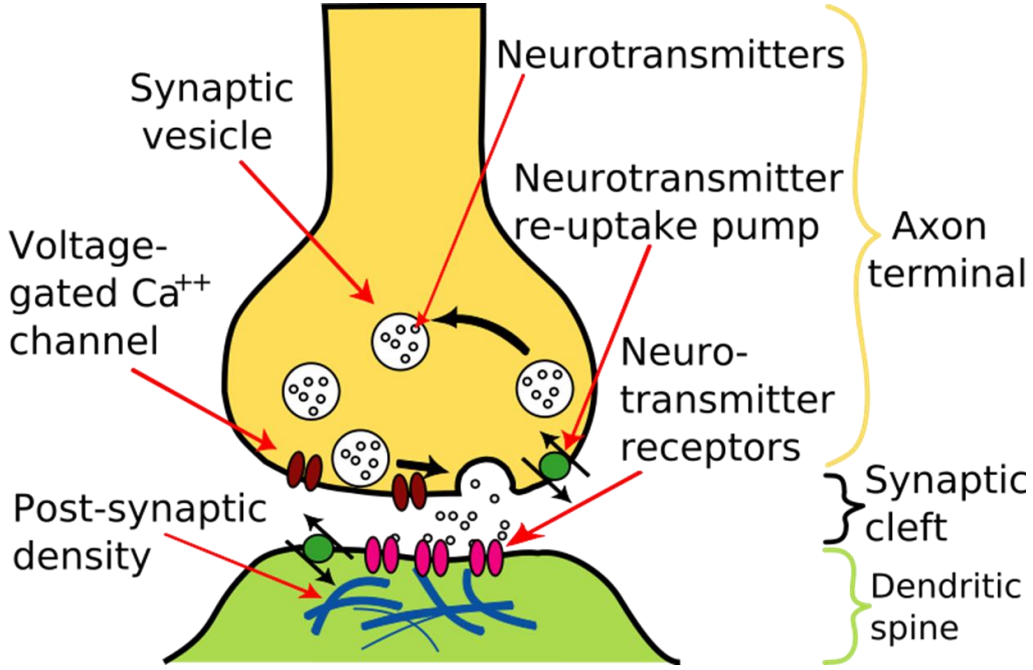
Amino Acids			
Glutamate		CNS, invertebrate neuromuscular junctions	Principal excitatory neurotransmitter in vertebrate brain; functions in learning and memory; excitatory effect at invertebrate neuromuscular junctions
Aspartate		CNS	Excitatory; functions in learning and memory
Glycine		CNS	Inhibitory (mainly in spinal cord)
Gamma-aminobutyric acid (GABA)		CNS, invertebrate neuromuscular junctions	Major inhibitory neurotransmitter in mammalian brain
Neuropeptides			
Endorphins and enkephalins	Y—G—G—F—M* (Methionine enkephalin)	CNS, PNS	Endogenous opiates; bind with opiate receptors on afferent fibers that transmit pain signals; inhibit release of substance P
Substance P	R—P—K—P—Q—Q—F—F—G—L—M	CNS, PNS	Activates ascending pathways that transmit pain signals
Gaseous Neurotransmitters			
Nitric oxide	NO	Most neurons?	Retrograde messenger; transmits signals from postsynaptic to presynaptic neuron
Carbon monoxide	CO	Most neurons?	May be neuromodulator

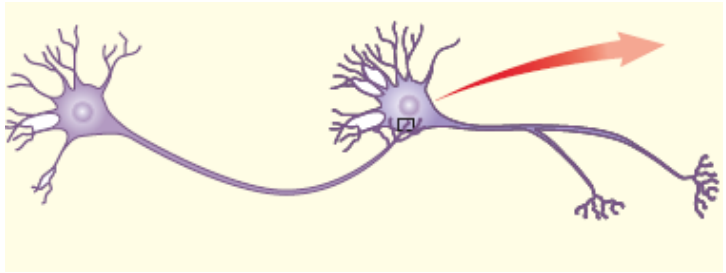
Neurotransmitters bind with receptors on postsynaptic cells

Neurotransmitters are stored in synaptic terminals within hundreds of small membrane-enclosed sacs called **synaptic vesicles**. Each time an action potential reaches a synaptic terminal, voltage-gated Ca2+ channels open. Calcium ions from the extracellular fluid then flow into the synaptic terminal. The Ca2+ induce synaptic vesicles to fuse with the presynaptic membrane and release neurotransmitter molecules into the synaptic cleft by exocytosis.

Neurotransmitter molecules diffuse across the synaptic cleft and bind with specific receptors on the dendrites or cell bodies of postsynaptic neurons (or on PM of effector cells). Many neurotransmitter receptors are chemically activated ion channels known as **ligand-gated ion channels.** When the neurotransmitter, binds with the receptor, the ion channel opens. The acetylcholine receptor, for example, is a ligand-gated ion channel that permits the passage of Na+ and K+.

Some neurotransmitters, such as serotonin work indirectly through a **second messenger.** Binding of the neurotransmitter with a receptor activates a **G protein**, which then activates an enzyme, such as adenylyl cyclase, in the postsynaptic membrane. Adenylyl cyclase converts ATP to **cyclic AMP (cAMP),** which acts as a second messenger. Cyclic AMP activates a kinase that phosphorylates a protein, which then closes K+ channels.

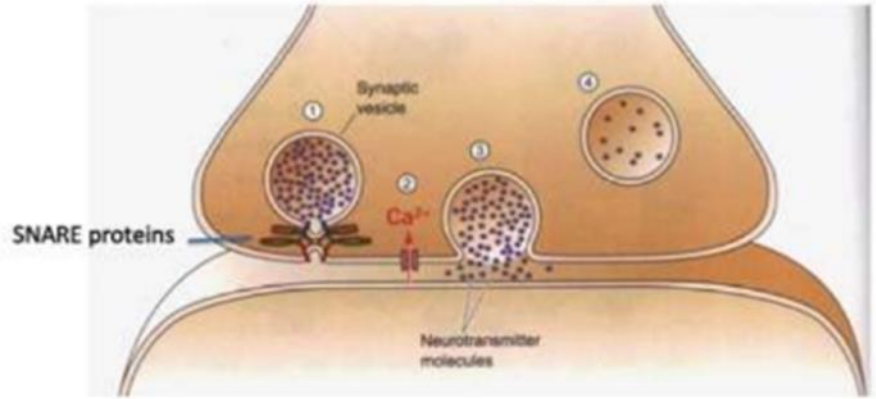


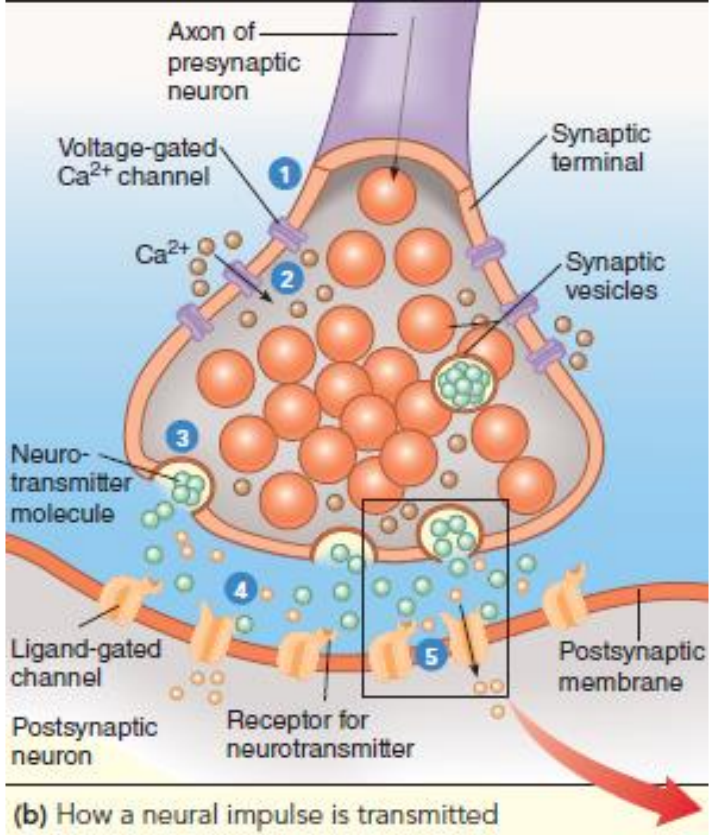


At most synapses the action potential cannot jump across the synaptic cleft between the two neurons. This problem is solved by chemical signaling across synapses

Neurotransmitter Release

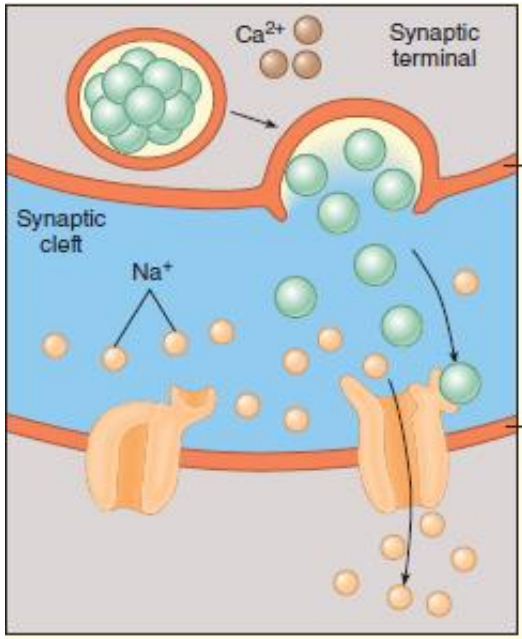
1) Synaptic vesicles containing neurotransmitter 'docked' at the synaptic membrane (snare proteins)
2) Depolarisation of the presynaptic neuron leads to the opening of calcium channels and calcium influx (concentration gradient)
3) Vesicles fuse with the synaptic membrane and release neurotransmitter into the synapse (synaptic cleft)
4) Eventually, the vesicle detaches from the docking zone and this is what drives neurotransmitter release
***voltage-gated calcium channels are key in this release process.





(b) How a neural impulse is transmitted across a synapse.

1. Action potential reaches synaptic terminals at end of presynaptic neuron.
2. Calcium channels open in membrane, letting Ca^{2+} from extracellular fluid enter the synaptic terminal.
3. Ca^{2+} cause synaptic vesicles to fuse with plasma membrane and release neurotransmitter into synaptic cleft.
4. Neurotransmitter binds with receptors on membrane of postsynaptic neuron.
5. In response, specific ion channels open or close, resulting in either depolarization or hyperpolarization. When depolarization reaches threshold level, an action potential is generated in postsynaptic neuron.



(c) Neurotransmitter binds with receptor. Ligand-gated channel opens, resulting in depolarization.

DISCLAIMER

All the original contributors of the concept and findings published elsewhere are gratefully acknowledged while preparing the E-content for the purpose of student reading material in convenient form for biochemistry and allied discipline).

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