

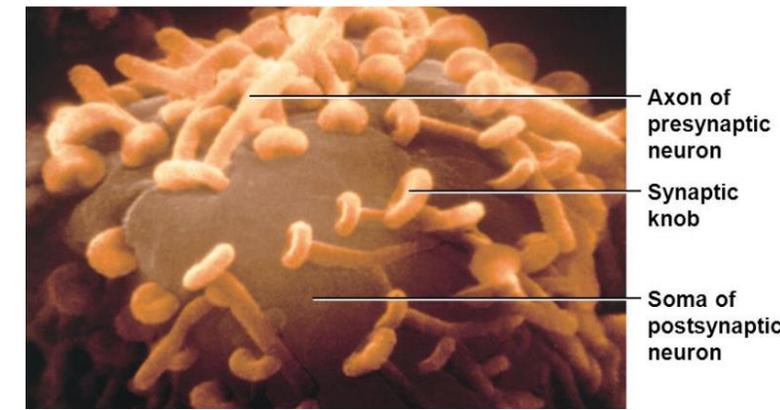
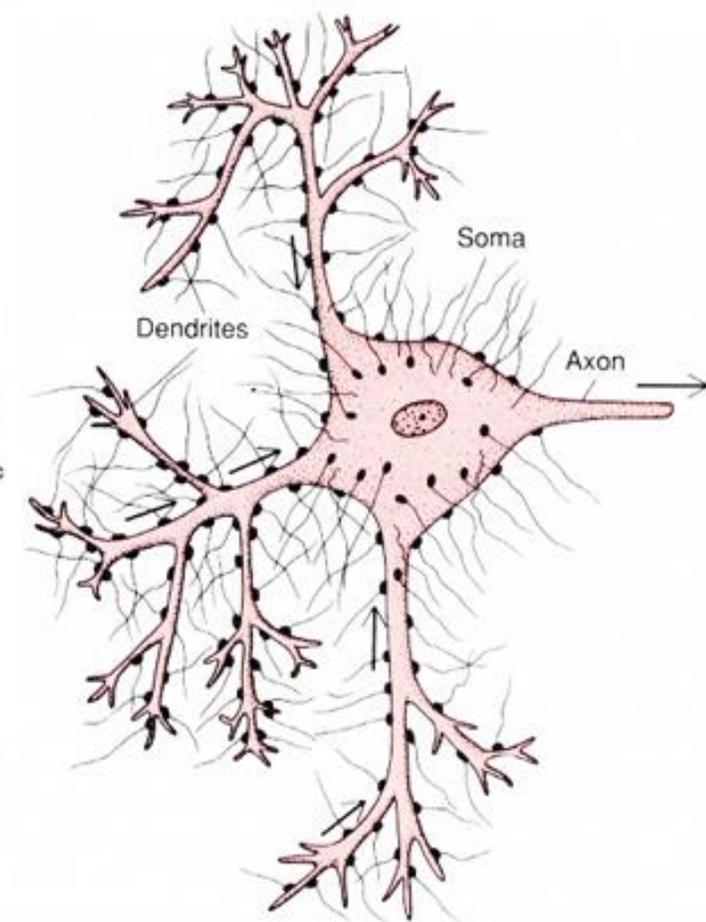
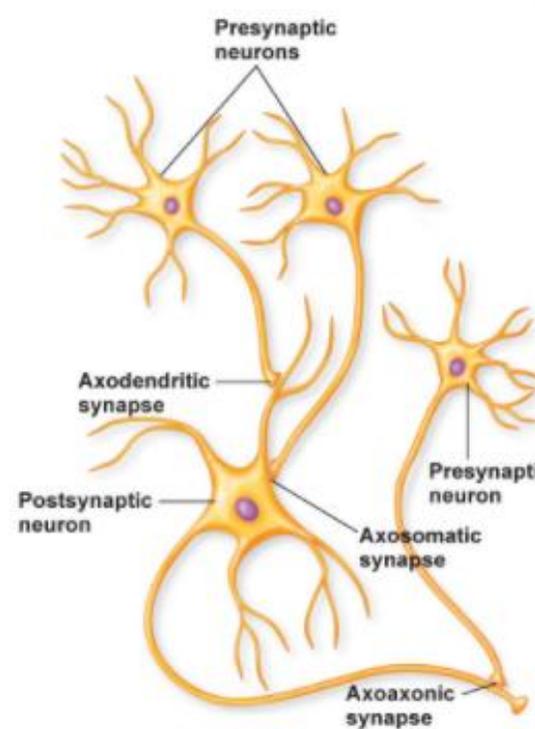
Synaptic Transmission

Functional anatomy:

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, with about **80 to 95 percent** of them on the dendrites and only **5 to 20 percent on the soma**

The ends of the pre-synaptic fibers are generally enlarged to form (terminal buttons or synaptic knob) and it will synapse with:

- I. Axo-dendritic: In **the cerebral and cerebellar cortex**, ending are commonly located, on dendrites and frequently on (**dendritic spines**: which are small knobs projecting from dendrites).
- II. Axo-somatic: The terminal branches of the axon of the pre-synaptic neuron form a basket or net around the soma of post-synaptic cell (**"basket cells" of the cerebellum and autonomic ganglia**).
- III. Axo-axonal: they terminate on the axon of the post-synaptic cell.



- **Types of synapses:**

- 1. Electrical synaptic transmission:

📖 In a few locations (e.g., within the retina and olfactory bulb), synaptic transmission is accomplished by the passive electronic spread of current between two cells.

📖 Specialized junctions called (**gap junctions**) allow the spread of current between two cells. Only 2-4nm separates the pre and post-synaptic membranes at the site of gap junctions (and the distance between the cells).

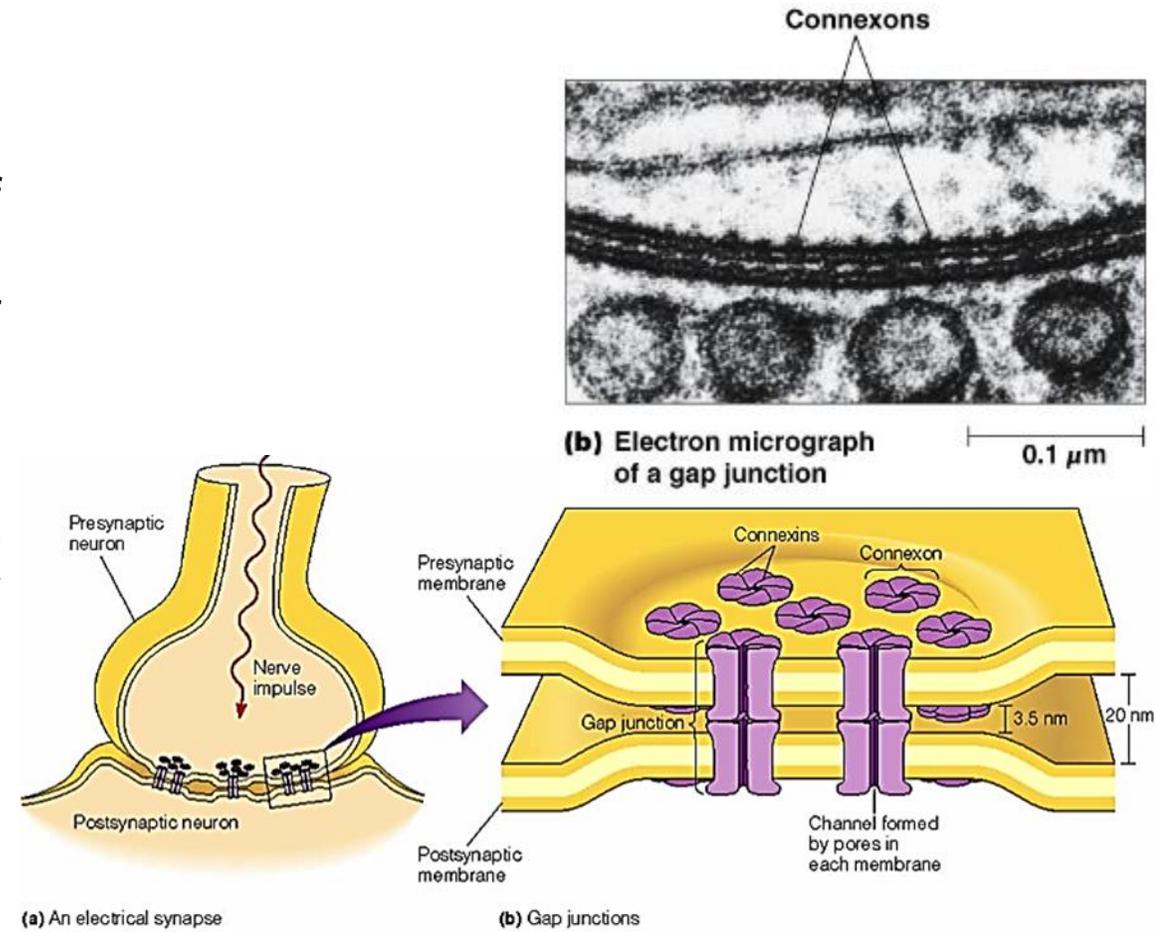
📖 Gap junctions are formed by (membrane bridges) that are constructed from integral membrane proteins called (**connexin**).

📖 An aqueous channel is formed in the membrane by six molecules of connexin.

📖 The channel in one cell merges with a channel in the membrane of another cell to form the gap junction, enabling small molecules and ions to pass from one cell to the other, thus establishing cytoplasmic continuity.

📖 When an action potential propagating along the membrane in one cell reaches the gap junction, an electrical current flows passively through the gap from one cell to another.

📖 Electrical current can pass through the gap in both directions, allowing either cell to serve as the pre- and post-synaptic cell.



2. Chemical synaptic transmission:

Introduction:

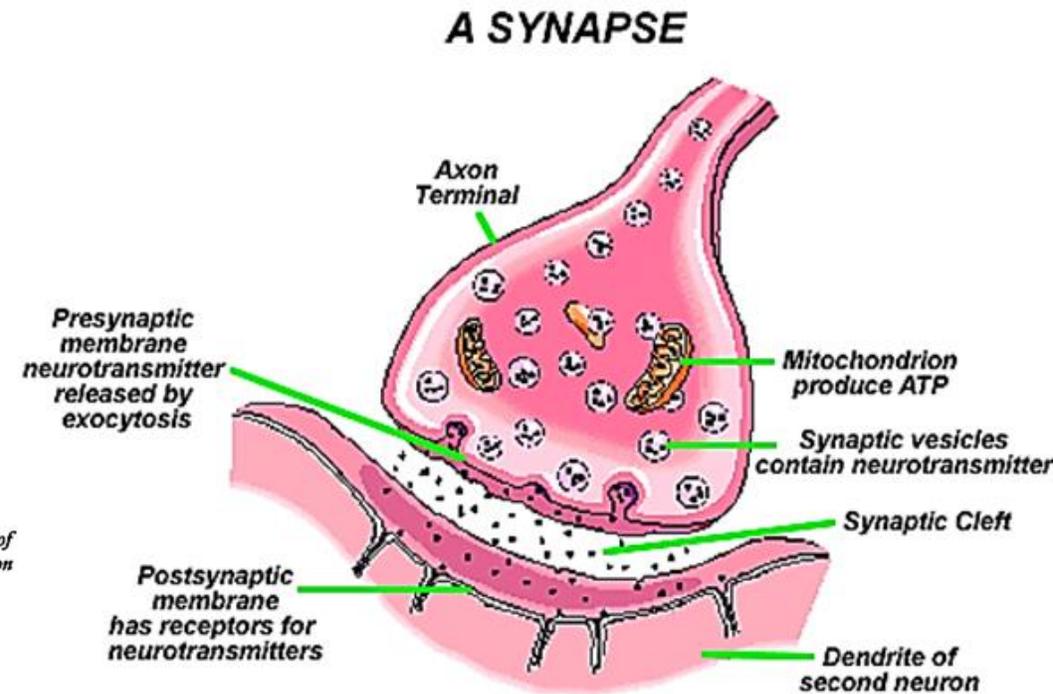
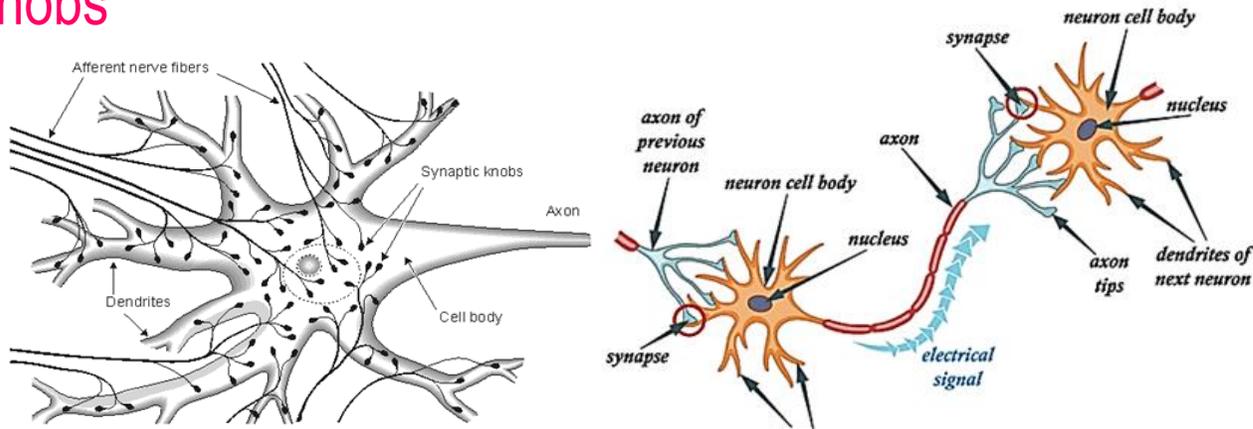
There is always **more than one neuron** involved in the transmission of a nerve impulse from its origin to its destination, whether it is sensory or motor.

There is **no physical contact** between these neurons.

The point at which the nerve impulse passes from one to another is the **synapse**.

There are the junctions where the axon or some other portion of one cell (the **pre-synaptic cell**) terminates on the **dendrites, soma, or axon** of another neuron, or in some cases **a muscle or gland cell** (the **post-synaptic cell**). The transmission at most synaptic junction is chemical; the impulse in the pre-synaptic axon causes secretion of a (**neuro-transmitter**) such as acetylcholine.

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



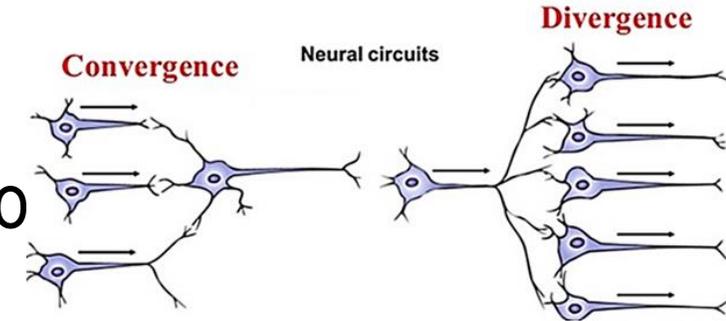
The vesicle and the proteins contained in their walls are synthesized in the **Golgi apparatus in the neuronal cell body** and migrate down the axon to the ending by fast **axo-plasmic transport**.

Role of synapses in processing information:

1. Synapses **determine the directions** that the nervous signals will spread through the nervous system.
2. **Facilitate or inhibit** signals
3. Postsynaptic neurons respond with **large numbers of output** impulses, and others respond with **only a few numbers** of output impulses

Convergence: many pre-synaptic neurons converge on any single post-synaptic neurons.

Divergence: the axon of most pre-synaptic neurons divided into branches that diverge to end on many post-synaptic neurons.



4. Synapses perform a **selective action**, **often blocking weak signals while allowing strong signals to pass**
5. Synapses perform **amplifying certain weak** signals
6. **channeling** **توجيه** signals in **many directions** rather than in only one direction

General events at pre-synaptic end:

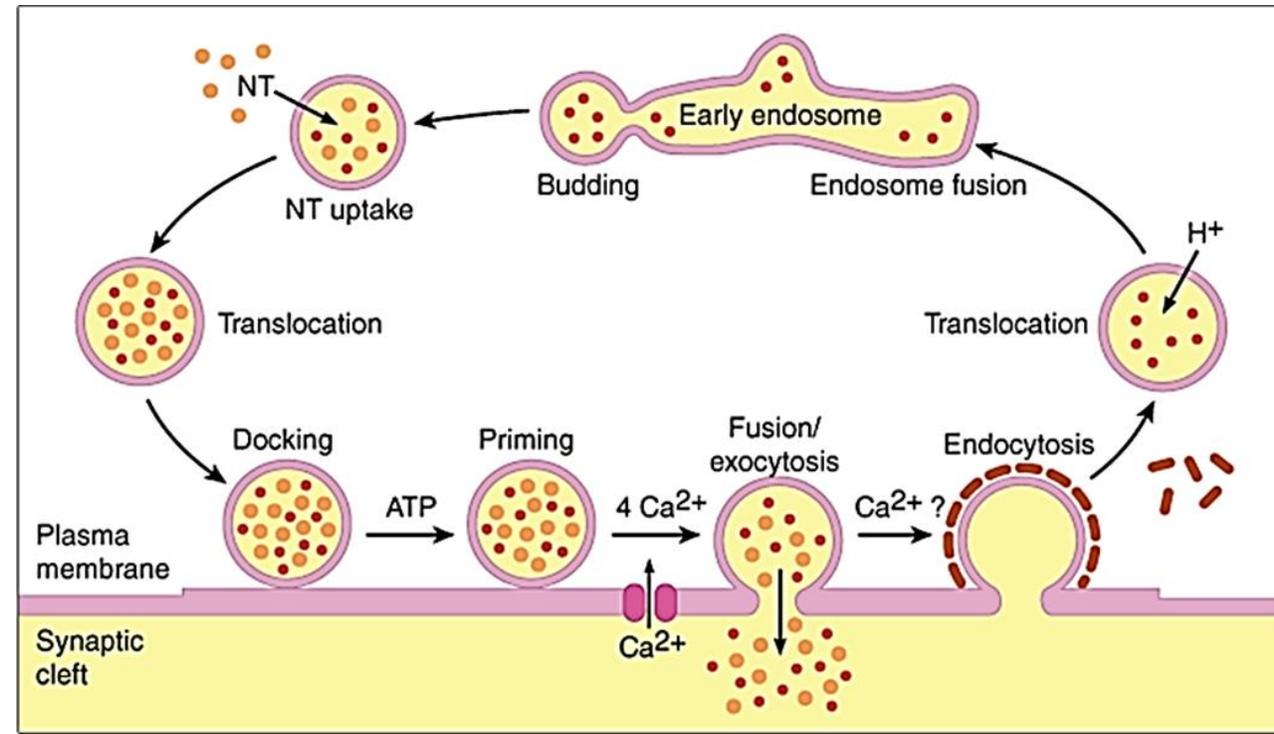
1. An action potential in the pre-synaptic cell causes **depolarization** of the pre-synaptic terminal.
2. As a result of the depolarization, **Ca²⁺ enters** the pre-synaptic terminal by **N-type calcium channels** (voltage-gated calcium channels),
3. The vesicles are loaded with transmitter in the ending, fuse with the membrane, and causing release of neurotransmitter into the synaptic cleft by exo-cytosis, and then are retrieved by endo-cytosis. They enter endosomes and are budded off the endosomes and refilled, starting the cycle over again.

For the 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.

Calcium is the key to synaptic vesicle fusion and discharge.

The calcium content is then restored to the resting level by rapid sequestration and removal from the cell, primarily by **a Ca-Na anti-port**.

4. Neurotransmitter diffuses across the synaptic cleft and combines with receptors on the postsynaptic cell membrane



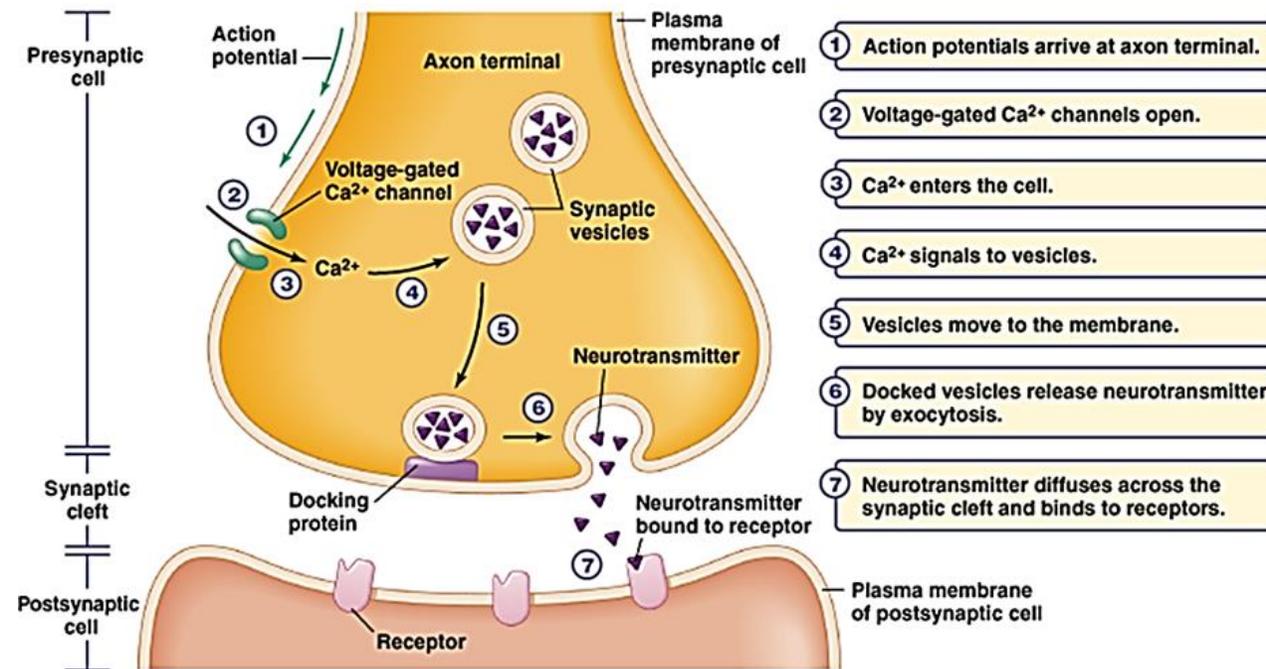
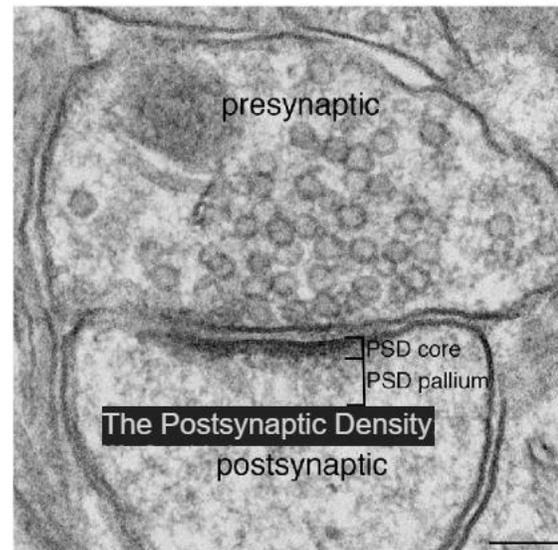
General events at post-synaptic end:

Across the synaptic cleft, there are many neurotransmitter receptors in the post-synaptic thickening called the (**post-synaptic density**).

The molecules of these receptors have two important components:

1. Binding component that protrudes outward from the membrane into the synaptic cleft (here it binds with the neurotransmitter from the pre-synaptic terminal).
2. Intracellular component that passes all the way through the postsynaptic membrane to the interior of the postsynaptic neuron.

Receptor activation controls the opening of ion channels in the postsynaptic cell in one of two ways:



(a) Ionotropic receptor:

Neurotransmitter receptors that **directly gate ion channels** are often called ionotropic receptors.

Ionotropic receptors **gating ion channels directly and allowing passage** of specified types of ions through the membrane

The ionophore in turn is one of two types:

- 1 **Carrier ionophores** that bind to a particular ion and shield its charge from the surrounding environment
- 2 **Channel ionophores** introduce a hydrophilic pore into the membrane, allowing ions to pass through without coming into contact with the membrane's hydrophobic interior

b) Metabotropic receptors

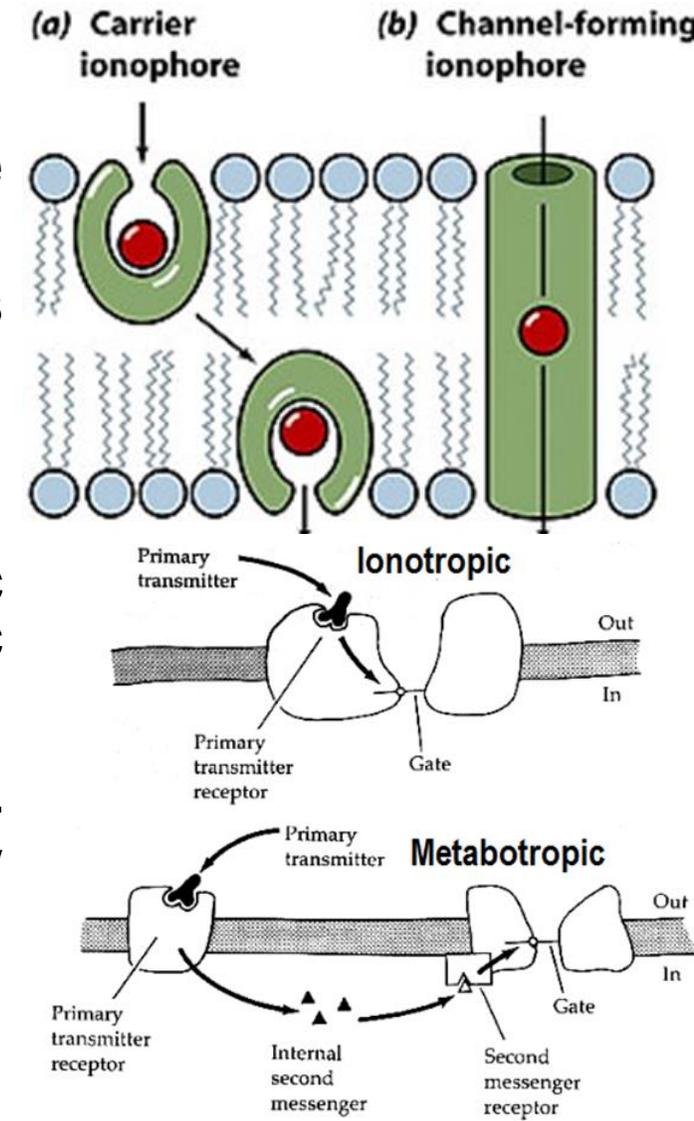
Metabotropic receptors act through second messenger systems

Activating a “**second messenger**” is suitable for causing **prolonged** postsynaptic neuronal changes (for instance, the **process of memory**); while activating a “ionic channels” is suitable for causing **short term** postsynaptic neuronal changes

One way conduction:

Synapses generally permit conduction of impulses in one direction only, from the pre- to post-synaptic neurons. Chemical mediation at synaptic junction explains one-way conduction.

A one-way conduction mechanism allows signals to be directed toward specific goals.



Chemical transmission of the synaptic activity:

Receptors:

The general characteristics of the receptors are:

First: For each ligand there are many **sub-types of receptors**, for example, nor-epinephrine act on alpha1 and alpha2.

Second: there are receptors on the **pre-synaptic as well as the post-synaptic** elements for many secreted transmitter. These (**pre-synaptic receptors or auto-receptors**) **often inhibit further** secretion of the ligand, providing feedback control.

Third: although there are many ligands and many sub-types of receptors for each ligand, the **receptors tend to group in large families as far as structure and function** are concerned.

Fourth: **receptors are concentrated in cluster in post-synaptic structure close** to the ending of neurons that secrete the neurotransmitter specific for them. This is generally due to the presence of specific binding proteins for them.

Fifth: prolonged exposure to their ligands causes most receptors to become unresponsive, i.e., to undergo **down regulation or de-sensitization**. This can be of two types:

1. Homo-logous de-sensitization: with loss of responsiveness only to the particular ligand and maintain responsiveness of the cell to other ligands.
2. Hetero-logous de-sensitization: in which the cell become un-responsiveness to other ligands as well.

Desensitization also referred as **adaptation, refractoriness, down-regulation** while tolerance is describe more gradual decrease in response to ligand which may takes days or weeks to develop

Reuptake or re-uptake:

It is the reabsorption of a neurotransmitter by a **neurotransmitter transporter of pre-synaptic neurons** after it has performed its function of transmitting a neuronal impulse.

Reuptake is necessary for normal synaptic physiology because

- ① it allows for the **recycling** of neurotransmitter and
- ② **regulates the level** of neurotransmitter present in the synapse, thereby controlling how long a signal resulting from neurotransmitter release lasts.

Because neurotransmitters are too large and hydrophilic to diffuse through the membrane, **specific transport proteins** are necessary for the reabsorption of neurotransmitters.

Neurotransmitters

Small-Molecule, Rapidly Acting Transmitters

Class I: Acetylcholine

Class II (The Amines): Norepinephrine, Epinephrine, Dopamine, Serotonin, Histamine

Class III (Amino Acids): Gamma-aminobutyric acid, Glycine, Glutamate, Aspartate

Class IV: Nitric oxide

Class I:

Acetylcholine (ACh):

☎ Acetylcholine is found in neurons release acetylcholine (**cholinergic neurons**).

☎ Synthesis of acetylcholine involves the reaction of **choline with acetate**.

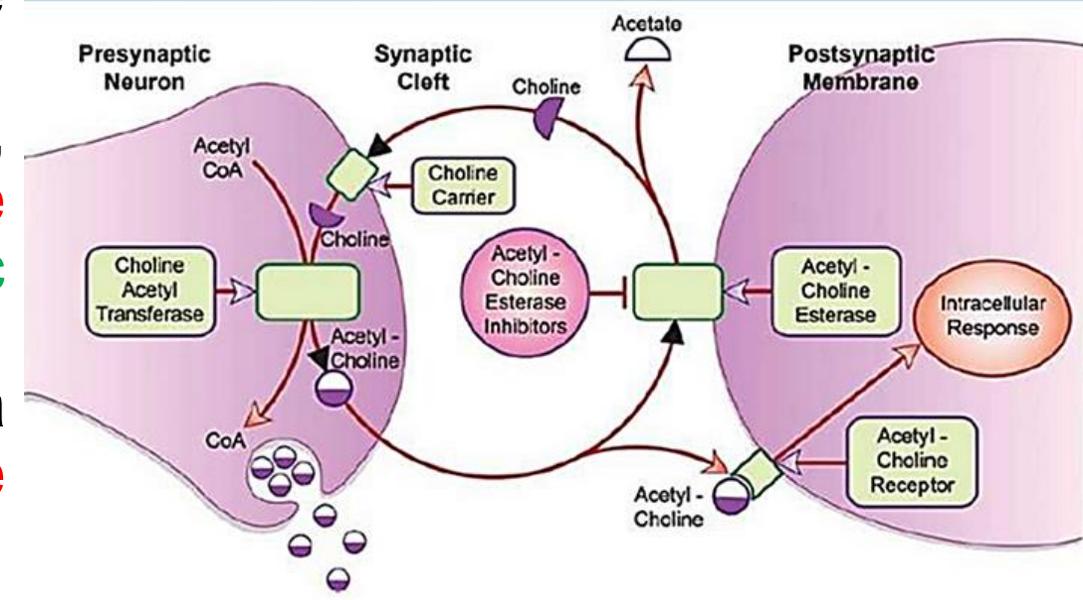
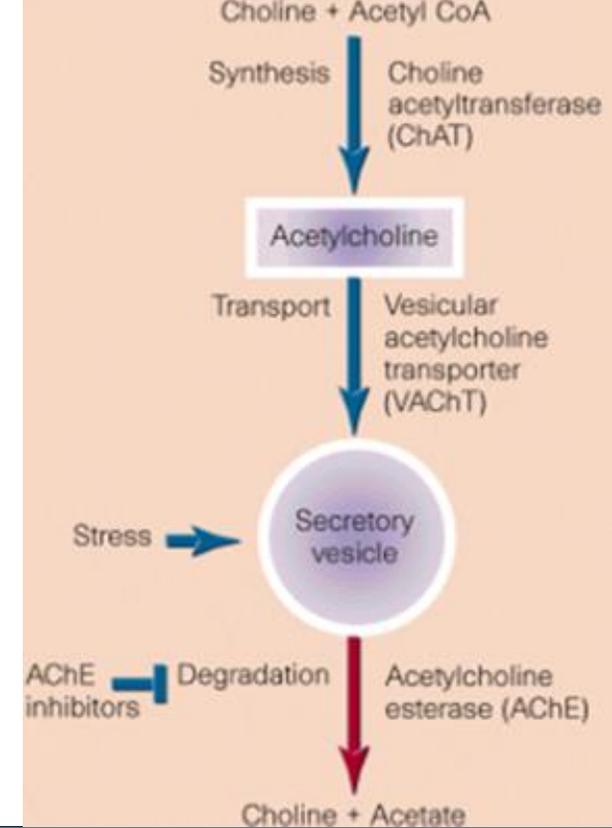
☎ Choline is an important amine that is also precursor of ① membrane phospholipids phosphatidyl-choline and ② sphingo-myline and ③ the signaling phospholipids platelet-activating factor.

☎ Choline is also synthesized in neurons.

☎ The acetate is activated by the combination of acetate groups with reduced coenzyme A.

☎ The reaction between active acetate (acetyl-coenzyme A, acetyl-CoA) and choline is catalyzed by enzyme (**choline acetyl-transferase**). **Acetylcholine is stored in synaptic vesicles with ATP and proteoglycan for later release.**

☎ Acetylcholine is then taken up into synaptic vesicle by a **vesicular transporter (VACHT: vesicular acetylcholine transporter)**.



Destruction of the Released Acetylcholine by Acetylcholinesterase

The acetylcholine, once released into the synaptic space, continues to activate the acetylcholine receptors as long as the acetylcholine persists in the space. However, it is removed rapidly by two means:

(1) Most of the acetylcholine is destroyed to **Choline and acetoacetate** by the enzyme **acetylcholinesterase**, which is attached mainly to the spongy layer of fine connective tissue that fills the synaptic space between the presynaptic nerve terminal and the post synaptic muscle membrane

One-half of the choline is taken back into the pre-synaptic ending by **Na⁺-choline co-transport** and used to synthesize new of Acetylcholine.

(2) a small amount of **acetylcholine diffuses out of the synaptic space** and is then no longer available to act on the muscle fiber membrane.

Class II: The Amines

1. Nor-epinephrine, epinephrine, and dopamine

(1) Nor-epinephrine:

- is the primary transmitter released from **postganglionic sympathetic neurons**.
- is synthesized in the nerve terminal and released into the synapse to bind with **α or β** receptors on the postsynaptic membrane.

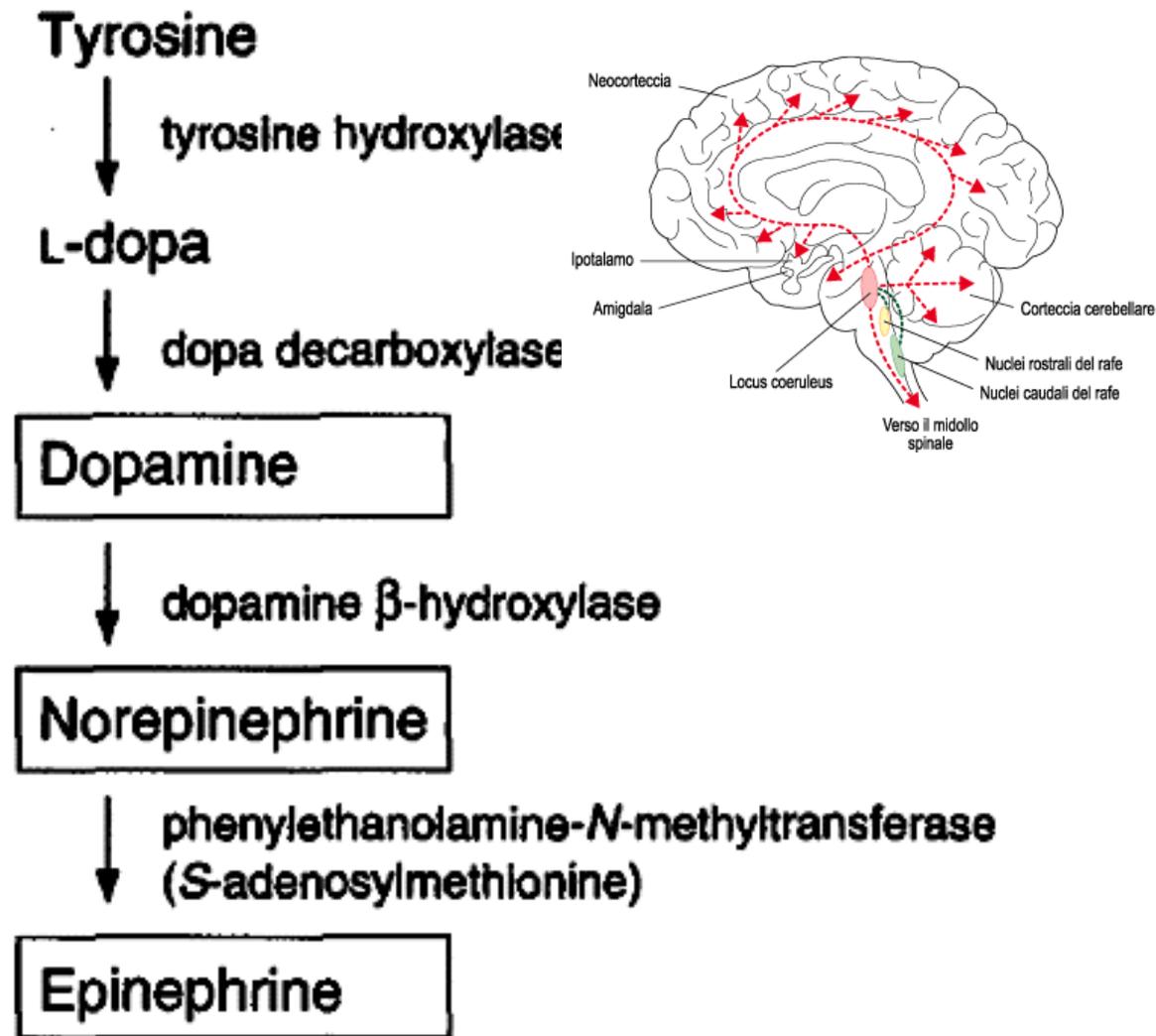
Specifically, **nor-epinephrine** secreting neurons located in the **locus coeruleus in the pons** send nerve fibers to widespread areas of the brain to help control overall activity and **mood** of the mind, such as increasing the **level of wakefulness**.

In most of these areas, norepinephrine probably activates **excitatory receptors**, but in a **few areas**, it **activates inhibitory** receptors instead

- is removed from the synapse by

① reuptake or

② is metabolized in the pre-synaptic terminal by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).



(2) Epinephrine

- is synthesized from nor-epinephrine
- is secreted, along with nor-epinephrine, from the **adrenal medulla**.

(3) Dopamine

There are 5 different types of dopamine receptors (D1, D2, D3, D4, and D5)

Dopamine is prominent in **midbrain** neurons.

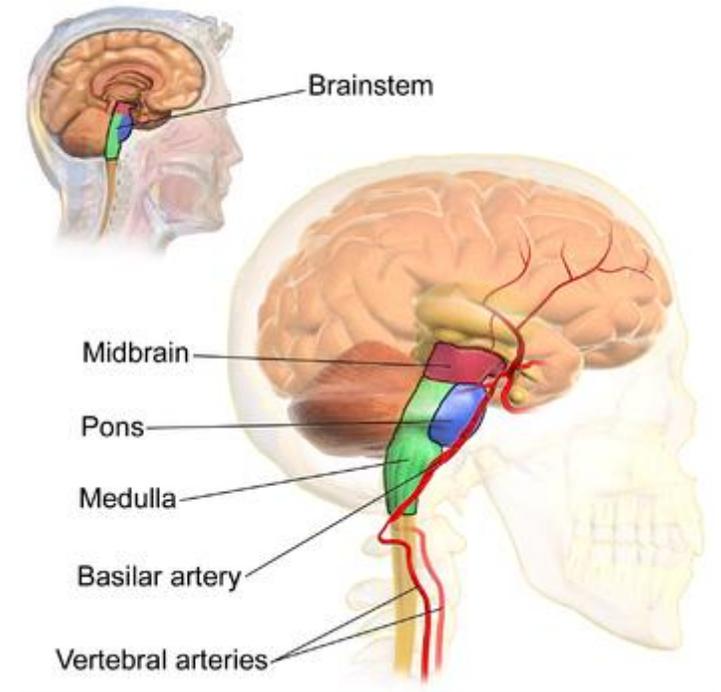
Dopamine is released from the **hypothalamus and inhibits prolactin** secretion; in this context it is called prolactin-inhibiting factor (PIF).

Dopamine is secreted by neurons that originate in the **substantia nigra**.

The termination of these neurons is mainly in the striatal region of the basal ganglia.

The effect of dopamine is **usually inhibition**.

- is metabolized by **MAO and COMT**



2. Serotonin (5-Hydroxy-tryptamine: 5-HT)

There are different types of 5-HT receptors: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃ and 5-HT₄)

Serotonin is formed from **tryptophan and converted to melatonin in the pineal gland.**

Serotonin is present in highest concentration in **blood platelets and in the GIT**, lesser amount is found in the **brain and retina**

Serotonins receptors (HT) have been found as:

① 5-HT_{2A} receptors **mediate platelet aggregation and smooth muscle contraction**

② 5-HT₄ receptors are present in **GIT**, **where they facilitate secretion and peristalsis**

③ 5-HT₆ and 5-HT₇ receptors in the brain are distributed throughout **the limbic system.**

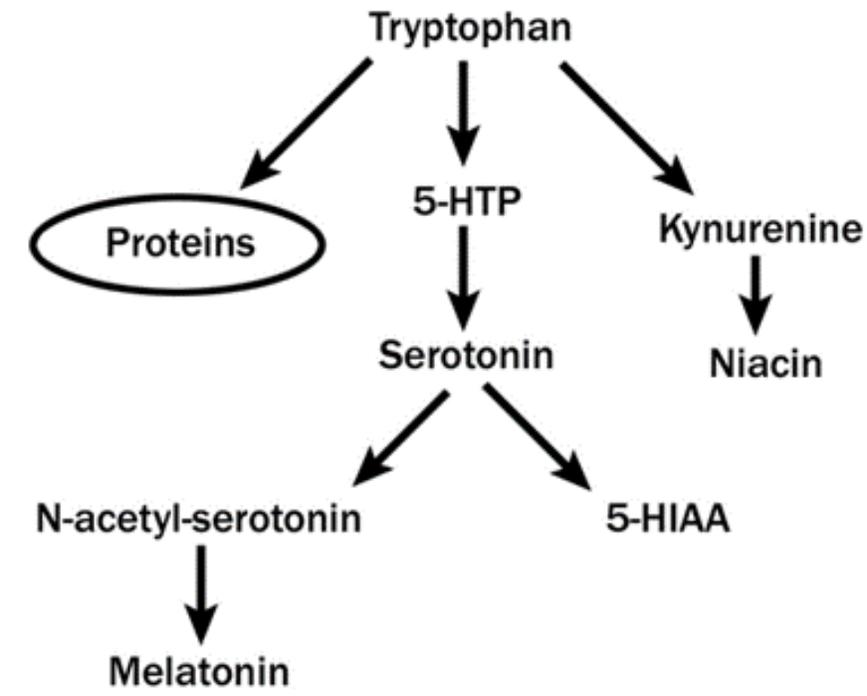
Serotonin is secreted by nuclei that originate in the **median raphe of the brain stem**

▼
project to many brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus.

Serotonin acts **as**

① **an inhibitor of pain pathways in the cord,**

② **an inhibitor action** in the higher regions of the nervous system is believed to help control the **mood of the person, perhaps even to cause sleep**



3. Histamine

There are two receptors (H_1 , H_2)

- is formed from **histidine**.
- is present in the neurons of the **hypothalamus**.

Class III: Amino Acids

1. Glutamate

- is the most prevalent **excitatory neurotransmitter** in the brain.

2. GABA (Gama amino-butyric acid)

- is an **inhibitory** neurotransmitter.
- is synthesized from **glutamate** by **glutamate de-carboxylase**.
- It has two types of receptors:
 - (1) The $GABA_A$ receptor increases Cl^- conductance.
 - (2) The $GABA_B$ receptor increases K^+ conductance.

3. Glycine

- is an **inhibitory neurotransmitter** found primarily in the **spinal cord and brain stem**.
- Increases Cl^- conductance

Class IV

Nitric oxide (NO)

Nitric oxide is a **short-acting inhibitory** neurotransmitter in the **gastrointestinal tract, blood vessels, and the central nervous system.**

Nitric oxide is especially secreted by nerve terminals in areas of the brain responsible for **long-term behavior and for memory.** Therefore, this transmitter system might in the future explain some **behavior and memory functions** that thus far have defied understanding.

Nitric oxide is different from other small molecule transmitters in its mechanism of **formation in the presynaptic terminal and in its actions on the postsynaptic neuron.**

Nitric oxide is **not preformed and stored in vesicles** in the presynaptic terminal as are other transmitters. Nitric oxide is synthesized almost instantly as needed,



Nitric oxide then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets



Nitric oxide **diffuses** into postsynaptic neurons nearby.



Nitric oxide in the postsynaptic neuron, it usually does **not greatly alter the membrane potential but instead changes intracellular metabolic functions** that **modify neuronal excitability for seconds, minutes, or perhaps even longer.**

Any change in potential in any part of the intra-somal fluid causes an almost exactly equal change in potential at all other points inside the soma (that is, as long as the neuron is not transmitting an action potential) because:

- 1 The interior of the neuronal soma contains a highly conductive electrolytic solution, the intracellular fluid of the neuron.
- 2 The diameter of the neuronal soma is large (from 10 to 80 micrometers), causing almost no resistance to conduction of electric current from one part of the somal interior to another part.

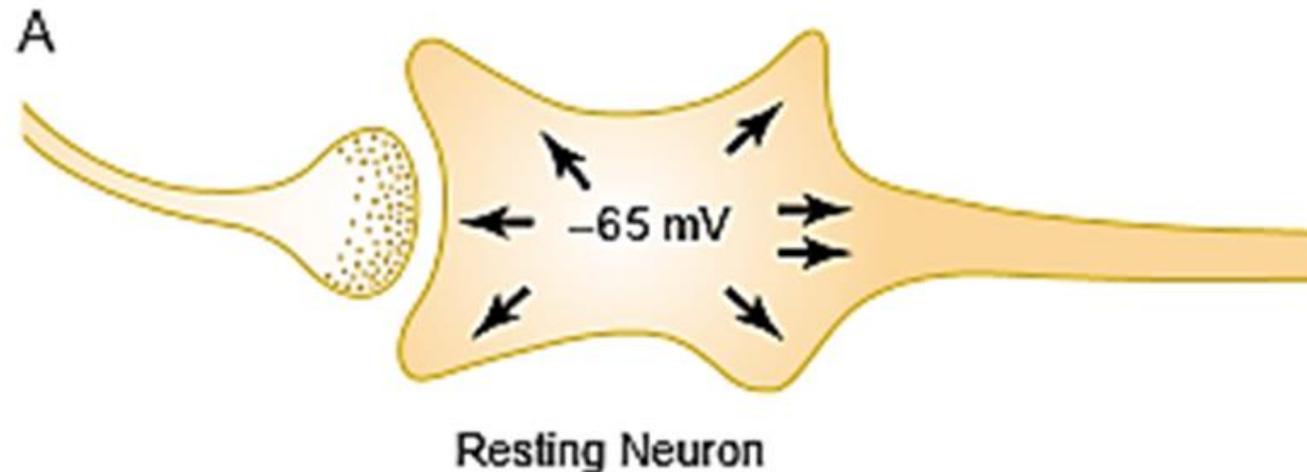
This is an important principle, because it plays a major role in “summation” of signals entering the neuron from multiple sources

- The postsynaptic cell integrates excitatory and inhibitory inputs.
- When the sum of the input brings the membrane potential of the postsynaptic cell to threshold, it fires an action potential.

a. Effect of Synaptic Excitation on the Postsynaptic Membrane (Excitatory postsynaptic potentials (EPSPs)):

Excitatory neurotransmitters include ACh, nor epinephrine, epinephrine, dopamine, glutamate, and serotonin.

A. The resting membrane potential everywhere in the soma is -65 millivolts



B. a presynaptic terminal that has secreted an excitatory transmitter into the cleft between the terminal and the neuronal somal membrane

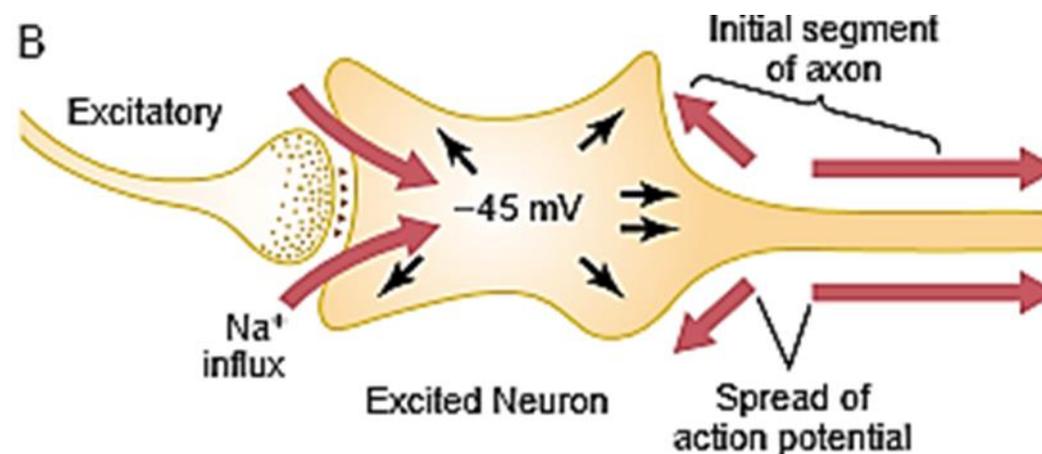
1. Neurotransmitter acts on the membrane excitatory receptor to increase the membrane's permeability to Na^+ . Because of the large sodium concentration gradient and large electrical negativity inside the neuron, sodium ions diffuse rapidly to the inside of the membrane.

2. The rapid influx of positively charged sodium ions to the interior neutralizes part of the negativity of the resting membrane potential. Thus, the resting membrane potential has increased in the positive direction from -65 to -45 millivolts.

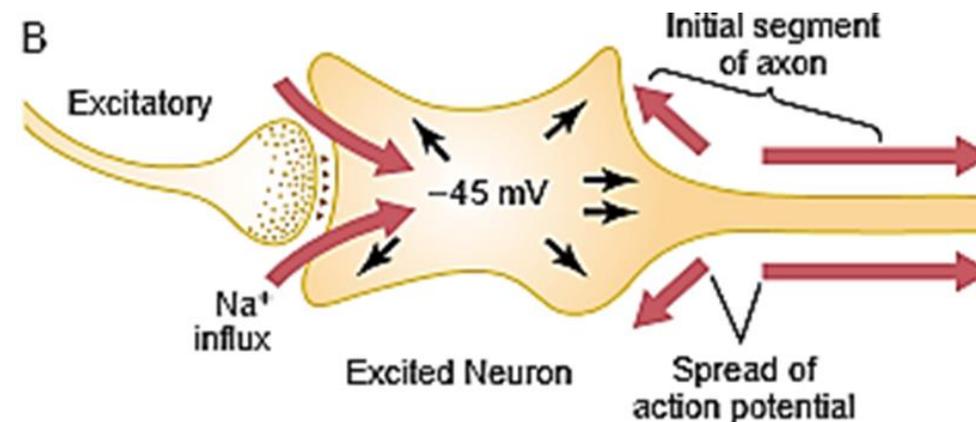
This positive increase in voltage above the normal resting neuronal potential—that is, to a less negative value—is called the excitatory postsynaptic potential (or EPSP), because if this potential rises high enough in the positive direction, it will elicit an action potential in the postsynaptic neuron, thus exciting it. (In this case, the EPSP is $+20$ millivolts—that is, 20 millivolts more positive than the resting value.) However, we must issue a word of warning.

Discharge of a single presynaptic terminal can never increase the neuronal potential from -65 millivolts all the way up to -45 millivolts. An increase of this magnitude requires process called summation

3. Generation of action potentials in the initial segment of the axon leaving the neuron (Threshold for Excitation) and the soma or the dendrites WHY?



- When the EPSP rises high enough in the positive direction (reaching the threshold for excitation), there comes a point at which this initiates an action potential in the neuron. However, the action potential does not begin adjacent to the excitatory synapses.
- Instead, it begins in the initial segment of the axon where the axon leaves the neuronal soma.
- **Why it is not in the soma** but the initial segment of the axon:
 - (1) The soma has relatively few voltage-gated sodium channels in its membrane, which makes it difficult for the EPSP to open the required number of sodium channels to elicit an action potential. Conversely, the membrane of the initial segment has seven times as great a concentration of voltage-gated sodium channels as does the soma and, therefore, can generate an action potential with much greater ease than can the soma.
 - (2) The EPSP that will elicit an action potential in the axon initial segment is between +10 and +20 millivolts. This is in contrast to the +30 or +40 millivolts or more required on the soma



Why it is not in the dendrites but the initial segment of the axon:

Between 80 and 95 percent of all the presynaptic terminals of the anterior motor neuron terminate on dendrites, in contrast to only 5 to 20 percent terminating on the neuronal soma.

The dendrites often extend 500 to 1000 micrometers in all directions from the neuronal soma, and these dendrites can receive signals from a large spatial area around the motor neuron

The conduction of excitation begins from dendrites to soma and then to axon

Most dendrites fail to transmit action potentials because

(1) Dendrites membranes have relatively few voltage gated sodium channels

(2) Dendrites thresholds for excitation are too high for action potentials to occur.

Yet they do transmit electro-tonic current down the dendrites to the soma.

(3) A large share of the EPSP is lost before it reaches the soma.

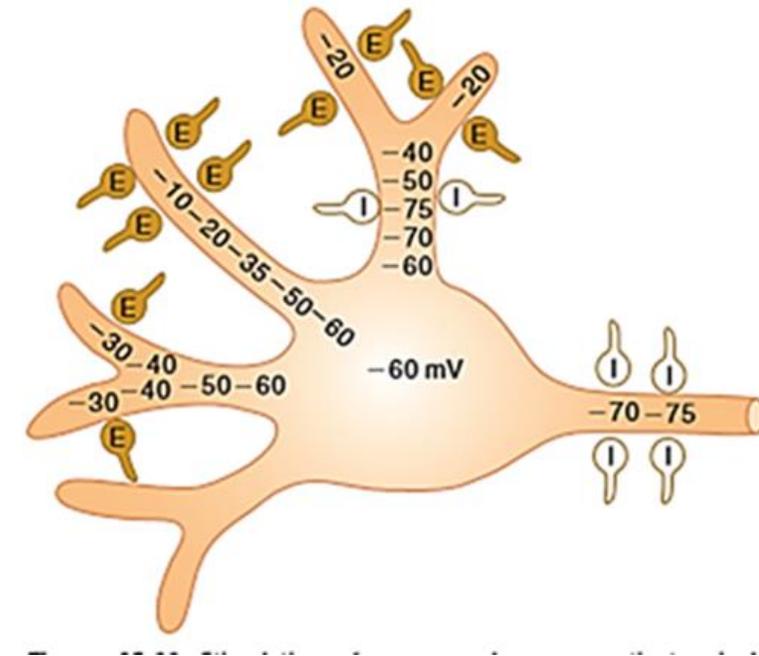
The reason a large share is lost is that

❶ Dendrites are long,

❷ Dendrites membranes are thin

❸ Dendrites membranes at least partially permeable to potassium and chloride ions, making them “leaky” to electric current. Therefore, before the excitatory potentials can reach the soma, a large share of the potential is lost by leakage through the membrane. This decrease in membrane potential as it spreads electro-tonically along dendrites toward the soma is called decremental conduction

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



Once the action potential begins, it travels peripherally along the axon and usually also backward over the soma. In some instances, it travels backward into the dendrites, too, but not into all of them, because they, like the neuronal soma, have very few voltage gated sodium channels and therefore frequently cannot generate action potentials at all.

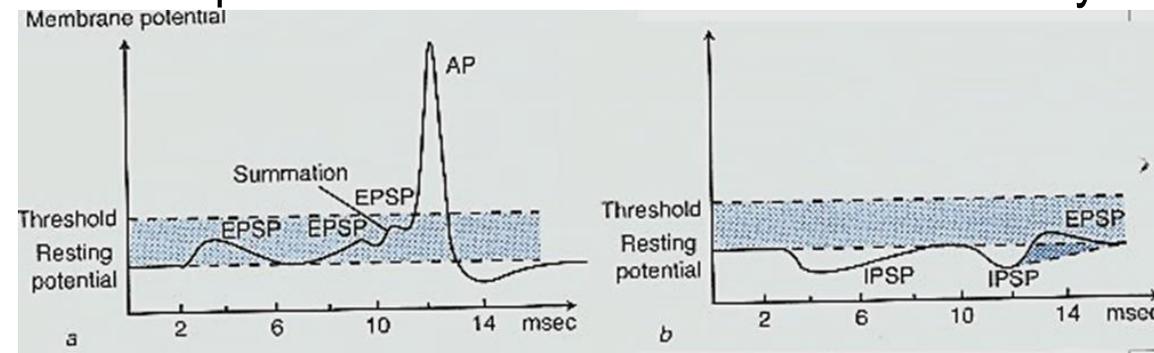
Thus, the threshold for excitation of the neuron is shown to be about -45 millivolts, which represents an EPSP of +20 millivolts—that is, 20 millivolts more positive than the normal resting neuronal potential of -65 millivolts.

Possible mechanisms of EPSP

1. Opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell. This action 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 action 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.



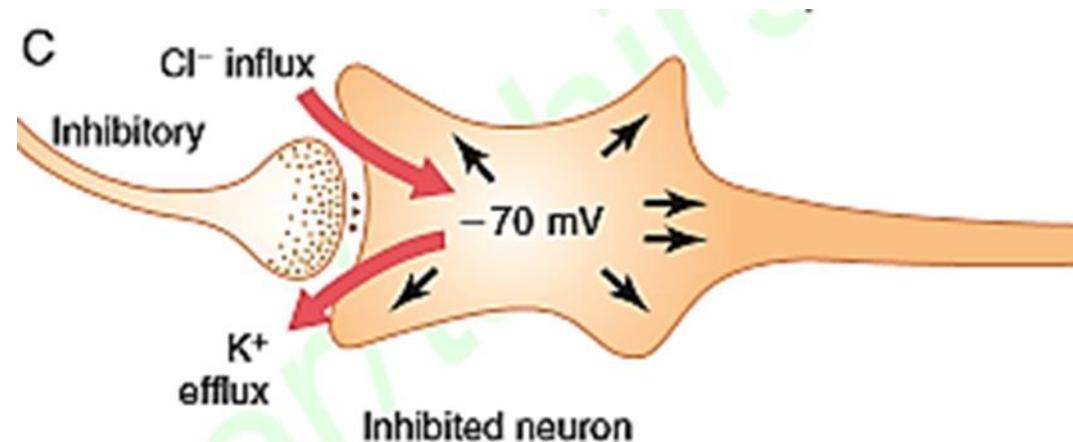
b. Effect of Inhibitory Synapses on the Postsynaptic Membrane (Inhibitory postsynaptic potentials (IPSPs)):

Inhibitory neurotransmitters are γ -amino-butyric acid (GABA) and glycine.

Possible mechanisms of IPSP

A. Effect of opening of Chloride Channels:

Calculated Nernst potential for chloride ions to be about -70 millivolts: this potential is more negative than the -65 millivolts normally present inside the resting neuronal membrane. Therefore, opening the chloride channels will allow negatively charged chloride ions to move from the extracellular fluid to the interior, which will make the interior membrane potential more negative than normal, approaching the -70 millivolt level.



B. Effect of opening of Potassium Channels:

Opening potassium channels will allow positively charged potassium ions to move to the exterior, and this will also make the interior membrane potential more negative than usual.

Thus, both chloride influx and potassium efflux increase the degree of intracellular negativity, which is called hyperpolarization. This inhibits the neuron because the membrane potential is even more negative than the normal intracellular potential. Therefore, an increase in negativity beyond the normal resting membrane potential level is called an inhibitory postsynaptic potential (IPSP).

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

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

Summation at synapses

Many presynaptic terminals are usually stimulated at the same time. Even though these terminals are spread over wide areas of the neuron, their effects can still summate; that is, they can add to one another until neuronal excitation does occur

a. Spatial summation occurs when two excitatory inputs arrive at a postsynaptic neuron simultaneously **في آن واحد**.

In spatial summation multiple postsynaptic potentials from different synapses occur about the same time and sum. Together, they produce greater depolarization.

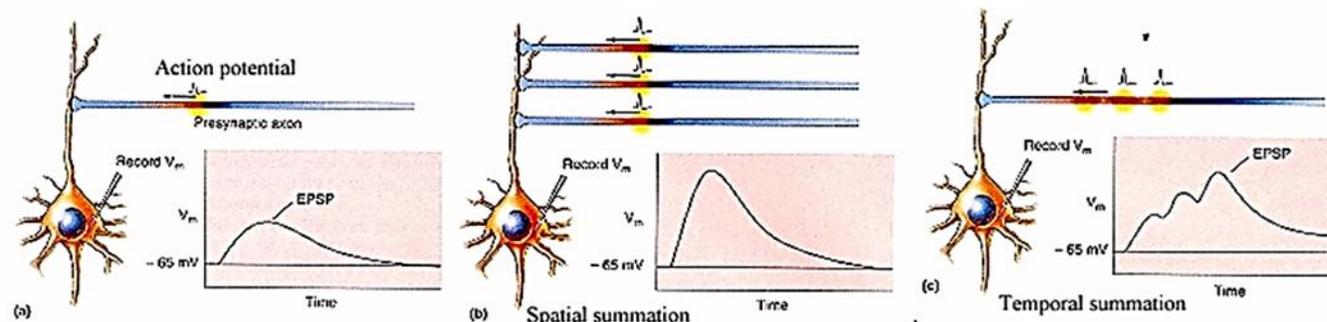
b. Temporal summation occurs when two excitatory inputs arrive at a postsynaptic neuron in rapid succession **توال سريع**.

In temporal summation postsynaptic potentials at the same synapse occur in rapid succession.

Because the resulting postsynaptic de-polarizations overlap in time, they add in stepwise fashion.

1. If a neuron is being excited by an EPSP, an inhibitory signal from another source can often reduce the postsynaptic potential to less than threshold value for excitation, thus turning off the activity of the neuron; thus summation can occur by both EPSP and IPSP at the same time.

2. When the cell has excite and membrane potential is nearer the threshold for firing than normal but is not yet at the firing level (the neuron is said to be facilitated). Consequently, another excitatory signal entering the neuron from some other source can then excite the neuron very easily.



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 phenomenon is called **fatigue of synaptic transmission**. Fatigue is an exceedingly important characteristic of synaptic function because when areas of the nervous system become **overexcited, fatigue causes them to lose this excess excitability after a while**. For example, fatigue is probably the most important means by which the excess excitability of the brain during an **epileptic seizure** is finally subdued so that the seizure ceases. Thus, the development of fatigue is a **protective mechanism against excess neuronal activity**.

The mechanism of fatigue is mainly

① **exhaustion or partial exhaustion of the stores of transmitter substance** in the presynaptic terminals.

The excitatory terminals on many neurons can store enough excitatory transmitter to cause **only about 10,000 action potentials**, and the transmitter can be exhausted in only a few seconds to a few minutes of rapid stimulation.

② progressive **inactivation of many of the postsynaptic membrane receptors** and

③ slow development of **abnormal concentrations of ions inside the postsynaptic neuronal cell**.

Effect of Acidosis or Alkalosis on Synaptic Transmission

Most neurons are highly responsive to changes in pH of the surrounding interstitial fluids.

Normally, **alkalosis greatly increases neuronal excitability**.

For instance, a rise in arterial blood pH from the **7.4 normal to 7.8 to 8.0 often causes cerebral epileptic seizures** because of increased excitability of some or all of the cerebral neurons.

In a person who is predisposed to epileptic seizures, even a **short period of hyperventilation, which blows off carbon dioxide** and elevates the pH, may 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** almost always develops.

Effect of Hypoxia on Synaptic Transmission

Neuronal excitability is also highly dependent on an adequate supply of oxygen.

Cessation of oxygen for only a few seconds can cause complete in-excitability of some neurons. This effect is observed when the brain's blood flow is temporarily interrupted because within **3 to 7 seconds, the person becomes unconscious**.

Effect of Drugs on Synaptic Transmission

Many drugs are known to increase the excitability of neurons, and others are known to decrease excitability.

For instance,

- ① 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.
- ② 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 سحق, and the neurons become so excited that they go into rapidly repetitive discharge, resulting in severe tonic muscle spasms. نفي النفي
- ③ Most anesthetics increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system. Because many of the anesthetics are especially lipid soluble, it has been reasoned that some of them might change the physical characteristics of the neuronal membranes, making them less responsive to excitatory agents

Synaptic Delay

During transmission of a neuronal signal from a presynaptic neuron to a postsynaptic neuron, a certain amount of time is consumed in the process of

- (1) discharge of the transmitter substance by the presynaptic terminal,
 - (2) diffusion of the transmitter to the postsynaptic neuronal membrane,
 - (3) action of the transmitter on the membrane receptor,
 - (4) action of the receptor to increase the membrane permeability, and
 - (5) inward diffusion of sodium to raise the EPSP 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, which is called the synaptic delay.**

Neurophysiologists can measure the minimal delay time between an input volley **وابل** 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.

Because of it, conduction along a chain of neurons is slower if there are many synapses in the chain than if there are only a few.