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Number

17

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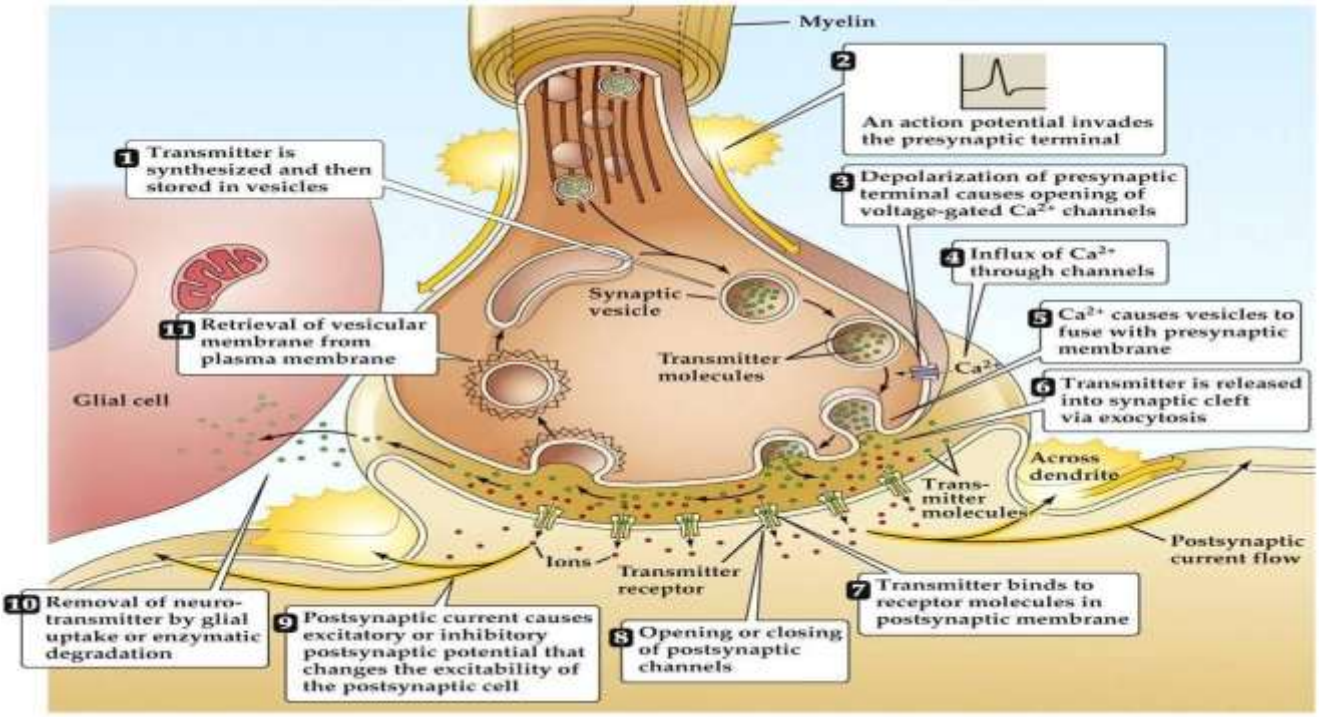
Review : Summary of synaptic transmission:

1) Action potential arrives to presynaptic terminals of a nerve and causes depolarization by opening Ca^{2+} voltage-gated channels in the presynaptic membrane.
2) Number of voltage gated Ca^{2+} channels that open, depends on the amplitude of the action potential. The amplitude differs between NEURONS (some neurons change from -90 to +30, others from -70 to +10….).
3) Ca^{2+} causes the releasing of a NT from its vesicles at the terminals.
4) NT binds to the receptor in the postsynaptic membrane whether it is ionotropic or metabotropic. This receptor opens or closes chemical gated channels in the postsynaptic neuron.
5) Transmitter Inactivation: • Reuptake by presynaptic terminals • Diffusion •Uptake by glial cells • Enzymatic degradation • Presynaptic receptor •Combination of them

For classical NTs (small molecules) the vesicles are recycled.



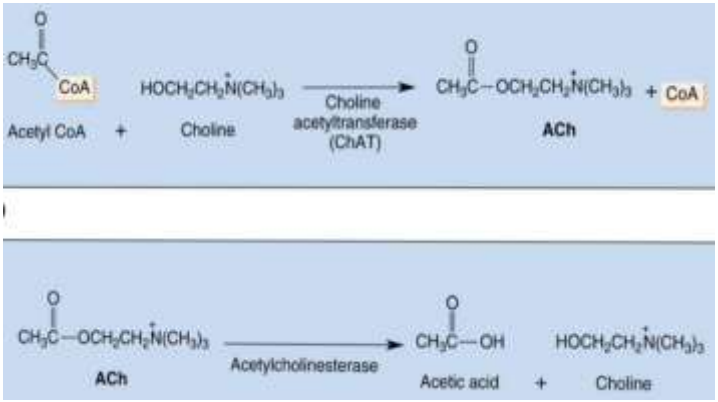
Types of receptors :

1- **Ionotropic receptors:** receptors are connected **directly** to ion channels. **They are** fast. The **binding of the NT changes the permeability of the channel.**
2- **Metabotropic receptors:** receptors that are not coupled to ion channels directly, or are not coupled to ion channels at all, instead they work through **G-protein system, they are slow.** G-protein uses a second messenger and it might be (c-AMP, c-GMP, calcium, calmodulin, phospholipids….)**.**

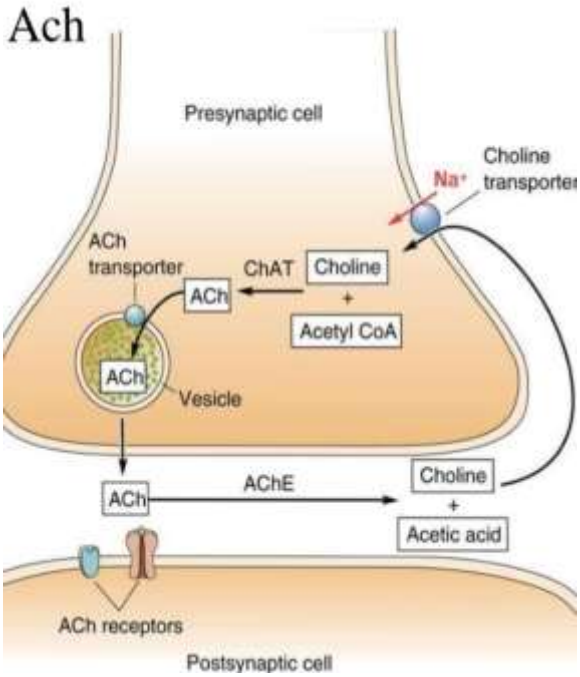
Some Important Transmitters

1-Acetylcholine

Life Cycle:



1) **Acetylcholine** is synthesized according to the equation by **choline acetyltransferase (ChAT):** Choline + acetyl CoA ➔ ACh + CoA
2) ACh is transported to vesicles by transporter in the membrane of the vesicles.
3) When depolarization occurs, ACh is released to the synaptic cleft.
4) ACh binds to its receptor causing IPSP or EPSP in the postsynaptic neuron.
5) ACh is inactivated in the synaptic cleft by **ACh Esterase** (Enzymatic Degradation): ACh ➔ acetic acid + choline
6) Choline is transported back to the presynaptic terminals for recycling.



Synthesis and Degradation:

Remember that:

- The source of acetyl CoA is the metabolism of carbohydrates, lipids, or proteins (Kreb's cycle, biology)
- The enzymatic degradation of ACh occurs by: Acetylcholinesterase (AChE) enzyme.
- It is found on postsynaptic membrane or immediately outside the membrane.
- Prevents continuous stimulation.

ACh Distribution:

1) *Peripheral N.S.:*

In Neuro-Muscular junction: ACh is found in the junction between a skeletal muscle and its neuron, it Excites somatic skeletal muscle (neuro-muscular junction).

2) *In the Autonomic N.S.:*

The Ganglia of sympathetic and parasympathetic NS.

At Neuroeffector junctions of The Parasympathetic NS and little trunks of the sympathetic NS (sweat glands).

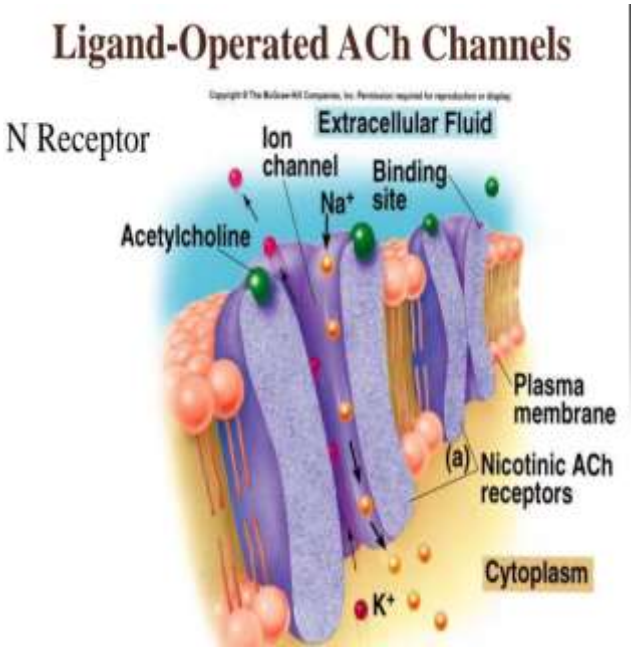
3) *In the Central N.S.:* it's widespread in many areas of CNS such as:

■ Hippocampus. ■ Hypothalamus.

Ach Receptors

•ACh is both an excitatory and inhibitory NT, depending on the organ involved, according to the type of the receptor.

Causes the opening of chemical gated ion channels.



Nicotinic ACh receptor :

- Ionotropic receptors.
- They are Membrane Channels for Na+ and K+ Open on ligand binding.
- Cause Depolarization of target (neuron, muscle).
- Stimulated by Nicotine and Blocked by Curare.
- It has two types:

I. ***N1***: found in All autonomic ganglia and in hormone producing cells of adrenal medulla.
II. ***N2:*** found in Motor endplate between the neuron and the skeletal muscles (somatic).

Curare is a local Anesthetic, it also causes relaxation of the skeletal muscles because it blocks the nicotinic receptors.

Muscarinic ACh receptor:

- Metatropic receptors.
- Found in the plasma membrane of smooth and cardiac muscle cells, and in cells of some glands.
- Stimulated by Muscarine, Blocked by Atropine.

Atropine is also used as a treatment for pesticide toxicity. These pesticides contain organic phosphate which causes pupil constriction (Atropine is used for pupil dilation).

- It has two types (in slides):

I. *M1:*

a. This type Uses signal transduction system: Phospholipase C, IP3, DAG, cytosolic Ca++
b. Effect on target: cell specific (heart ↓, smooth muscle intestine ↑).
c. Found in:
   - ✓ All parasympathetic target organs.

- ✓ Some sympathetic targets.
- ✓ Smooth muscles of gastrointestinal tract: *Excitation*.
- ✓ The circular muscle of the iris of the eye: Excitation=> *Contraction*.
- ✓ Endocrine sweat glands: Excitation increasing sweating.
- ✓ Skeletal muscle blood vessels: Inhibition: *relaxation and vasodilation.*

II. *M2:*

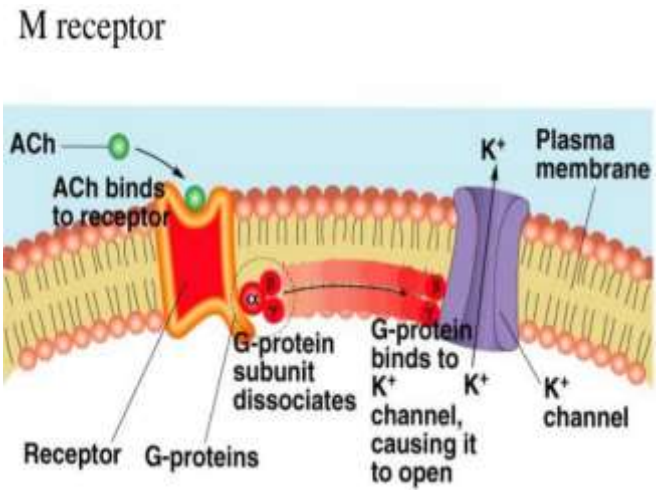
a.

b. Uses signal transduction system: via G-proteins, opening K+ channels, decreasing cAMP levels.

c. Effects on target: cell specific

d. Found in the: 1-CNS

2-heart: Inhibition: *decreasing* the heart rate.



Cholinergic neurons: release the NT **acetylcholine**.

Cholinergic Agonists: <u>increases the response</u> in the effector cells which are innervated by cholinergic ne0urons. Cholinergic Agonists act as ACh.

A-Direct Agonists:

– **Muscarine**: stimulates muscarinic receptors.

– **Nicotine**: stimulates nicotinic receptors.

b-Indirect Agonists:

AChE Inhibitors: block acetylcholinesterase enzyme to prolong the effect of ACh (works like an agonist).

Cholinergic Antagonists:

i. Curare: inhibits Nicotinic Receptors.
ii. Atropine: inhibits Muscarinic Receptors.

Monoamines

Derivatives of amino acids which act as NT, they are classified to:

- ❖ **<u>Catecholamines:</u>** Dopamine (DA), Norepinephrine (NE), Epinephrine (E)
- ❖ **<u>Indolamines:</u>** Serotonin, histamine

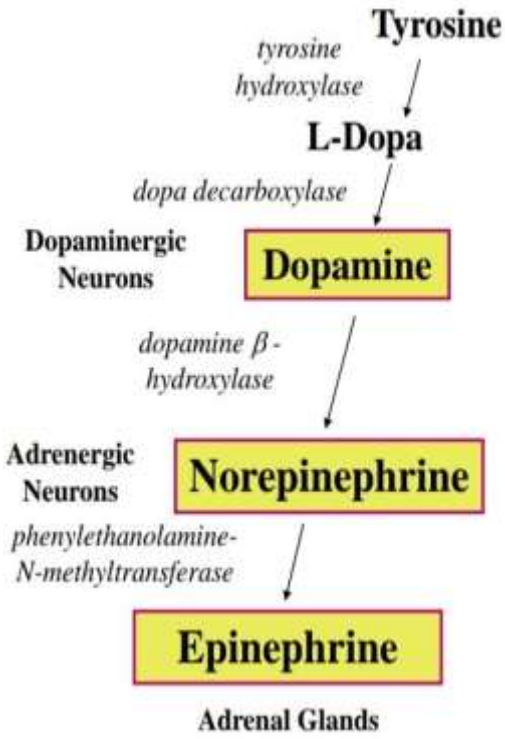
: Notes

Hydroxylation is addition of OH^-.

Decarboxylation is the removal of CO_2.

Nor: doesn't contain methyl group.

So addition of a methyl group to norepinephrine gives is epinephrine.



Dopamine as NT:

It is used in some Brain Neurons that are active during:

- Emotional responses
- Addictive behaviours
- Pleasurable experiences.

Dopamine-releasing neurons help regulate:

- Skeletal Muscles Tone.
- Some Aspects of movement due to Contraction of skeletal muscles.

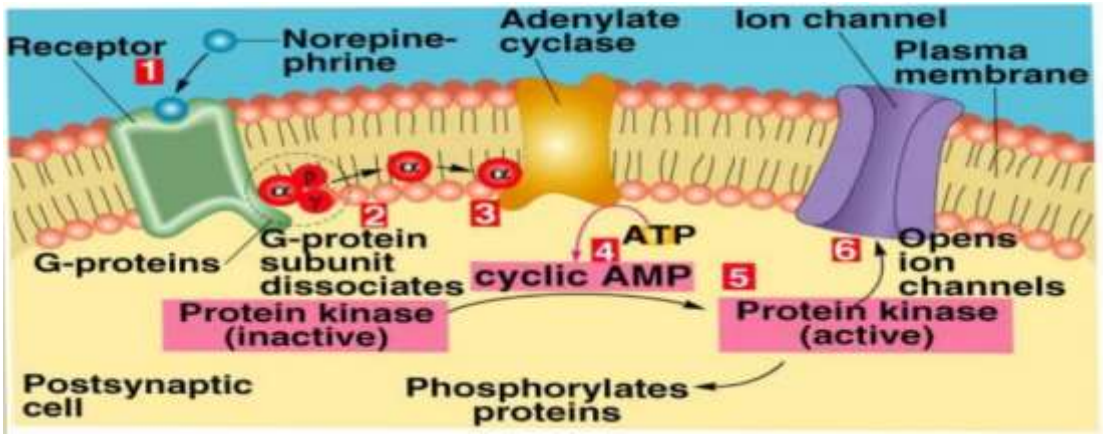
Parkinson Disease: occurs due to the deficiency and degeneration of neurons that release dopamine causing muscular stiffness and muscles may alternately contract and relax.

Norepinephrine (NE) as NT

• In the PNS:

a. Smooth muscles of blood vessels: causes *vasoconstriction*, so Increases blood pressure.
b. Smooth muscles of the gastrointestinal tract: *Relaxation* (inhibition).
c. Cardiac muscle: *increases* the heart rate and the force of contraction.
d. Glands: *increasing* sweating (Excitation), *Inhibition* of digestive enzyme secretion.

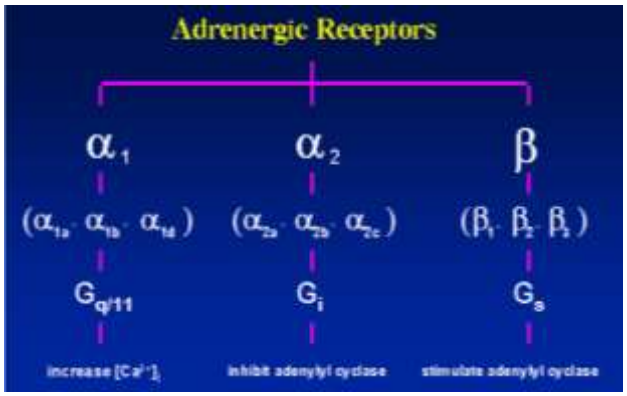
In the CNS: General behavior.



Note that phosphorylation doesn't always mean activation, it can be cause activation or inhibition of the protein

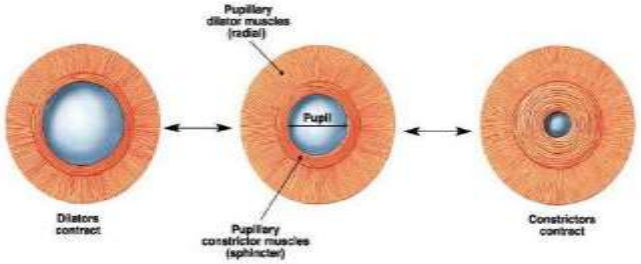
Androgenic Receptors

Integral proteins are activated by norepinephrine (as NT or hormone) and Epinephrine (as a hormone).



Alpha 1 Receptor

A. Stimulated by: NE, E. This results in *Excitation effect*; Contraction.
B. In the Blood vessels of skin, mucosa, abdominal viscera, kidney and salivary glands: it causes *constriction.*
C. Sphincter muscles of stomach and urinary bladder: it causes *Constriction.*
D. Radial muscle in the iris of eye: it causes *Pupil Dilation* due to the contraction of that muscle



Alpha 2 Receptor

A. Stimulated by: NE, E.
B. In the membrane of adrenergic axon terminals (presynaptic receptors).
C. In Platelets: it causes *aggregation* to form plug.
D. *Inhibition* of NE release (autoreceptor).
E. In Cells of Pancreatic islets: it *decreases* insulin secretion.
F. In Pancreatic Acinar Cells: it *decreases* the digestive enzyme secretion.

Beta 1 receptor

A. Stimulated by E.
B. Mainly In the heart muscle cells *increases* heart rate and strength of contraction.

Beta 2 receptor

A. Stimulated by E
B. In Lungs, most other sympathetic organs: it causes *Dilation of bronchioles* to get more oxygen.
C. In Blood vessels serving the heart (coronary vessels): it causes *Dilation* to transport more oxygen.
D. In Smooth muscle in GI tract and Pregnant Uterus: it causes *Relaxation* (Inhibition).

B3 Receptor

A. Stimulated by E.
B. In Adipose Tissue: it causes stimulation of *Lipolysis.*

☆☆An additional information: **B3 Receptors** are found specifically in Brown adipose tissue and cause Heat Production.

Amino Acids as NT

Several amino acids are neurotransmitters in the CNS.

A. Excitatory Amino Acid (EAA): producing EPSP by opening cation channels, such as:

- Glutamate/glutamic acid
- Aspartate/aspartic acid

Don't forget that we add -ate suffix for the conjugated base of an acid.

B. Inhibitory Amino Acids (IAA): producing IPSP by opening Cl- channels, such as:

- Gamma-amino-butyric acid (GABA): the common inhibitory neurotransmitter in the CNS.
- Glycine: is used in spinal nerves.

Polypeptides as NT

CCK: is found in brain and GI. Promotes satiety following meals by dealing with Appetite, is used as a NT for obesity.

High appetite results in overweight, Low appetite results in Hyposomia (thin and lean body).

Substance P: Major NT in sensations of pain.

Adrenocorticotropic hormone (ACTH): pituitary peptide.

Monoxide Gas:

They are *lipid-soluble* and can diffuse to the postsynaptic neurons and work through cGMP.

Nitric Oxide (NO):

I. was known as endothelial-cells-derived-relaxing factor because it was thought that this factor is secreted by endothelial cells of blood vessels walls and causes relaxation.
II. Now, this factor is known as NO.
III. Exerts its effects by stimulation of cGMP.
IV. Involved in *memory and learning.*
V. In Smooth muscle: causes *relaxation.*
VI. In blood vessels: causes *vasodilation*, decreasing blood pressure.

Carbon monoxide (CO):

I. Stimulate production of cGMP within neurons.
II. Promotes odor adaptation in olfactory neurons.
III. May be involved in neuroendocrine *regulation in hypothalamus.*
IV. Also Involved in *memory and learning.*
V. In Smooth muscle: causes *relaxation.*

Sensory Receptors

Any receptor that sense a change by a certain stimulus, proteins in the membranes of sensory receptors can be stimulated by a hormone, neurotransmitters, certain chemicals etc.

1. Sensory Receptors: *Organs* that sense a change in the stimulus NOT proteins in the cells membranes.
2. Sensory Receptors convert any kind of stimulus (ENERGY) to Electrical Potential, this process is called Transduction.
3. Sensory Receptors are also called Transducers.
4. They can be simulated by pain, pressure, light, temperature, touch etc.
5. They don't have Voltage gated channels (very small amount).
6. Sensory Receptors CAN'T generate action potential (not excitable cells).
7. They generate *local potential* also called receptor potential or generator potential, which can decrease or increase according to the strength of the stimulus.
8. This receptor potential is converted to action potential in the neuron, Then it reaches **the cerebral Cortex.**
9. When an action potential *reaches the cerebral cortex, we sense the stimuli (pain, touch, pressure….we become consciously aware of it).*
10. If a sensory impulse doesn't reach the cerebral cortex, we don't sense it.
11. We differentiate between sensations by the specificity of the receptor and its special pathway:
    - Pain Receptors can be only stimulated by pain. Also, they have certain pathways which transmit impulses for pain only, wherever it was stimulated, it would transmit impulses of pain only.
    - Touch Receptors can be only stimulated by touch and have certain pathways which transmit impulses for touch only.
12. The Strength, The Type, and The Location of sensation stimulus are Coded (explained in the next lecture).
13. An important characteristic of sensory receptors is The Adaptation: *decreasing the amplitude of the generator or receptor potential during a maintained, constant stimulus.*