# Physiology
## Sheet No.
# 9


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lecture objectives (consider it as a checklist for what you need to know)

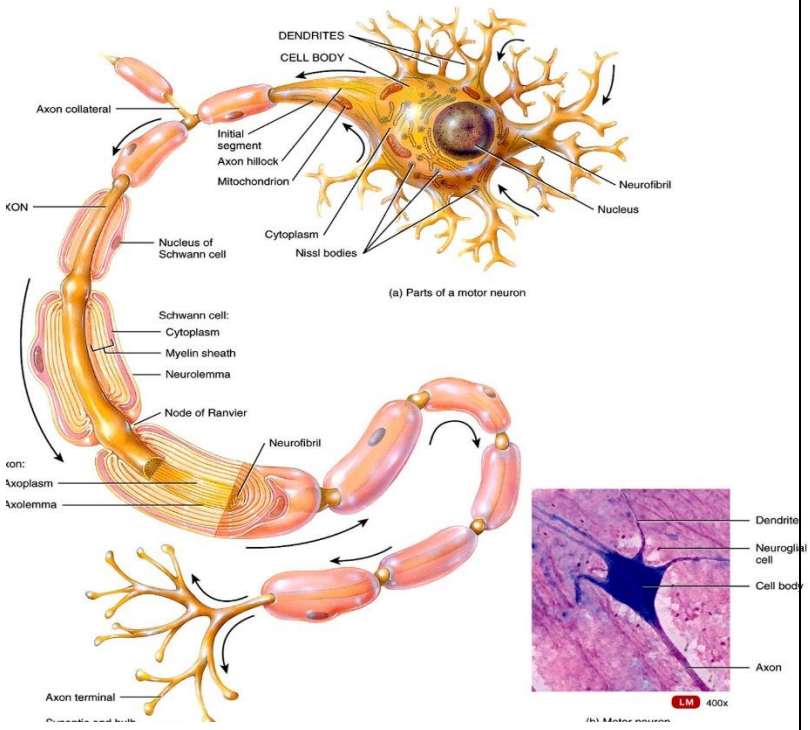
- Understand synaptic transmission---what happens at the synapse
- List types of sensory neurons.
- Classify neurotransmitters and explain their mechanism of neurotransmission.
- Judge the types of receptors for the neurotransmitters.

**Functional and Anatomical unit** of the Nervous System is the **neuron**.

main parts of the neuron:

1- cell body. 2- dendrites. 3-axon.

1-**Cell body** (the soma): contains most of the organelles of any cell like the nucleus, endoplasmic reticulum (ER), mitochondria, nissl bodies and granules which are the site of protein synthesis in neurons they're synonymous to ribosomes. مماثلة




-the organelle that neurons lack is the centriole because neurons don't divide nor regenerate, once they're damaged, they die and won't be replaced with new cells.

-this explains why these cells are delicate, and as a result the central nervous system is enclosed within bones, the hardest connective tissue in our body, to offer protection.
the brain is protected by the skull and the spinal cord is enclosed in the vertebral column.

after the cell body comes the first part of the axon that's unmyelinated,
the axon hillock that:
1-has the largest number (highest density) of voltage gated sodium channels
2-has the lowest threshold for the action potential
3-its the site where action potential **mainly** occurs.


*the action potential can occur in the soma as well because it has some voltage gated sodium channels, but it has higher threshold than axon hillock's threshold. the soma has a very large diameter, low resistance so as a result it has high conductance for action potential.

2- **Dendrites:** tree-like shaped structures with a small diameter that collect information from a large area.

they lack voltage gated sodium channels, almost nonexistent, which makes their threshold very high, and they have very high resistance for action potential conduction due to its small diameter.
so, it's rare for the action potential to occur there.

3- **Axon:** two types of axons: 1- myelinated axons. 2- unmyelinated axons.

-myelin is the membrane of the cells that secrete it, meaning it's a lipid rich substance that forms around the neuron's axon.

-myelin is white in color, so it gives myelinated neurons a white appearance, and in the central nervous system myelinated neurons are called white matter.

- myelin has very high insolation properties in which ions can't pass through them.

-the unmyelinated distances between myelin sheaths in neuron are called nodes of Ranvier.

-myelin is responsible for saltatory conduction in myelinated neurons that occurs between nodes of Ranvier.

-in the **peripheral** nervous system: myelin secreting cells are **Schwan** cells.

-in the **central** nervous system: **oligodendrocytes** form the myelin.

at the end of the axon there are **axon terminals** that contain chemical substances that are released once the action potential (nerve impulse) reaches the terminals

these chemical substances are called neurotransmitters because they act as transmitters (mediators) between the two neurons: presynaptic neuron and postsynaptic neuron.

axonal terminals are known as knobs or buttons.

## Transmission of Receptor Information to the Brain

side info 😊 we don't feel almost 99% of the sensations.

sensation stimuli is transmitted through different neurons to its final destination the brain, specifically the cerebral cortex. قشرة الدماغ

if the information is transmitted in large nerve fibers (large diameter), which means lower resistance, and fast conductance so the nerve impulse will travel very fast.

the fastest transmission velocity is 120m/sec. → in some myelinated neurons

or it can be as slow as 0.5m/sec. → of course in unmyelinated neurons

### Nerve fiber classifications

1-alphabetical classification. 2- roman numbers classification.

3- ***physiological** (functional) classification. 4-Anatomical classification.

### Alphabetical classification

- **type A** (myelinated fiber): subdivided according to diameter (size) to alpha $\alpha$, Beta $\beta$, Gamma $\gamma$, and delta $\delta$. *A-delta is the smallest fiber.
- **type B** : partially myelinated fibers found in the autonomic nervous system (sympathetic and parasympathetic) with conduction speed 3-14m/sec.
- **type C** (unmyelinated fiber), small in size and has slow transmission.

### Roman Numbers Classification -according to myelination

**Types Ⅰ, Ⅱ and Ⅲ** are myelinated fibers BUT they're not equivalent to type A and it's subdivisions: you can't say type A-alpha = type Ⅰ because both are different classifications.

**Type Ⅳ** is unmyelinated fibers and you can consider it equivalent to type C.

**NOT FOR MEMORIZATION** just know the mentioned information below

Myelinated fibers:

*diameter ranges between 1mm to 20mm.

*speed of transmission ranges 6-120 m/sec fastest transmission speed + largest diameter found in alpha fibers

unmyelinated fibers:

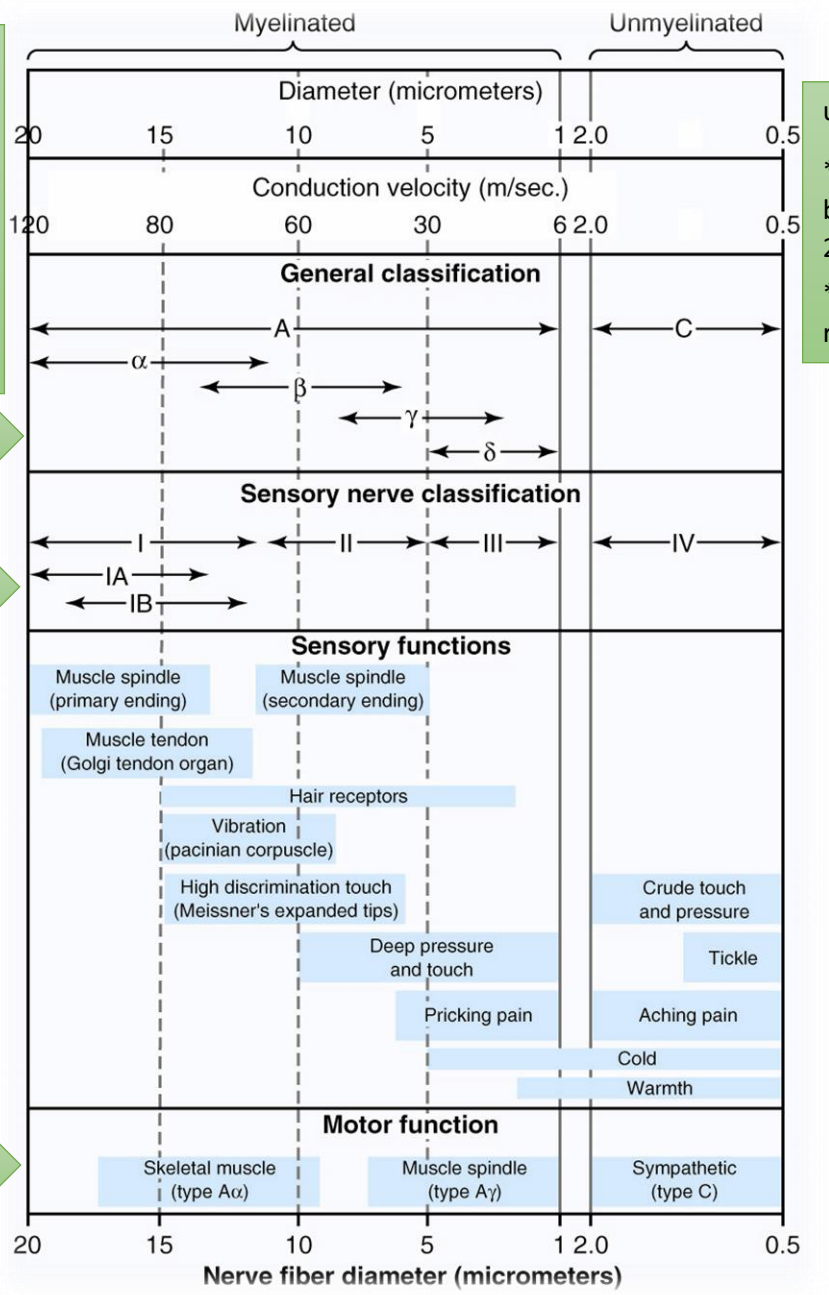
*diameter ranges between 0.5 mm to 2mm.

*speed of transmission ranges 0.5-2 m/sec

alphabetical classification

roman numbers classification

this is where they're found




**Physiological (Functional) classification of neurons**

1-sensory neurons. 2-interneuron. 3- motor neurons.

1- **sensory neurons** (afferent neurons): that collect the information (sensations) by receptors at the dendrites, or the terminal itself could be the receptor, from our body and carry it to the central nervous system.

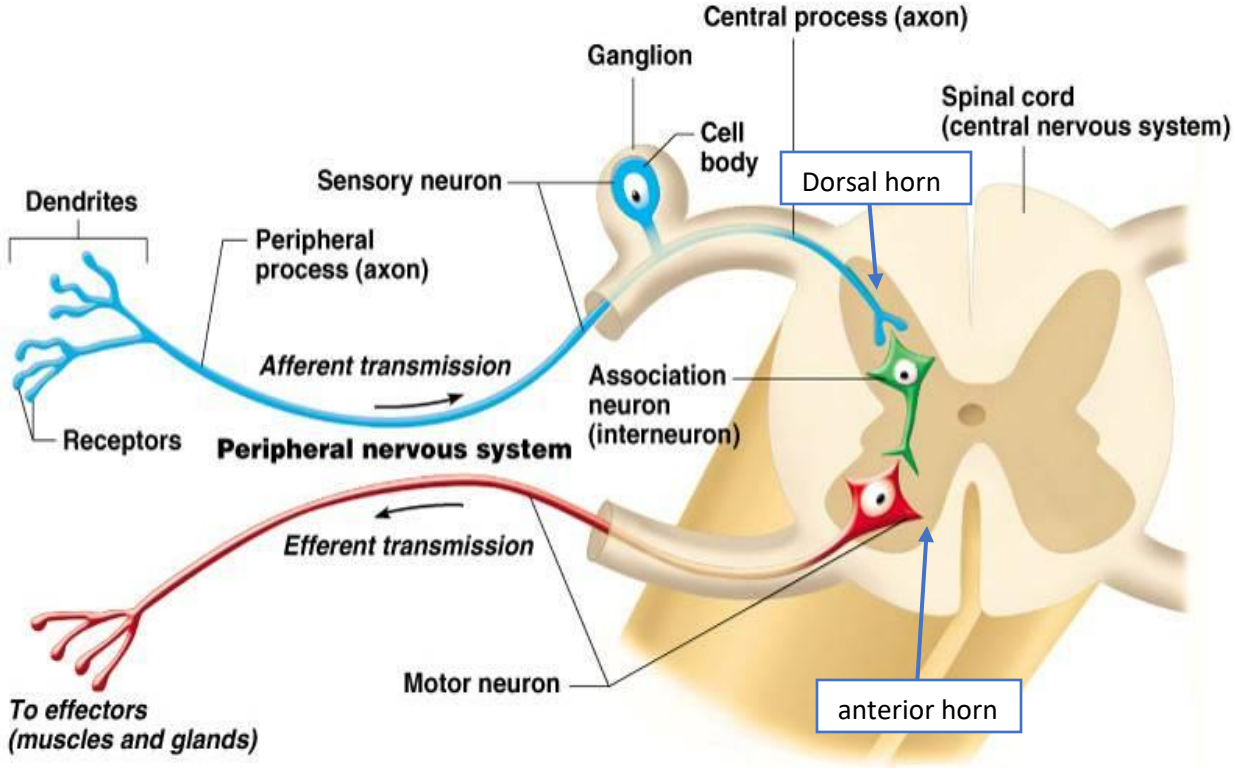
sensory neurons pass through the ganglion to enter the dorsal horn at the spinal cord, where it is at synapse with another neuron called Association neuron (interneuron).

2- **Interneuron** (association neuron): from its name you can تستنتج infer that it is between two neurons; sensory and motor, and it connects them together.

3-**Motor neuron** (Efferent neuron): goes out from the anterior horn of the spinal cord and supplies the effectors that could be glands or muscles.

-in the **peripheral** nervous system: there are **ganglions**, which are a collection of cell bodies and dendrites

-in the **central** nervous system: **nucleus** is the collection of cell body and dendrites

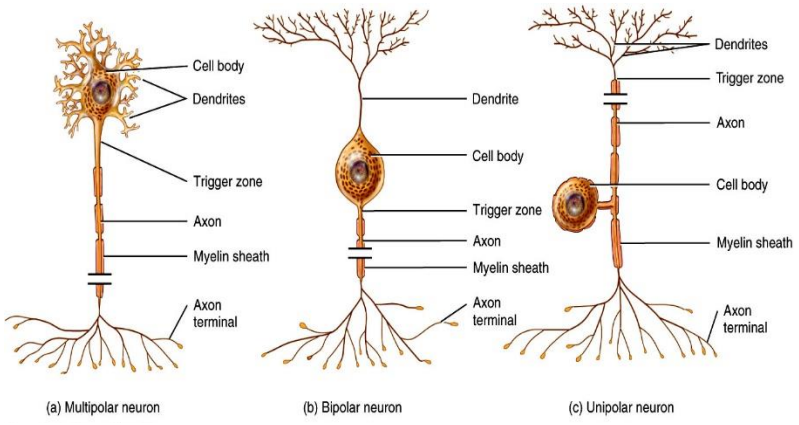



**Anatomical (structural) classification of neurons** اعرفهم لا تحفظهم

1-Multipolar neuron: *most common

2- Bipolar neurons: found in the visual system (optical) and the olfactory.

3- Unipolar neuron: also found in the olfactory system (smelling)



الاسماء بالأمثلة مش للحفظ بس قراءة فقط

**you're not required to memorize the names of neurotransmitters and hormones, just read them, some might be familiar like acetylcholine.

## Neurotransmitters

- neurotransmitters are chemical substances that act as mediators between the action potential in the first neuron and action potential in the second neuron at the synapse.

Classification of neurotransmitters:

1-**small molecules** rapidly acting neurotransmitters (**NT**) sometimes they're called neurotransmitter proper.

**Examples**: acetylcholine, norepinephrine(noradrenaline), epinephrin(adrenaline), dopamine, serotonin, GABA: gamma-Aminobutyric acid, glycine, glutamate, and gases like NO nitric oxide and CO carbon monoxide.

2-**Neuropeptides (NP)** or they're called neuromodulators because they modulate the action of small molecules.

-They're all peptides (proteins) that are formed at the cell body(soma) by the Nissl granules as a long chain of amino acids, and then they undergo post-translational modification at Golgi complex where it gets broken down into a smaller peptide chain and packaged in vesicles. *don't forget this process takes place at the soma.

-then neuropeptides travel by axonal transport to the terminal which is a very slow process (1mm/day), and this gives me them certain **properties** like:

1-they're secreted in small amounts. 2- more potent; prolonged action.

**Examples:** endorphins, enkephalins, VIP; vasoactive intestinal peptide, hypothalamic releasing hormones, TRH; thyrotropin releasing hormone, LHRH; luteinizing hormone-releasing hormone, pituitary peptides, ACTH; adrenocorticotropic hormone, prolactin, vasopressin. ALL are peptides.

## Synaptic Transmission

types of neurotransmitters:

1- small molecules **NT**. 2- neuropeptides **NP**. 3- gaseous transmitters.

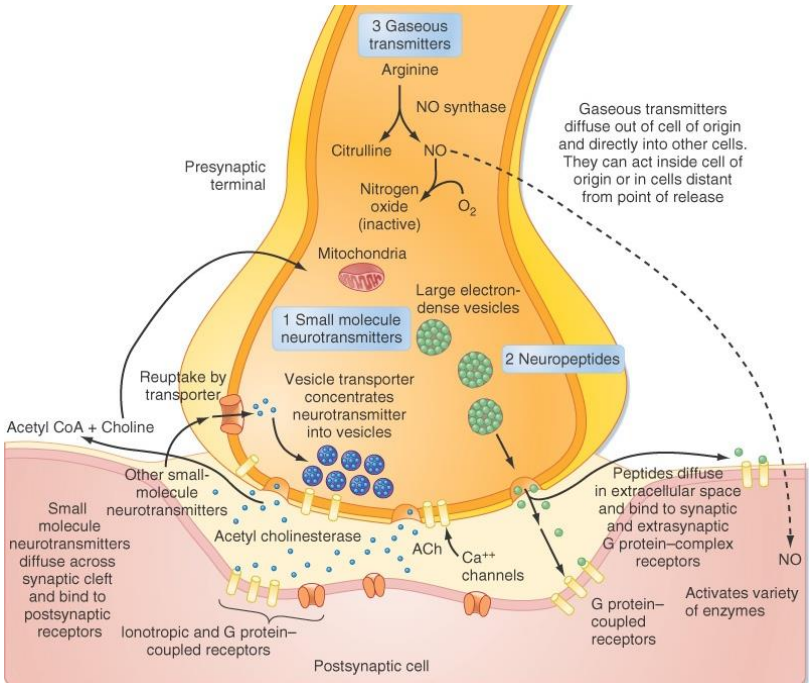
-when action potential reaches the terminal, voltage gated calcium channels that are located on the presynaptic membrane open, and calcium enters the cell, which increases calcium ion's $Ca^{+2}$ concentration intracellularly (inside the terminal).

*extracellular concentration for $Ca^{+2}$ is $10^{-3}$ molar
*intracellular concentration for $Ca^{+2}$ is $10^{-7}$ molar
*concentration outside is higher.

-increase in $Ca^{+2}$ concentration will cause the vesicles that carry either small molecules neurotransmitters or neuropeptides to fuse with the membrane and release its contents in the synaptic cleft.

*the mitochondria plays a role in charging the whole process with energy.

*synaptic **cleft** is a small extracellular space or distance between the presynaptic and postsynaptic neurons.




**-At the postsynaptic neuron** (neuron after the synapse)

-the neurotransmitters NT bind to their specific receptors at the postsynaptic membrane, but gases diffuse directly through the postsynaptic membrane.

-peptides also directly diffuse through the cleft and binds to their receptors that are called synaptic and extra synaptic G protein-complex receptors inside the cytoplasm of the postsynaptic neuron.

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**Example on transmission**: when acetyl choline, which is a small molecule rapidly acting neurotransmitter, gets released from the presynaptic membrane, it will afterwards diffuse and spread through the synaptic cleft, and then finally binds to its receptor that's usually chemical (ligand) gated channels on the postsynaptic membrane

if these channels were sodium channels, they'll open and cause depolarization of the postsynaptic neuron, if the depolarization reaches the threshold action potential will be generated at the postsynaptic neuron.

if these channels were potassium channels, they'll open and potassium ions $K^+$ will exit the postsynaptic neuron causing hyperpolarization.

on the postsynaptic membrane there are enzymes that breaks acetyl choline such as acetyl cholinesterase into acetyl coA + Choline.

Acetyl choline $\xrightarrow{\text{acetyl cholinesterase}}$ **choline** + acetyl coA

choline gets re-uptaken by an active transporter more specifically sodium coupled transport (secondary active transport) and gets back into the presynaptic membrane; choline is used to form acetyl choline again, that gets packed in vesicles and used again as a neurotransmitter.(recycling)

**neuropeptides are broken down by the enzymes peptidases or protease.

## **Nitric oxide** gaseous neurotransmitter

-Nitric oxide (NO) is a gas that's formed by the enzyme NO synthase from the amino acid (Arginine).

Arginine $\xrightarrow{\text{NO synthase}}$ **NO** + citrulline

-because it's a gas, its highly lipid soluble which means its **not** carried in vesicles and it'll directly diffuse and pass through the presynaptic membrane and enter the postsynaptic membrane **without** any need for **membrane receptors**.
its receptor lies inside the cytoplasm of the postsynaptic neuron, and acts through GMP second messenger (guanosine monophosphate).

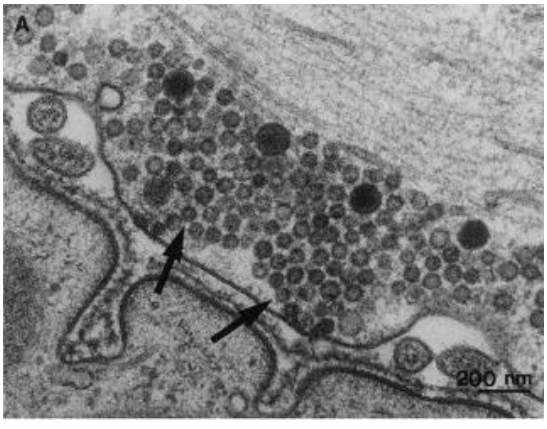
## Synaptic vesicles

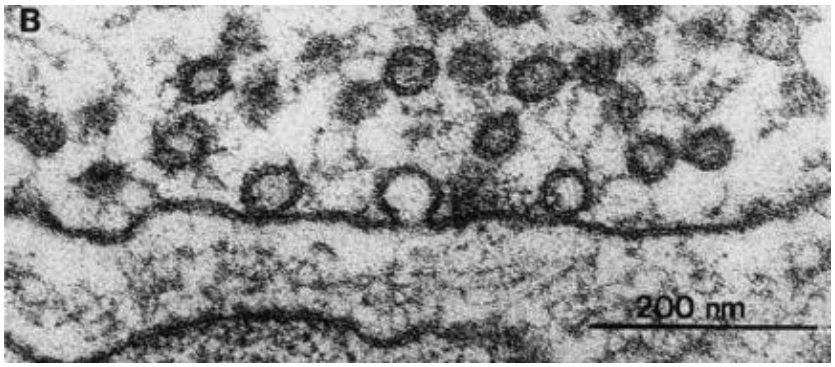
vesicles concentrate and protect neurotransmitters and can be docked at active zone.

we can differentiate between small molecules vesicles and neuropeptides vesicles through electron microscope.

**small molecules neurotransmitter's vesicles**
-small, more dense in number vesicles
-clear core.
-formed at the terminals.

**Neuropeptides vesicles**
-large, less in number
-dense-core
-formed at the soma.



**Recycling of vesicles**

after vesicles release their contents in the synaptic cleft, they get removed either by recycling or fusion with the presynaptic membrane.

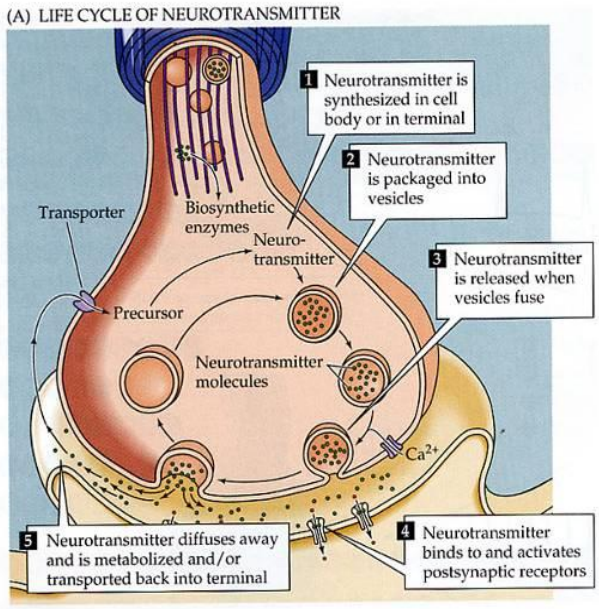
vesicles that carry small molecules rapidly acting neurotransmitters are recycled, meaning they get pushed back to the presynaptic membrane to be reused again in packing small molecules neurotransmitters, because their formation site is at the terminals.

in **contrast** vesicles that carry neuropeptides fuse with the presynaptic membrane they won't be recycled nor used again, because their formation site is at the soma not in the terminals, and its not reasonable to transfer them back again from the terminals to the soma.

## five key steps in neurotransmission

if one of these processes wasn't completed, we can't consider the chemical substance a neurotransmitter.

- **Synthesis**; small molecules NT are formed in the terminals, and NP are formed in the soma.
- **Storage**; stored in vesicles.
- **Release**; neurotransmitter is released when it's vesicle fuses with the presynaptic membrane.
  -if they're not released, they're not considered neurotransmitters.
- **Receptor Binding**; each neurotransmitter binds to its specific receptor in the postsynaptic membrane.
- **Inactivation**; any transmitter can be inactivated in 3 ways.(diffusion, degradation, uptake)



## Summary of synaptic transmission

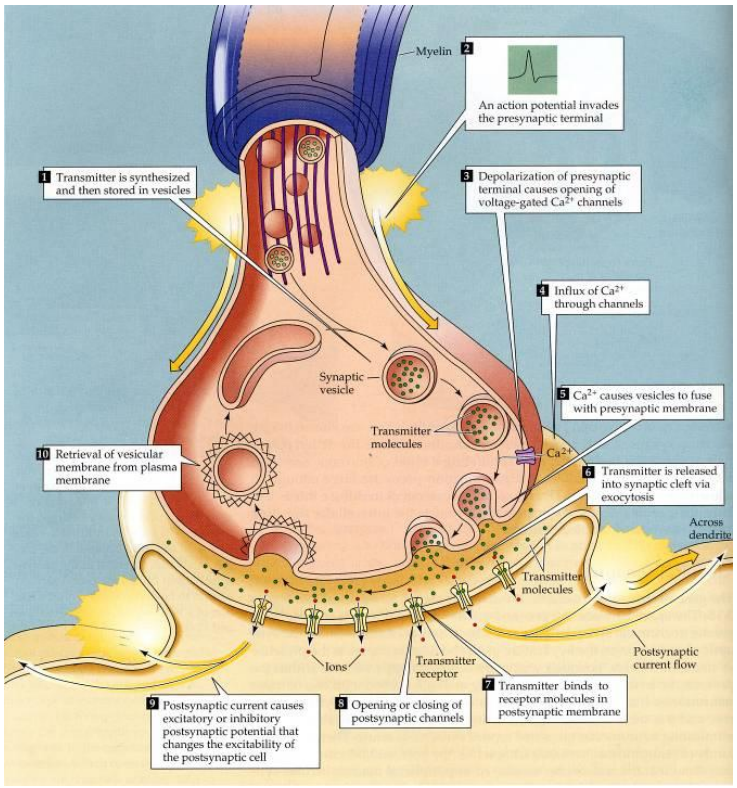
1- synthesis and storage of neurotransmitters.

2-action potential invades the presynaptic terminal.

3-voltage gated calcium channels open and causes depolarization of presynaptic terminal.

4-inlux of $Ca^{+2}$ through channels inside the terminal.

5-$Ca^{+2}$ causes the vesicles to fuse with the membrane.




6-transmitter is released by exocytosis into the synaptic cleft.

7-trasnmitters bind to their receptor molecules.

8-opening or closing of postsynaptic channels.(change in permeability)

9-postsynaptic current causes excitatory or inhibitory postsynaptic potentials that changes the excitability of the postsynaptic cell.

postsynaptic currents are either EPSP associated with $Na^{+}$ ions

or IPSP associated with $K^{+}$ ions or $Cl^{-}$ ions.

10-retrieval of the vesicles; small molecules neurotransmitter vesicles go back to the terminal (Recycling), and neuropeptide's vesicle fuse with the presynaptic membrane.

Comparison between **NT** and **NP**

| Comparison aspect | Small molecules rapidly acting transmitters **NT** | Neuropeptides **NP** |
|---|---|---|
| Action speed rate | Rapidly acting | Slowly acting |
| Action duration | Short lived action | Long (prolonged action) |
| Type of neurotransmitters released together | One type only | More than one type |
| amount that's released | Large amounts | Small amounts |
| Recycling of vesicles | Recycled ✓ | Not recycled **X** |
| Formation site | At the terminals | At the soma |

- A neuron can release only one type of small molecule neurotransmitters, for example; when acetyl choline is released you can't find another type of small molecule neurotransmitter released with it like glycine or glutamate.
- small molecules neurotransmitters are directly released from the presynaptic neuron
- neuropeptides are not secreted alone, they are co-secreted with small molecules neurotransmitters NT, meaning when a neuron releases neuropeptide (NP) they're usually co-secreted with small molecules rapidly acting neurotransmitter, BUT both are contained in different synaptic vesicles.
- you can find more than one type of neuropeptide released together.

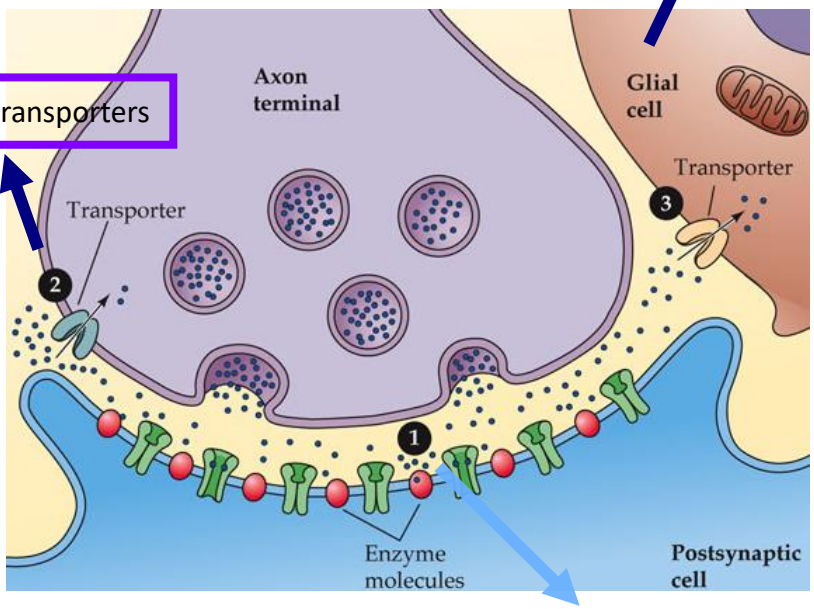
for example*: acetyl choline is co-secreted with ACTH, or endorphin.

## **Removal of Neurotransmitters** (termination)

1-**diffusion** in the interstitial fluid according to the concentration gradient; small molecules or neuropeptides can leave the synaptic cleft and diffuse to the interstitial fluid. (fluid between cells)

2-**Enzymatic degradation.**
Every neurotransmitter has a specific enzyme to break it down:
for example: acetyl choline is broken down by acetyl cholinesterase.
neuropeptides are broken down by peptidase or protease.

**EXTRA** examples (mentioned in the recorded video): epinephrine, norepinephrine both have an amino acid called catecholamines that's broken down by enzymes:
1- MAO: monoamine oxidases.
OR 2- COMT catechol-o-methyl transferase.




3- **Uptake** by neurons or glial cells (cells that are found in the central nervous system).
**throughout** neurotransmitter **transporters**, for example: when broken down acetyl choline is reuptaken by the presynaptic neuron through co-transport (sodium Na coupled transport) which is a form of secondary active transport.
- epinephrine and norepinephrine are also reuptaken by co-transport.

*its important to know how each neurotransmitter is terminated; this information can be used in drugs invention, for example Prozac; a psychiatric drug used for depression works as serotonin reuptake inhibitor and as a result prolongs the action of serotonin. people with depression have low amount of the neurotransmitter serotonin.

*the termination process is very important for example: if acetyl choline neurotransmitter wasn't terminated it'll cause epilepsy (صرع) that leads to seizure which is a prolonged action of muscle contraction that will lead to death.

## Basic Concepts on Neurotransmitter and Receptor

**Neurotransmitter**: is an Endogenous signaling molecule that alter the behavior of neurons of effector cells.
endogenous means found inside the body opposite of exogenous something that originates from outside of the body, outside factors like drugs.

**Receptor**: proteins on the cell membrane or in the cytoplasm that binds with specific neurotransmitter and alter the behavior of neurons or effector cells.
Myasthenia Gravis is a **disease** of muscle weakness caused by receptors inside the muscle cells **not binding** to their neurotransmitter acetyl choline.

- there are different types of molecules that serve as neurotransmitters, the same transmitter can have an excitatory or inhibitory effect, this is determined by the **properties** of the **receptor.**

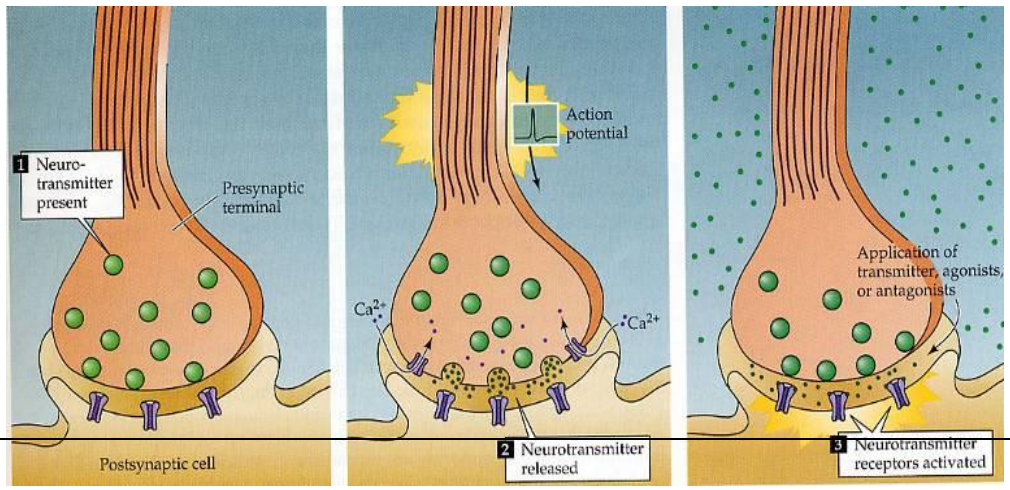
  **Example 1**: acetyl choline has an inhibitory effect in the heart and decreases its activity, its coupled with receptors on potassium $K^+$ channels which causes hyperpolarization.
  on the other hand, acetyl choline has an excitatory effect on the GI trackt because it's coupled with receptors on sodium Na channels which causes depolarization.

  **Example2**: epinephrine in the heart is excitatory and in the GI is inhibitory.

**conclusion**: the properties of neurotransmitters don't determine the effect on postsynaptic cells, and the same transmitter can bind to different receptors and have different effects.

**Classical definition of neurotransmitters,** a neurotransmitter must:

- Be synthesized and released from neurons.
- Be found at the presynaptic terminal.
- Have same effect on target cell when applied externally
- Be blocked by the same drugs that block synaptic transmission.
- Be removed in a specific way.



## Agonist and Antagonist

**Agonist**: a substance (drug) that mimics a specific neurotransmitter meaning it simulates the neurotransmitter in which it is able bind to the neurotransmitter's receptor.

and thereby have the same effect and action the neurotransmitter usually produces.

-agonist can be an outside source for the missed chemical substance in the body (neurotransmitter).

-some drugs are often designed as receptor agonists to treat a variety of diseases and disorders when the original substance is missing or depleted. مستهلكة

examples*(extra from the recorded video): beta receptor agonist, acetyl choline agonist.

**Antagonist**: a substance (drug) that binds to neuroreceptor and blocks their activation thereby blocks the action on neurotransmitters or the neuroreceptor agonists.

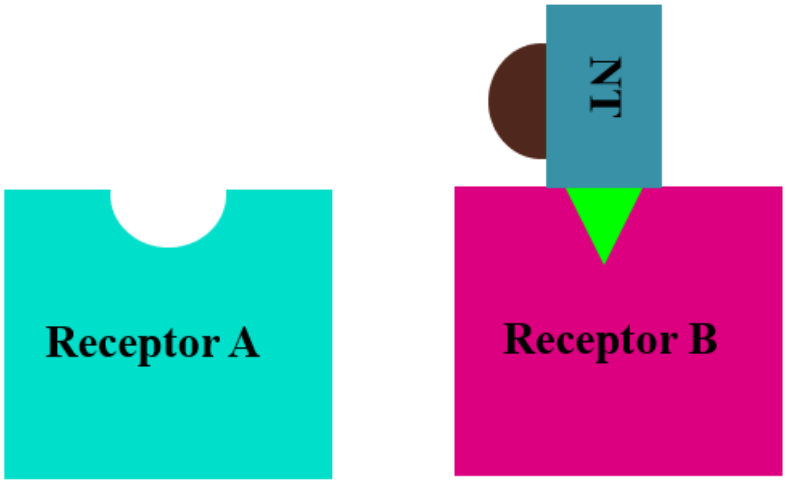
examples on antagonist*: beta receptor antagonist used to treat diseases related to the heart.

alpha receptor blocker that treats diseases related to blood vessels or hypertension.

to understand the mechanism of agonist and antagonist drugs; remember that the same neurotransmitter can bind to different receptors and have different effect; just like the acetyl choline, it has a receptor in the heart that's different from the receptor in the GI.

and just like the picture here the neurotransmitter NT can bind to different receptors:

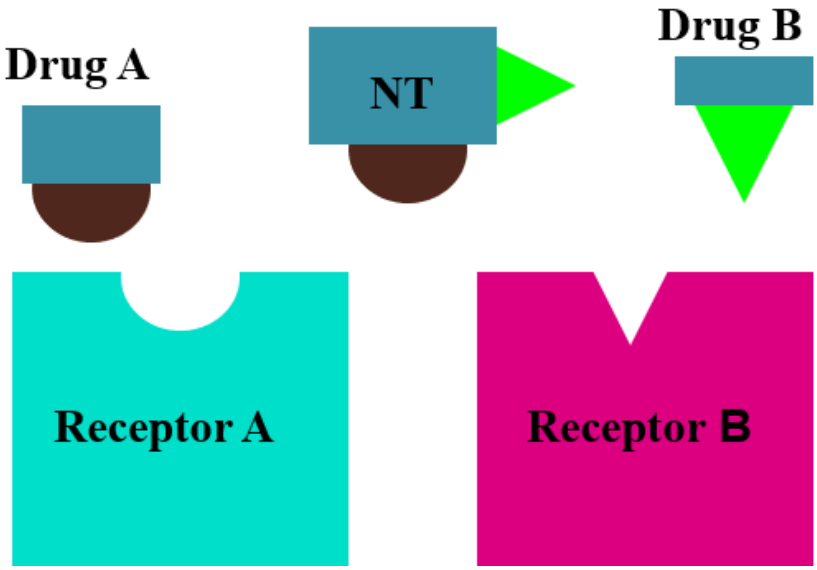
receptor A and receptor B



## Specificity of Drugs

in continuation with the example mentioned in the previous page:
we can make drug B that blocks the action of neurotransmitter NT when it binds to the receptor B.
we can also make another drug, drug A that blocks the action of the **same** neurotransmitter but when it binds to the receptor A.

don't forget that receptors are specific, so these receptors here can only bind to this neurotransmitter and only specific to it.




## Dale principle (Neurotransmitter Co-existence)

neuropeptides are co-secreted with neurotransmitters, some neurons in the peripheral nervous system (PNS) and in the central nervous system (CNS) produce both classical neurotransmitters like acetyl choline (Ach) or catecholamine (epinephrine and norepinephrine), and a polypeptide neurotransmitter **NP.**

thus, the neuron can release either the classical NT or both under different conditions.
**Dale principle** states that **co-existence** between the different types of neurotransmitters (NT + NP) can be possible.

and there's a theoretical example to elaborate.

- when a low frequency stimulation with 50 action potentials per second (50 AP/sec) stimulates a neuron, the neuron will release small molecules rapidly acting neurotransmitters.

- but when a high frequency stimulation with 100 action potentials per/second stimulates a neuron, the neuron will release both types of transmitters NT and NP.

so according to this theory, the rate/number of action potentials stimulating the neuron determines what type of neurotransmitters are released.

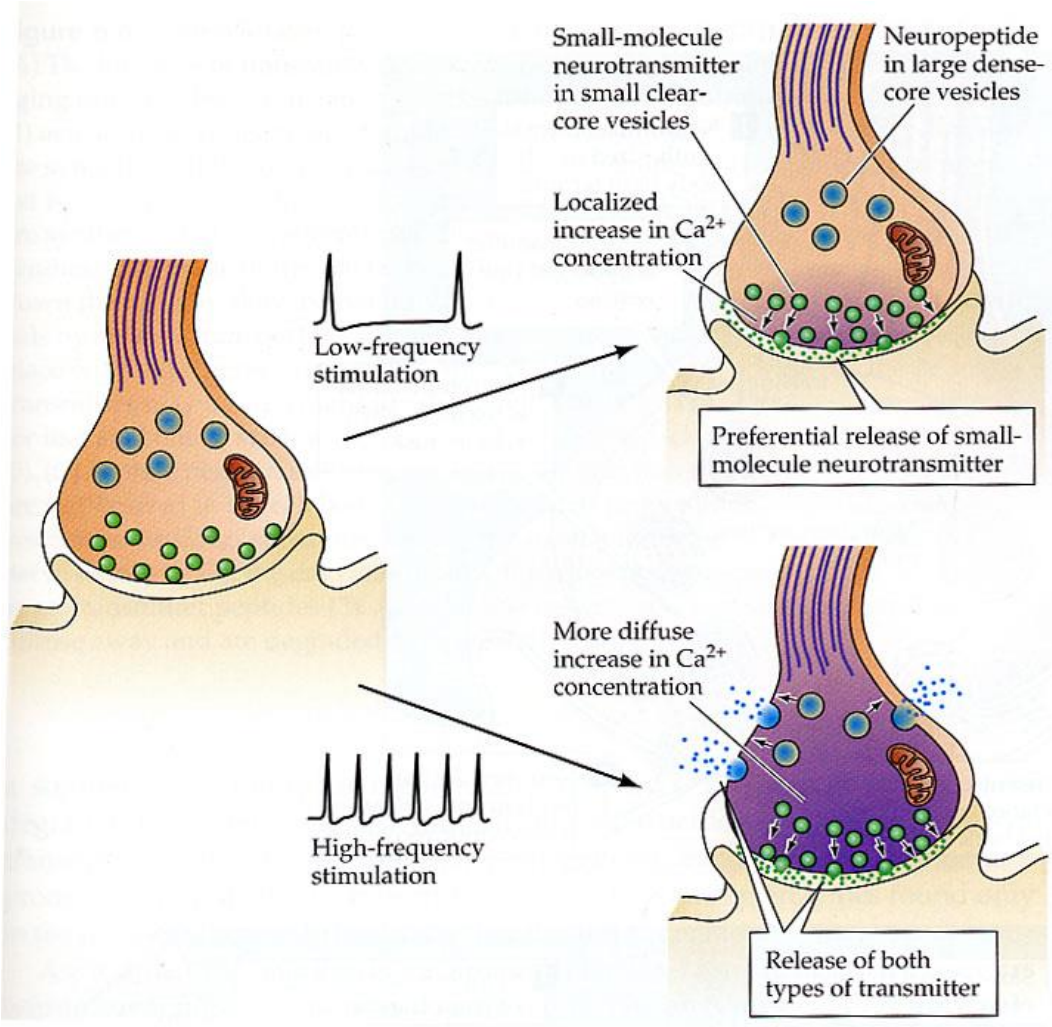
this is only an example, but in fact the release of different types of neurotransmitters depends on the function of organs and the co-existence differs from one system to another.

for example in another case; low frequency stimulation can cause release of both types NP+NT, and high frequency stimulation can only cause release of NT.

action potential rate

= firing rate.

= nerve signal.



## Receptor Activation

recall that a neurotransmitter can be excitatory at some synapse and inhibitory at others. and receptor properties determine whether the neurotransmitter is excitatory or inhibitory.

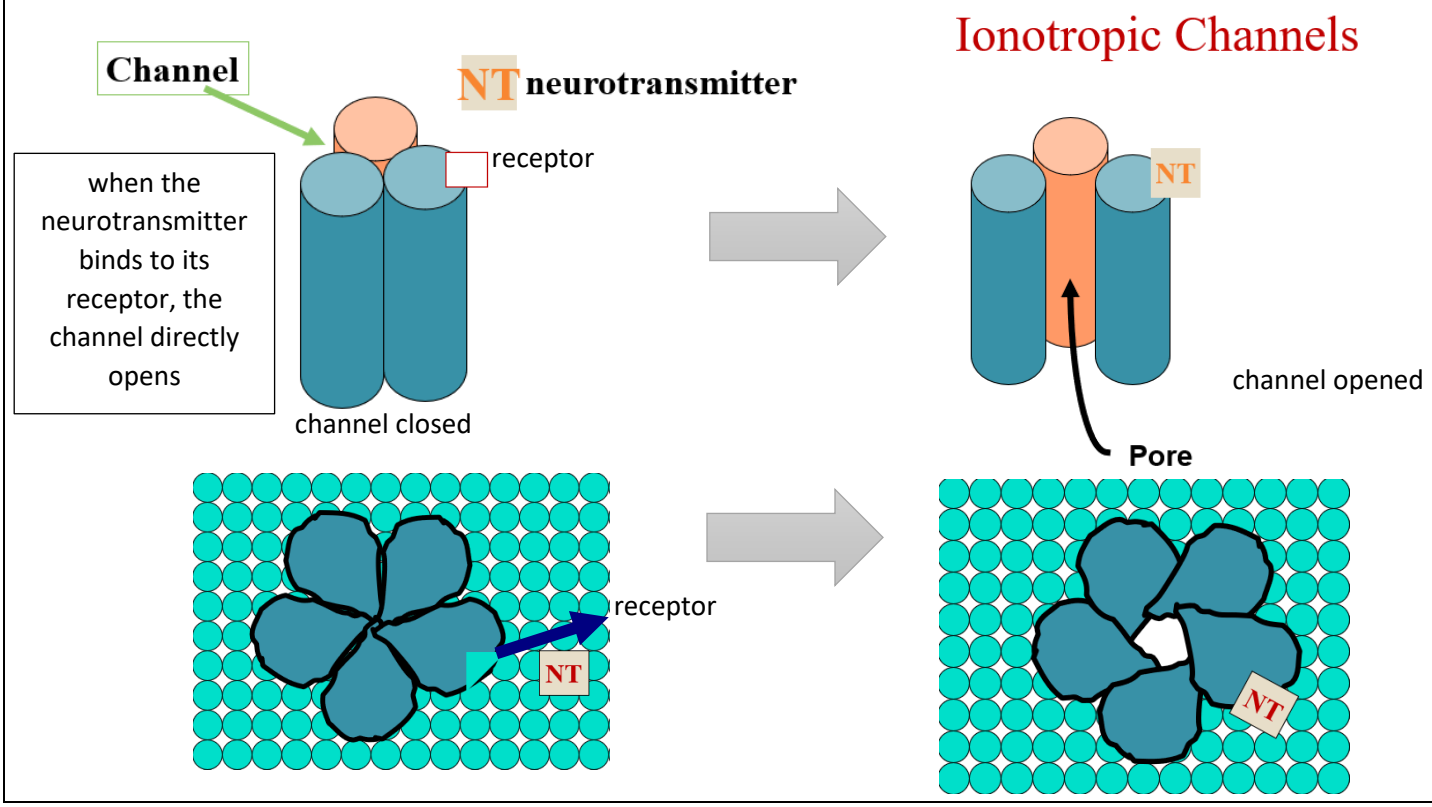
types of **receptors** are on the postsynaptic membrane:

1- **ionotropic** receptor(direct effect). 2- **metabotropic** receptor(indirect effect).

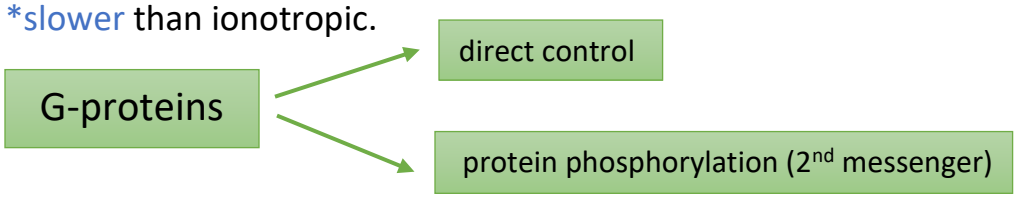
Transmitter binding to the receptor activates ion channel either:

- Directly
- Indirectly

1-**Direct activation**:
the receptor itself can be an ion channel, so transmitter binding to its receptor causes direct activation of the channel; opening of the channel and change in permeability.
in this case the receptor is called ionotropic receptor, it's activation is fast.
for example: if the channel was Sodium Na channel, and the receptor binds to this channel, the channel will open, sodium will enter the cell and causes depolarization.( excitatory effect)
and if it was potassium K channel it'll cause hyperpolarization.( inhibitory effect)



2- **Indirect activation**:
is present in metabotropic receptors, the receptor is separate from the channel and coupled with G-protein system that's on the postsynaptic membrane
*slower than ionotropic.

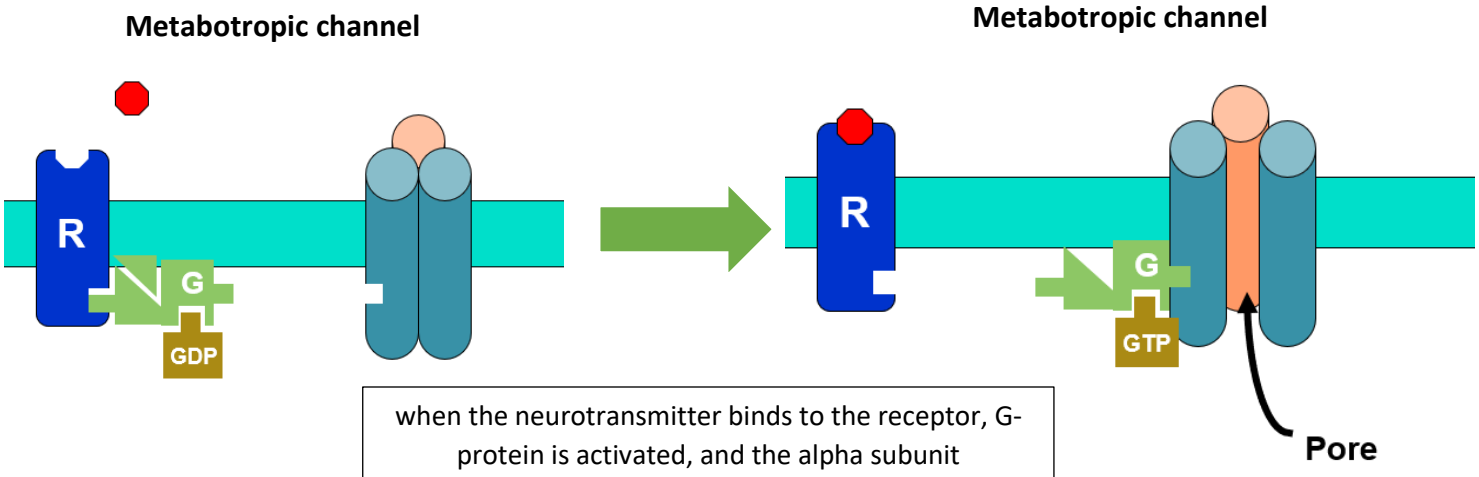



G-protein is composed of 3 subunits; alpha $\alpha$, Beta $\beta$, Gamma $\gamma$.
when the neurotransmitter is bound to the receptor, the alpha subunit of G-protein disassociates and does its action:
it can either activate a channel and open it, closes a channel (direct control)
or it can be associated with 2nd messenger system.

alpha subunit can bind to different 2nd messengers like cAMP, calcium, cGMP(guanosine monophosphate), and diacylglycerol (a phospholipid)

**Final Effects:**
1- control channels.
2-alter properties of receptors.
3-regulation of gene expression: alpha subunit could bind to the gene system DNA and alter the gene.

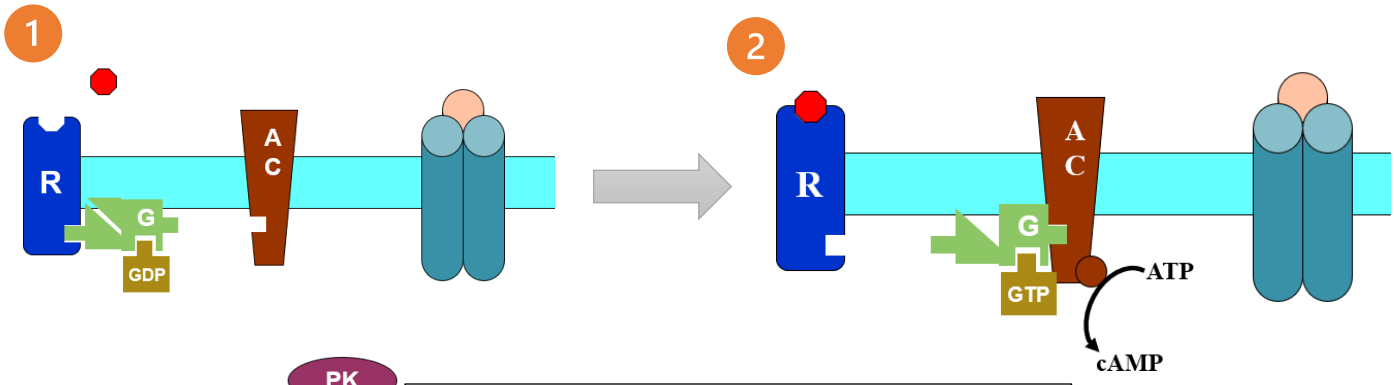
**1- direct control**.
G-protein binds to the channel directly and changes its permeability by opening or closing it.
this is a relatively fast process in comparison to protein phosphorylation, but not as fast as ionotropic receptors.




when the neurotransmitter binds to the receptor, G-protein is activated, and the alpha subunit disassociates, binds to the channel and changes its activity.

**2- protein phosphorylation.** (2nd messenger system)

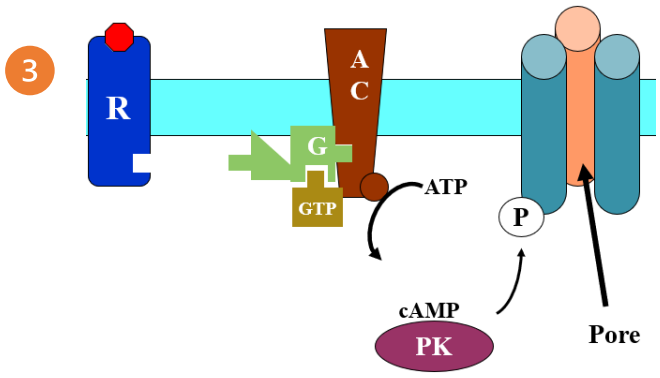
when the neurotransmitter binds to its receptor, G-protein system is activated, and then G-protein -through alpha subunit- stimulates a nearby enzyme (adenylate cyclase for example) that converts ATP to cyclic AMP (which is a 2nd messenger), cAMP activates a **protein kinase** called protein kinase A that causes **phosphorylation** of a channel, and in turn changes its activity.




**(1+2)** neurotransmitter binds to the receptor, G-protein is activated, and the alpha subunit disassociates, binds to adenyl cyclase. and then ATP is converted to cAMP.

**(3)** cAMP activates protein kinase.

protein kinase activates the channel and changes it permeability by phosphorylation (adds phosphate to the channel)




three main protein kinases: (stimulated by different 2nd messengers)

1-**protein kinase A**; is also named cAMP dependent protein kinase, stimulated by cAMP.

2-**protein kinase B**; calmodulin dependent protein kinase, stimulated by a protein called calmodulin that binds to calcium.

kinases can be activated by different 2nd messengers, the protein kinase that's stimulated by calcium is called

3-**protein kinase C**; stimulated by calcium + phospholipid.

Luck favors those who **believe** they're lucky, GOOD LUCK 😊