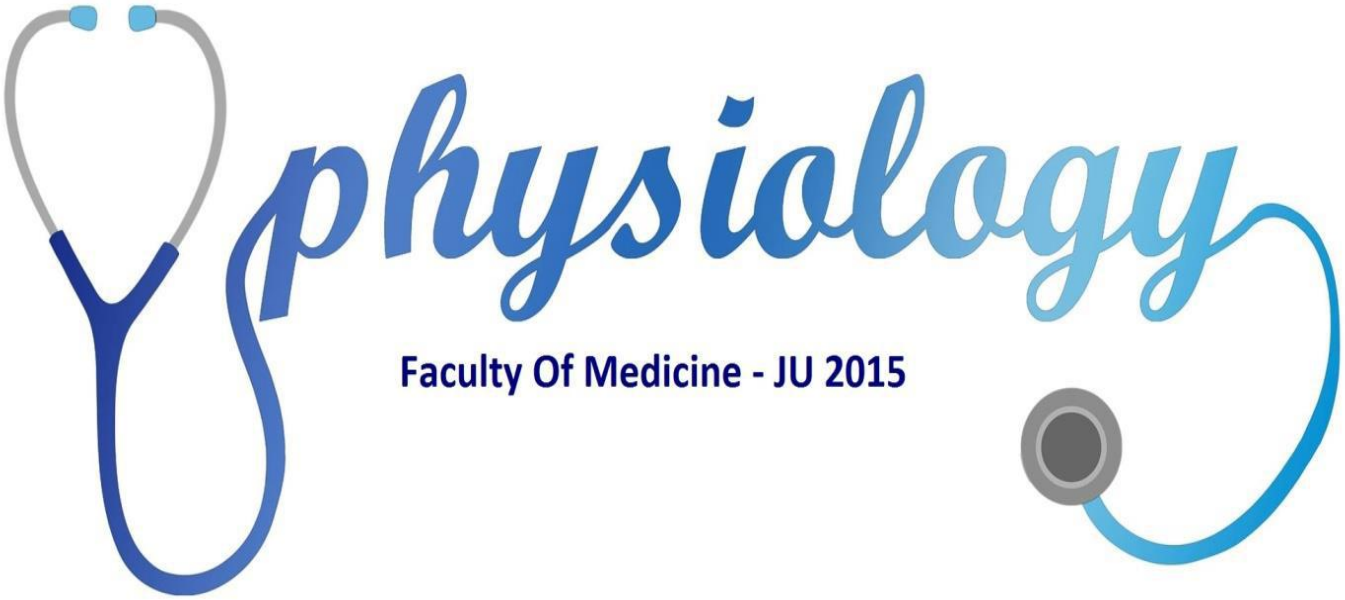


Lecture: 27

Faisal I. Mohammed, MD, PhD

Written by: Hamzeh Nakhleh

Revision:

Neurotransmitters are signaling molecules.

Receptors are proteins on the cell membrane or in the cytoplasm to bind a neurotransmitter.

The binding of the neurotransmitter to receptor is specific to alter the behavior of neurons or effector cells.

The properties of the transmitter do not determine its effects on the postsynaptic cells.

The properties of the receptor determine whether a transmitter is excitatory or inhibitory…

For instance, 1- If the receptor is coupled to Na channels, it's excitatory… but if it's coupled to K channels it's inhibitory..

2-Ach in the heart is inhibitory…but in the GI tract it's excitatory (increase all the GI tract actions like motility and secretion).

Neurotransmitters must :

1-Be synthesized and released from neurons

2-Be found in the presynapticterminals (in vesicles).

REM: NT is released when there is an increase in intracellular Ca that enters down it's electrochemical gradient through voltage-gated Ca channels when an action potential reaches these terminals.

3-Have same effect on target cell when applied externally

(If it's applied internally or externally, it has the same effect)

4-**Be blocked** by same drugs that block synaptic transmission (Antagonist)

5-Be removed in specific way (Diffusion, Enzymes, Uptake)

Agonist:

Is a substance that has the same effect of NT (It's like the NT).

Is able to attach to that NT's receptor and reduces the same effect

Antagonist:

It binds to the NT's receptor and blocks the action of the NT (Bind to but not activate neuroreceptors).

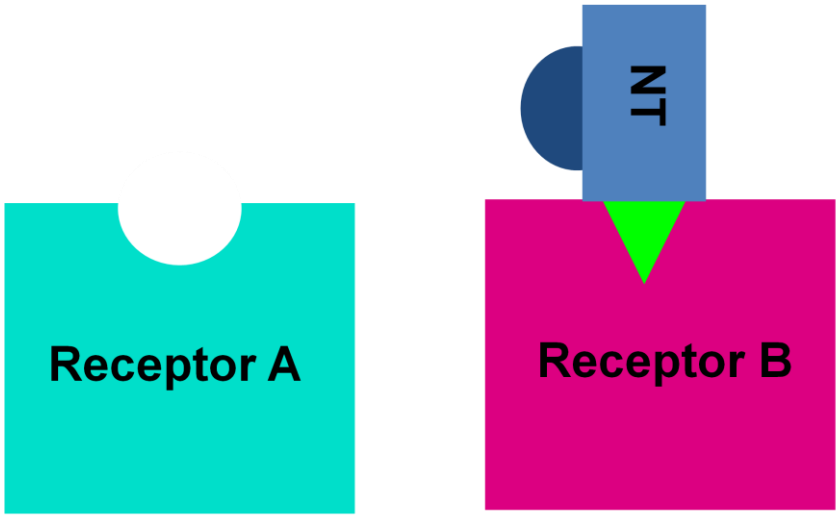
So drugs are: either receptor **agonist** (to treat a variety of diseases and disorders when the original chemical substance is missing or depleted.)

or **Antagonist** (Block the action of NT or receptor agonist).

A neurotransmitter can bind to different receptors. For instance, Ach can bind a receptor in the GI and a receptor in the Heart.

"Note the different parts of the NT".

- Same NT can bind to different -R
- different part of NT ~

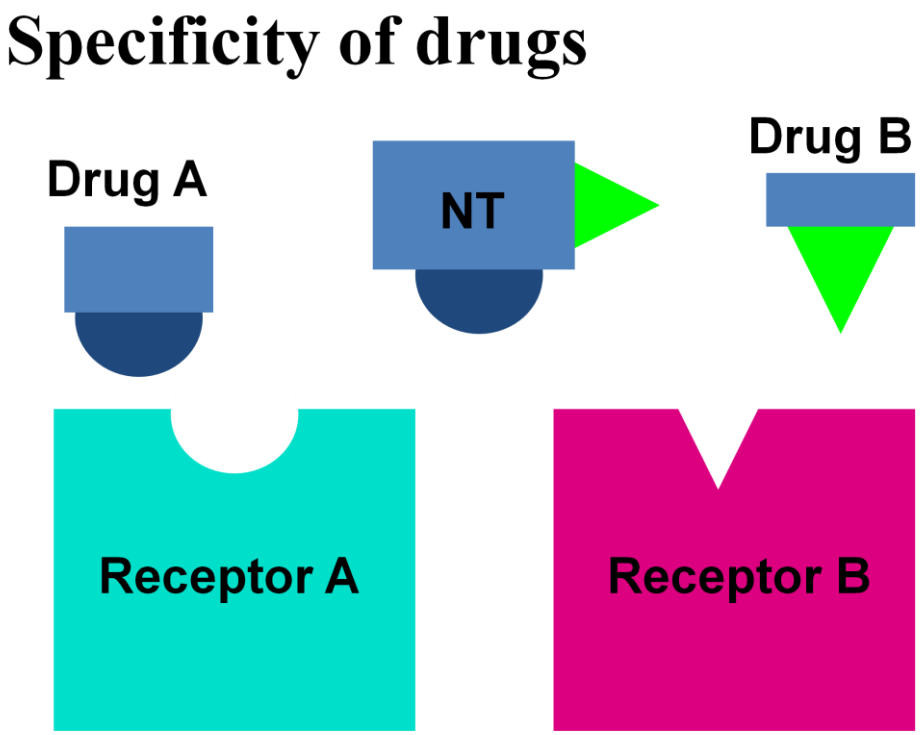


Specificity of Drugs…

The NT can bind to the receptors A & B... **But for drugs**:

Drug A can bind to receptor A only.

Drug B can bind to receptor B only.



How neurotransmitters are released..?

Action potential causes opening of voltage-gated Ca channels ➡ movement of vesicles toward the membrane ➡ fusion of these vesicles then release of NT in the synaptic cleft ➡ movement of the NT through the synaptic cleft to attach to the receptors on the postsynaptic membrane ➡ ACTION(through: either ionotropic channels "FAST"

or Metebotrobic G protein system "second messenger" ➡ "SLOW")

Five key steps in neurotransmission:

1. Synthesis of the NT (in cell body "neuropeptides" or terminals "small molecules")

⇩

2. Storage in vesicles

⇩

3. Release from vesicles

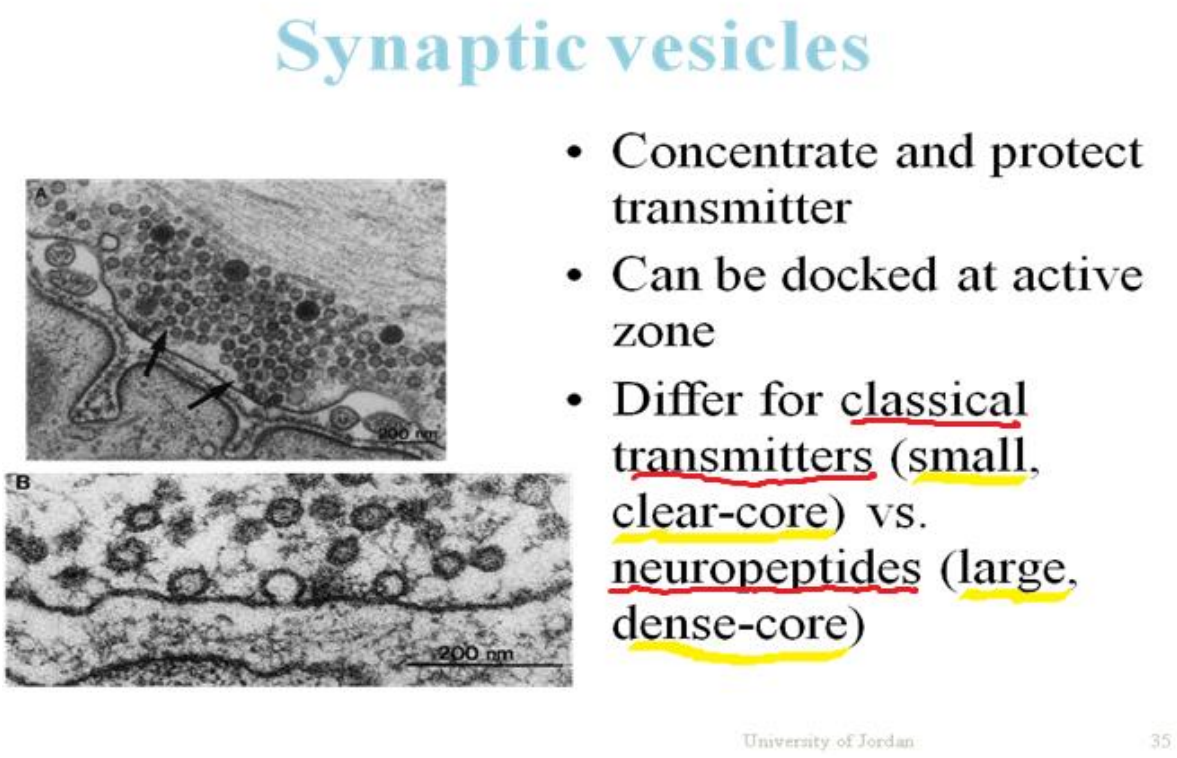
⇩

4. Bind to Receptor

⇩

5. The NT will be inactive by "Removal mechanisms"(like Diffusion, Enzymes, Uptake)

These are electron microscopic pictures where the vesicles are inside the membrane.



Neuropeptides/Neuromodulators : They are usually "co-secreted" with small molecules rapidly acting neurotransmitters.

Neurotransmitter **Co-existence**: Some neurons, in both peripheral and central nervous systems, **produce both classical NT and neuropeptides**.

REM: For each neuron there is only one type of small molecule rapidly acting neurotransmitter *BUT* you might have more than one type of Neuropeptides/Neuromodulators.

**Do we consider Epinephrine and Norepinephrine as two different classical neurotransmitters ??

NO, E and NE are one neurotransmitter and could be found in the same neuron.

NOTE: Neurons can release either classical NT or **both classical and neuropeptides (can't release only neuropeptides).**

*Neuromodulators: They modulate the action of the neurotransmitter in term of ***prolongation*** of the action.

*Classical NT (small molecules rapidly acting NT): causes ***fast*** action.

The Receptor determines whether the synapse is excitatory or inhibitory…

For instance, If it's coupled to Na "Excitatory"… if it's coupled to Cl "inhibitory".

Transmitter binding activates ion channel directly or indirectly:

Directly:

"Ionotropic channels ":

- FAST

-Ionotropic channels are for cations or anions

Indirectly:

"Metabotrobic Receptors"

-SLOW

- G protein system "second messenger "

Receptor Activation and Inactivation:

"Ionotropic Channels" :

- depend mainly on the presence or absence on the NT…

-**Mechanism: (very simple)**

NT bind to the channels ➡ they open. (ACTIVATION)
NT is broken down (by acetylcholinesterase for example) ➡ the channels close.(INACTVATION)

"Metabotrobic Receptors":

When we consider a cAMP dependent mechanism:

Activation: G alpha activates AC (Adenylate cyclase) to convert ATP to cAMP then cAMP activates PKA (protein kinase A) that might open the channel by phosphorylation.

Inactivation: is done by cAMP dependent phosphodiesterase which convert cAMP to AMP…then the action stops.

** Effects (End products of this mechanism):

A. Control channel.

B. Alter properties of receptors.

C. Regulation of gene expression.

'Second messengers like cAMP, Ca…'

NOTE: The first messenger is the NT.

REM: If the second messenger is Ca, there are:

1. "Ca/calmodulin"

2."Ca and DAG"

these two can activate proteins (like kinases) to get the effects.

G protein Mechanisms:

1. Direct control (NOT second messenger mechanism)

2. Second messenger mechanism.

Direct control:

Here, G protein is bound to a channel. G alpha subunit dissociate from beta and gamma subunits, then it (alpha subunit) opens or closes an ion channel.

It's faster than the second messenger mechanism and a little bit slower than ionotropic channels. So it's "Relatively Fast" mechanism as it's a (G protein system).

Second messenger mechanism:

Considering the example in the slides (48+49+50), which is a G protein coupled to activation of AC (Adenylate cyclase).G alpha activates AC to convert ATP to cAMP then cAMP activates PKA (protein kinase A) that might open the channel by phosphorylation. Note that the mechanism is slow, but it's not the slowest!

The slowest mechanisms are those that affect genes. Genes produce proteins and these proteins could be channels. For instance, under insulin effect, we want to increase the number of glucose transporters. In this case, insulin will affect genes causing production of new glucose transporters that will be transported to the cell membrane and then we will get an increase in glucose influx.

Transmitter Inactivation:

1. Reuptake by presynaptic terminal
2. Uptake by glial cells
3. Enzymatic degradation
4. **Presynaptic receptor (Remember alpha 2 adrenergic receptors on the postganglionic nerve teminals).**
5. Diffusion
6. Combination of above

Note: The Action potential goes in one way because there are no receptors for the NT on the presynaptic membrane. The receptors are on the postsynaptic membrane only.

Some Important Transmitters

1. Acetylcholine (Ach) 2. Monoamines 3. Amino Acids 4.Polypeptides"Neuromodulators" 5. Monoxide Gases (NO and CO)

1. Acetylcholine (Ach)

Acetylcholine is found in the presynaptic terminals. It's broken down by acetylcholinesterase into "choline" + "Acetate or Acetic acid".

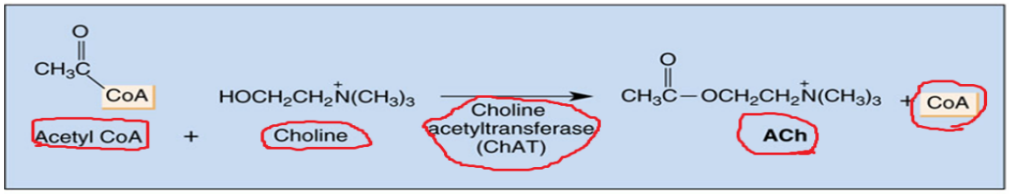
(Choline + Acetate or Acetic acid) might be reuptaken by "scavengers"/Macrophages or diffused or **reuptaken in the presynaptic terminals to be reused.**

Note: Ach "without breaking" can be **reuptaken** by "scavengers"/Macrophages or by **presynaptic terminals**.

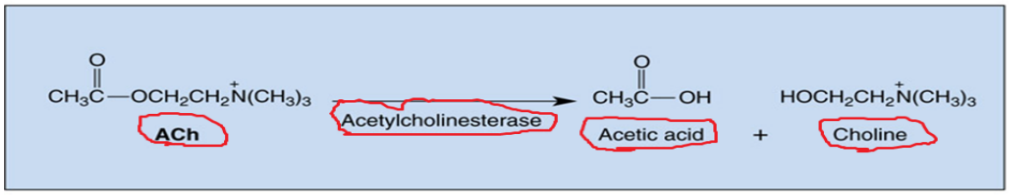
AchE present on postsynaptic membrane or immediately outside the membrane. **It prevents continued stimulation.**

---

*Ach synthesis and breaking down:



(a)



(b)

REM: Neuropeptides and "the vesicles" can't be reused.

Ach Receptors: (Cholinergic Receptors)

1. Nicotinic Receptors 2. Muscarinic Receptors

Ach is the NT at the preganglionic neuron in both sympathetic and parasympathetic.

Ach is the NT at the postganglionic neuron of the parasympathetic **<u>mainly</u>**.

- Nicotinic Receptors at the ganglia. (They are stimulated by Nicotine).

-Muscarinic Receptors at the neuro-effector junction.

Ach receptor is excitatory (in the GI) or inhibitory (Heart).

---

1. Nicotinic receptors:

-LOCATION:

1. (N1): -Found in **autonomic** ganglia. (sympathetic and parasympathetic).
   - Found in **Hormone producing cells in Adrenal medulla**
2. (N2): Found in skeletal muscles.(Motor endplate)

-Bound to Na channels."They are excitatory only"

-**Open on ligand binding.**

-Stimiulated by "Nicotine" and Blocked by "**Curare**".

Curare: is anesthetic drug.

---

2. Muscarinic receptors (M1-M5):

-LOCATION:

Found in smooth muscle and cardiac muscle cells and in the GI.

(All parasympathetic target organs and Some *sympathetic* targets (sweat glands))

-All coupled to G protein

-All stimulated by "Muscarine" and blocked by "**Atropine**"

M1:

MECHNISM: (Excitatory)

Phospholipase C ⇨ PIP2 ⇨ IP3 ⇨ 1. cytosolic Ca + 2. DAG

1+2 activate proteinkinase C which make phosphorylation.

M2:

MECHNISM: (Inhibitory)

Uses G protein that is coupled to K channels.

Cholinergic agonist:

Direct:

"Nicotine" & "Muscarine"

Indirect:

"Acetylcholinesterase" Inhibitors (Drugs that have stigmine).This causes prolongation of the action of Ach.

Cholinergic Antagonists:

"Atropine" & "Curare".

---

2. Monoamines: "They are produced from tyrosine"

A. Catecholamines (all from the precursor L-dopa)

Dopamine - DA

Norepinephrine – NE

Epinephrine – E

They are broken down by "monamineoxidases**".

NOTE: -Norepinephrine and epinephrine differ only in a **methyl group**

-Norepinephrine + methyl= **epinephrine. This is process uses *" methyltransferase*".**

B. Indolamines

Serotonin - (5-HT)

(5-HT)= 5-hydroxytryptamine.

Monoamines Recepotrs: "Adrenergic Receptors"

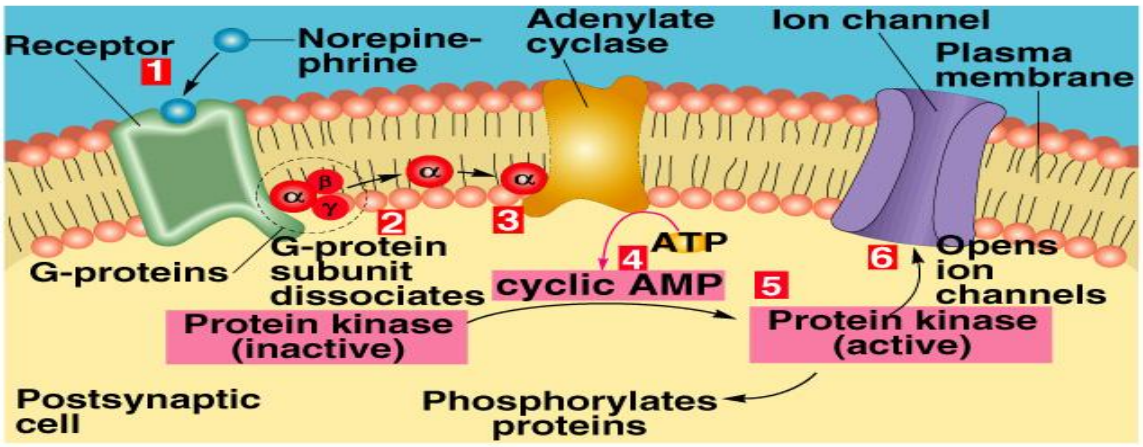
-Alpha (1 and 2).

-Beta: B1 in the heart.

B2 in the lungs.

THE Mechanism of "B receptors"

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



"

NE bind to the receptor activating Gs ⇨ activates AC ⇨ converts "ATP" to "cAMP" ⇨ activates Protein kinase A which activates many proteins (Like ion channels "Ca channels").

REM: Norepinephrine and epinephrine are the NT at the postgnglionic neuron of sympathetic nervous system.

Alpha 1 receptors cause:

A. Vasoconstriction

B. Sphincter constriction

C. Pupil dilation.

Alpha 2:

-Inhibition of NE release

Beta 1:

-In the heart

-Increases the heart rate (**Positive Chronotropic**)

-Increase contractility (strength of contraction)**(Positive Inotropic)**

-Positive Dromotropic.

Beta 2:

-In the lungs.

-Bronchodilation.

---

3. Amino Acids:

A-Glutamate acid and aspartate(aspartic) acid:

Excitatory Amino Acid (EAA) (found in the cerebral cortex)

B-Gamma-amino-butyric acid (GABA):

Inhibitory Amino Acids.

**They are coupled to Cl channels.

Remember that the resting membrane potential is roughly equal to the equilibrium potential of Cl. Then, if Cl channels open we don't get Cl influx and the membrane potential doesn't change (no hyperpolarization)…

How Cl channels are inhibitory ??

When another channels open, like Na channels, the membrane potential is changed (more positive inside the cell) then Cl ions enter and their effect is contrary to Na ions (increase the negative charge inside). So Cl ions prevent getting action potential "Inhibitory".

4.Polypeptides "Neuromodulators"

-CCK (Cholecystokinin)

5. Monoxide Gas (NO and CO)

-These NTs don't have receptors because they are lipid soluble-they pass through the postsynaptic membrane- (They are gases).

-They enter the postsynapticneuron and change the metabolism.

(NO):

-Exerts its effects by stimulation of cGMP.

-Involved in memory and learning.

-Smooth muscle relaxation.

REM: we divide the "small molecules rapidly acting NT" into 4 classes:

-Acetylcholine.
-Amines (like E & NE)
-Amino Acids.
-Nitric oxide (NO).

#سامحونا إذا في أخطاء...

Good Luck Good Luck Good Luck!