



physiology
premed 2018 - JU



Sheet

Slides

Number

12

Done by:

Hadeel Abdullah and Sara Basel

Corrected by:

Hadeel Abdullah and Sara Basel

Doctor

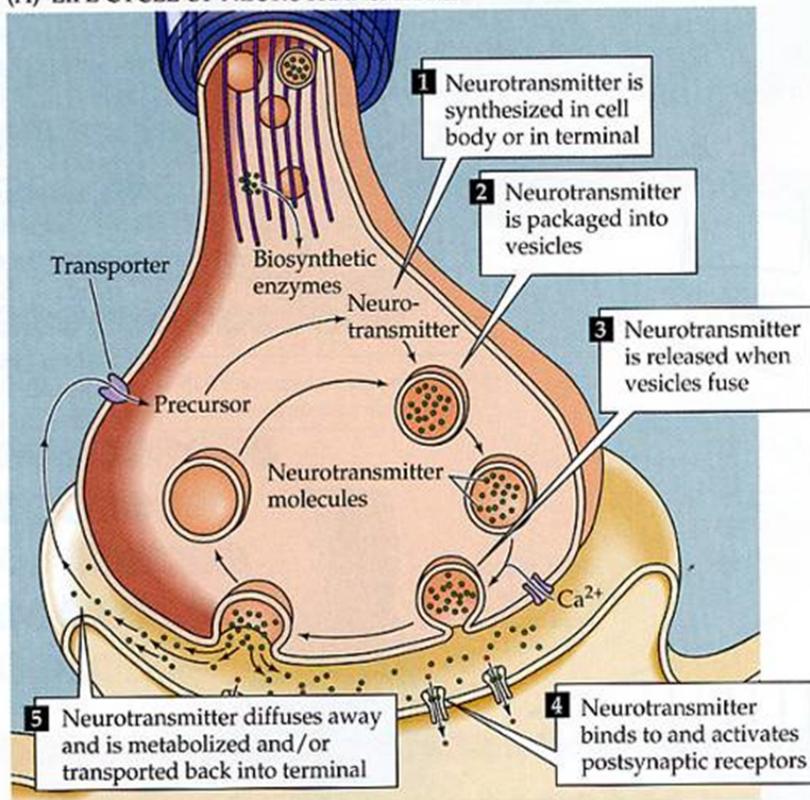
Faisal I. Mohammed

Neuron types and Neurotransmitters

Five key steps in neurotransmission:

- ✓ Synthesis in presynaptic neuron.
- ✓ Storage in vesicles.
- ✓ Release into the synaptic cleft.
- ✓ Binding to receptors on postsynaptic membrane.
- ✓ Inactivation or removal.

(A) LIFE CYCLE OF NEUROTRANSMITTER



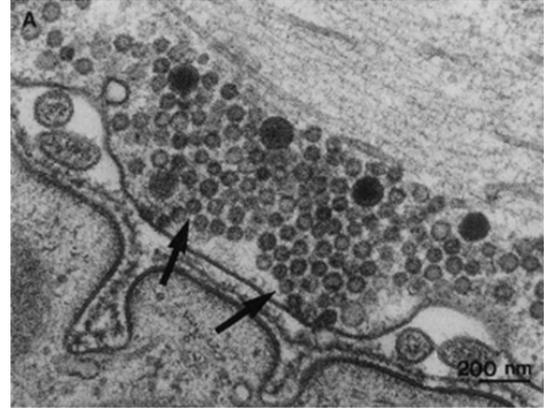
❖ **RECALL:**

<i>Comparison</i>	<i>Neurotransmitters</i>	<i>Neuropeptides</i>
<i>Activity</i>	<i>Fast acting</i>	<i>Slow acting</i>
<i>Response</i>	<i>Acute response</i>	<i>Slow response</i>
<i>Duration</i>	<i>Short term response</i>	<i>Prolonged action</i>
<i>Synthesis</i>	<i>In the Cytosol of presynaptic neuron terminals</i>	<i>Rough ER Golgi apparatus</i>
<i>Concentration</i>	<i>Synthesized in high concentrations</i>	<i>Synthesized in low concentration</i>
<i>Location</i>	<i>Only found in the axon terminals of presynaptic neurons</i>	<i>Found all over the neuron</i>
<i>Stored in</i>	<i>Small Clear core vesicles</i>	<i>Large dense core vesicles</i>
<i>Release</i>	<i>Released within few milliseconds upon an arrival of an action potential</i>	<i>Occurs in few cm/day</i>
<i>Cytosolic Ca⁺² concentration</i>	<i>Low frequency firing causes small [Ca⁺²] inside the axonal terminal</i>	<i>High frequency firing causes high [Ca⁺²] inside the cell</i>
<i>Released with</i>	<i>Released individually depending on the action potential</i>	<i>Released to the synaptic cleft along with another small molecule neurotransmitters</i>
<i>Potency</i>	<i>Less potent compared to neuropeptides</i>	<i>1000 times more potent than neurotransmitters</i>

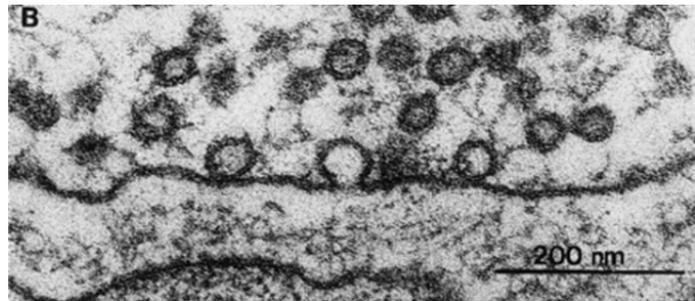
- **G-proteins:** guanine nucleotide-binding proteins, each is made up of three subunits (α , β and γ). When they are bound to GTP, they are 'on' (activated), and when they are bound to GDP, they are 'off' (inactivated).
- When a ligand binds to a G-protein coupled receptor (GPCR); the GPCR is activated and causes the G-protein to exchange GDP for GTP. Then G- protein separates into two pieces one is **the α subunit which interacts with other proteins causing cellular response**, and the other consisting of the β and γ subunits.

Synaptic vesicles

- ❖ **Classical neurotransmitter** are synthesised and packaged locally in synaptic vesicles in the cytosol of the **axon terminal** for protection. These chemical messengers are primarily amino acids or closely related compounds (derived from amino acids).



- ❖ **Neuropeptides** are larger molecules made up from amino acids. They are synthesized in the ER and Golgi complex of the neuronal cell body (**SOMA**) and are moved by "**axonal terminal**" (slow).



- ❖ **Neuropeptides** are NOT stored in small synaptic vesicles with the classical neurotransmitters but instead are packaged in large, **dense-core** vesicles, which are also present in the axon terminal. The **dense-core** vesicles undergo Ca^{+2} -induced exocytosis and release neuropeptides at the same time that the neurotransmitter is released from the synaptic vesicles.

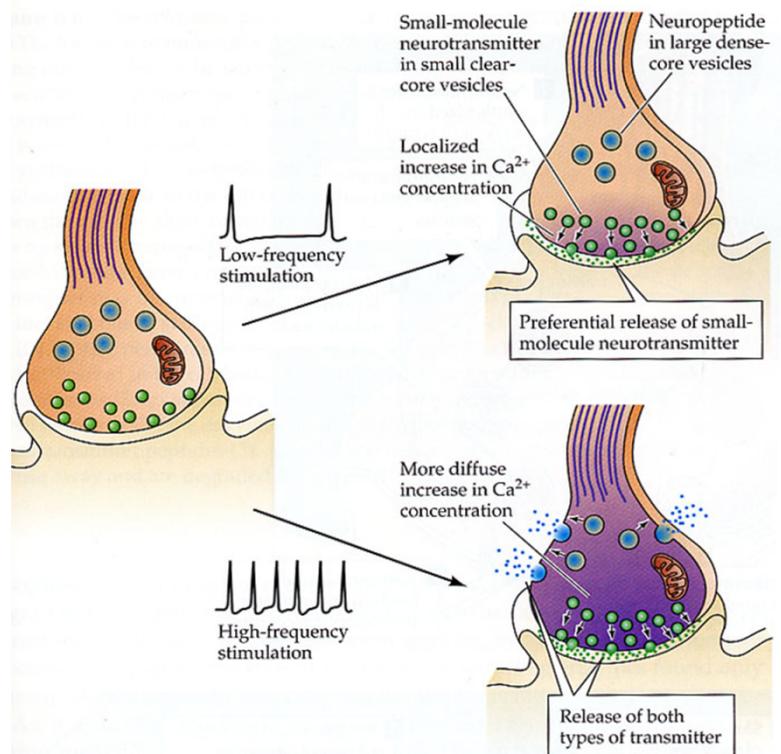
To Sum Up:

- ✓ Synaptic vesicles concentrate and protect transmitter, can be docked at active zone.
- ✓ They differ for classical transmitters (small, clear-core) vs. neuropeptides (large, dense-core).

Neurotransmitter co-existence (Dale Principle)

- ❖ Some neurons in both the PNS and CNS produce both a classical neurotransmitter (ACh or a catecholamine) and a polypeptide neurotransmitter.
- ❖ They are contained in different synaptic vesicles that can be distinguished using the electron microscope.
- ❖ The neuron can thus release either the classical neurotransmitter or the polypeptide neurotransmitter under different conditions.
- ❖ Most neuropeptides function as **neuromodulators**; which means that they don't cause the formation of EPSPs or IPSPs but rather bring about long-term changes that subtly **modulate** (depress or enhance) the action of the synapse.

- The figure shows differential release of neuropeptides and small-molecule transmitters. Low-frequency stimulation raises the Ca^{2+} concentration close to the membrane, favoring the release of transmitter from small **clear-core** vesicles docked at presynaptic neuron. High-frequency stimulation leads to a more general increase in Ca^{2+} , causing the release of neuropeptide transmitters from large **dense-core** vesicles as well as small-molecule neurotransmitters from small **clear-core** vesicles.

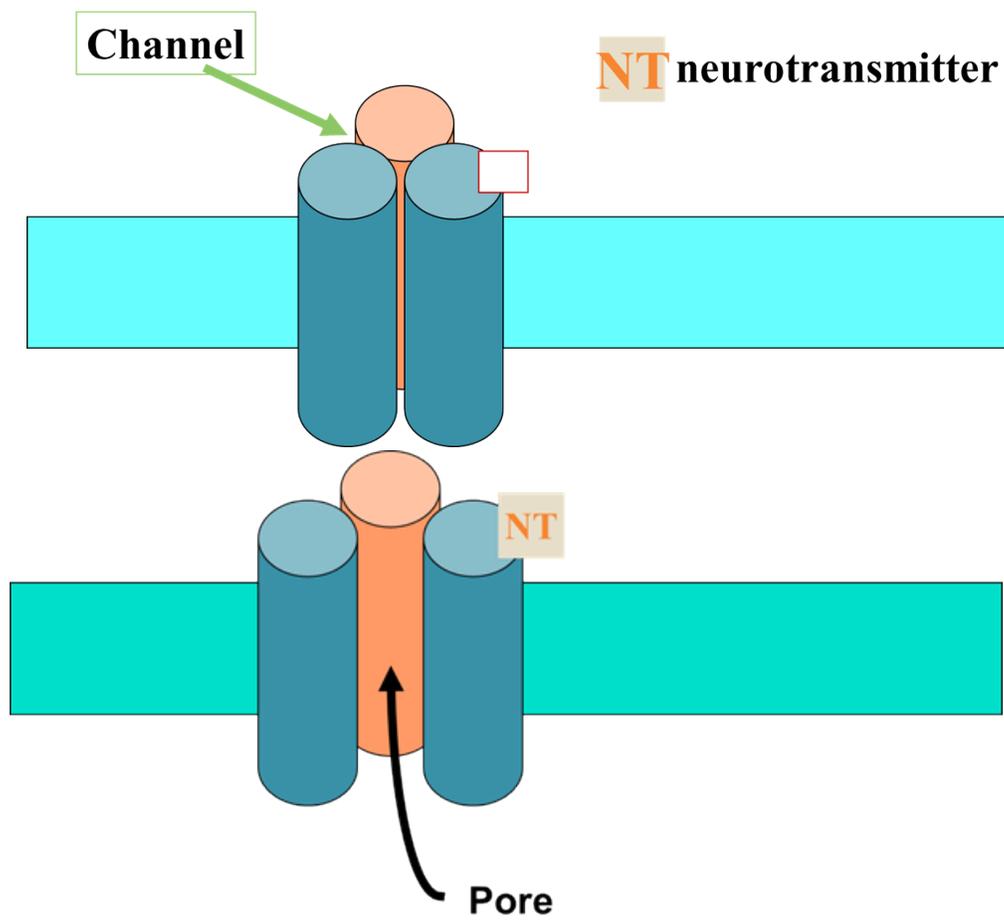


Receptor Activation

After neurotransmitters are released into the synaptic cleft, they diffuse until they reach the postsynaptic membrane. There, they bind with either directly through to ionotropic receptors (fast), or indirectly to metabotropic receptors (G-protein coupled and slow).

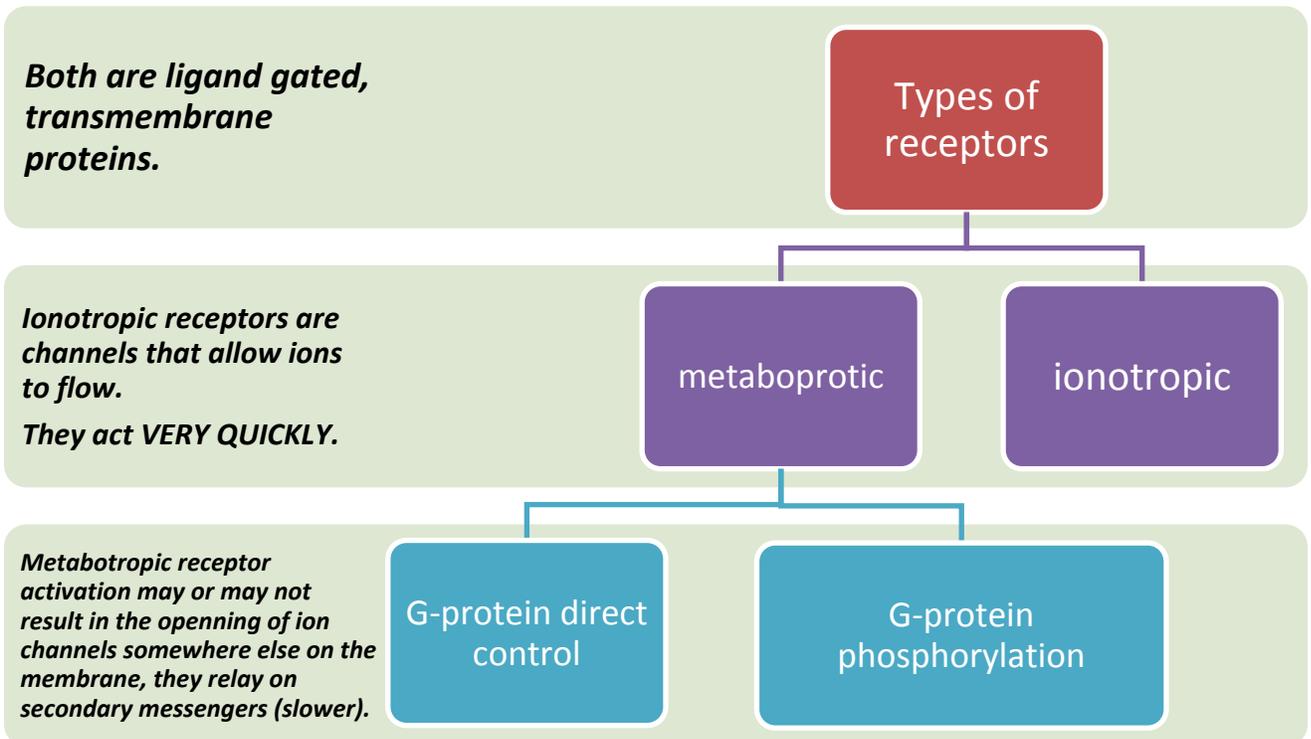
❖ ***Ionotropic receptors: FAST and DIRECT.***

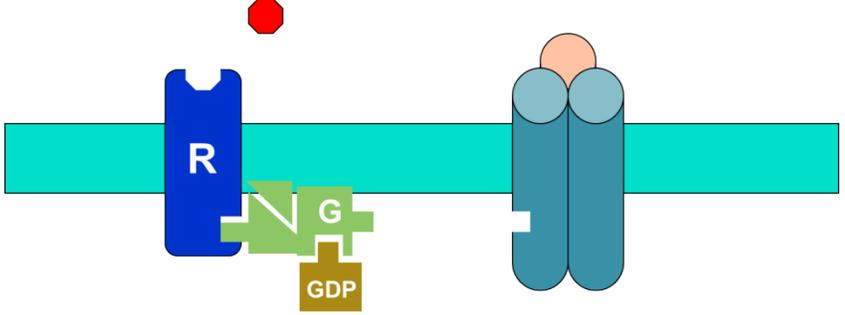
- ✓ *Ionotropic receptors are transmembrane molecules, they can “open” or “close” a channel that would allow smaller particles to travel in and out of the cell.*
- ✓ *As the name implies; **ION**otropic receptors allow different kinds of ions to travel in and out of the cell*



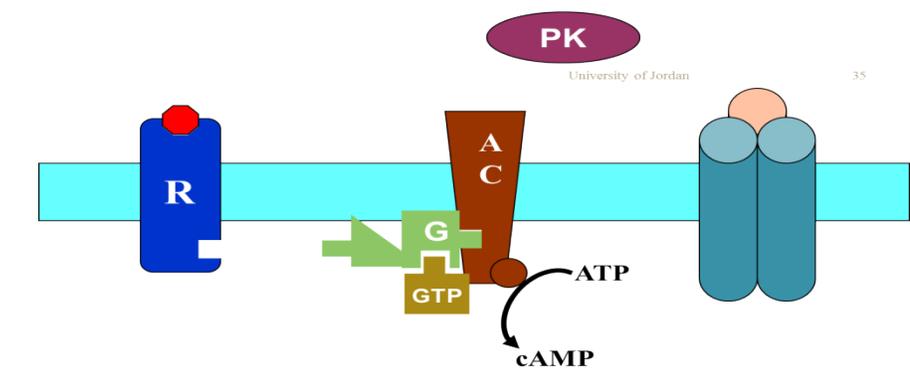
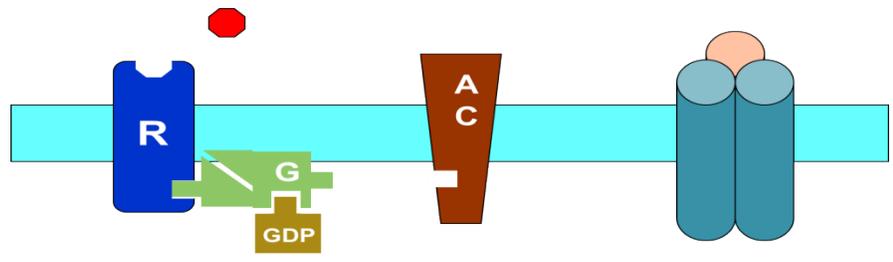
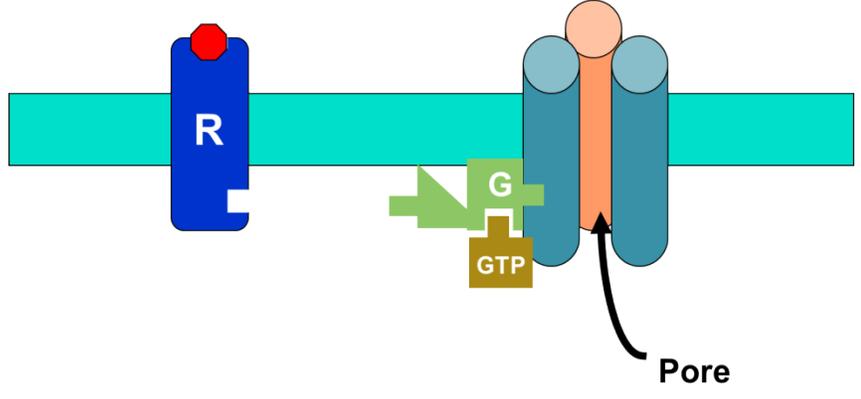
❖ *Metabotropic receptors:*

- ✓ *Metabotropic receptors do not have a “channel” that opens or closes (the effector channel is separated from the receptor). Instead, the receptor is activated by a neurotransmitter, and then it undergoes conformational change, exposing a binding site for the G-protein complex (alpha subunit).*
- ✓ *G-protein activation MAY cause the opening of specific ion channels; these channels stay open for prolonged time in contrast to rapid closure of directly activated ion channels that don't use the second messenger system (ionotropic).*
- ✓ *G-protein MAY ALSO activate an enzyme like adenylyl cyclase that converts ATP to cAMP which activates “Protein Kinase” that phosphorylates the channel causing change in its conformation.*

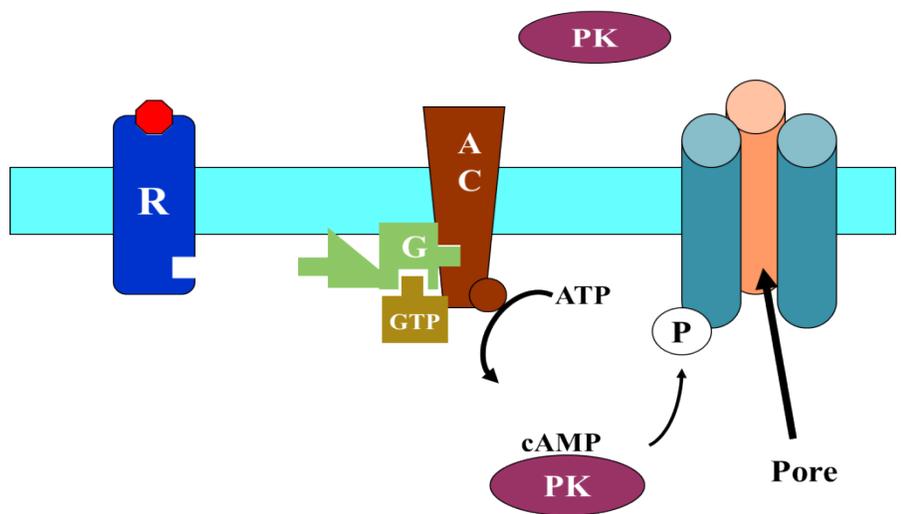




G-PROTEIN DIRECT CONTROL



G-PROTEIN PHOSPHORYLATION



***Transmitter inactivation:**

❖ Several mechanisms can remove neurotransmitter from the synaptic cleft, it may diffuse away from the synaptic cleft, be inactivated by specific enzymes within the subsynaptic membrane, or be actively taken back up into the axon terminal by transport mechanisms in the presynaptic membrane:

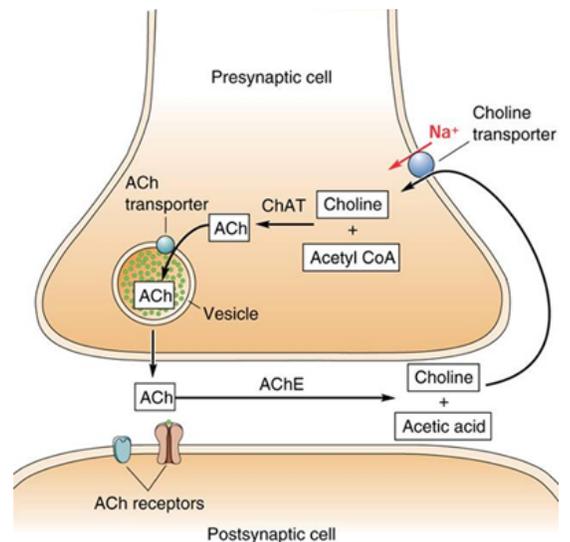
1. Reuptake by presynaptic terminal.
2. Uptake by glial cells.
3. Enzymatic degradation.
4. Presynaptic receptor.
5. Diffusion.
6. Combination of above.

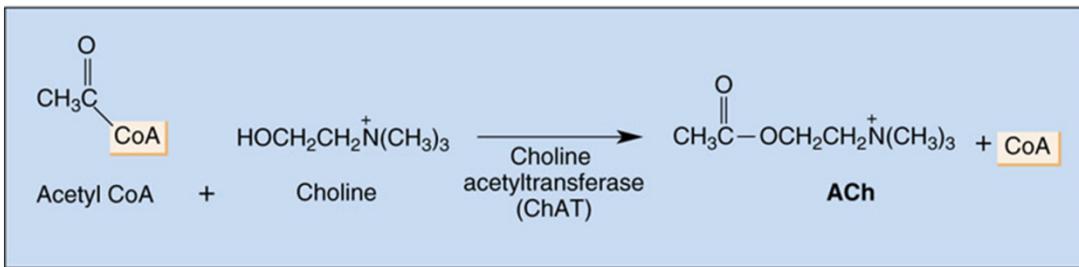
***Acetylcholine (ACh) – Synthesis and Inactivation:**

-Acetylcholine is a typical small-molecule transmitter it is synthesized in the presynaptic terminal from acetyl coenzyme A and choline in the presence of the enzyme “choline acetyltransferase (ChAT)”. It is then transported into specific vesicles.

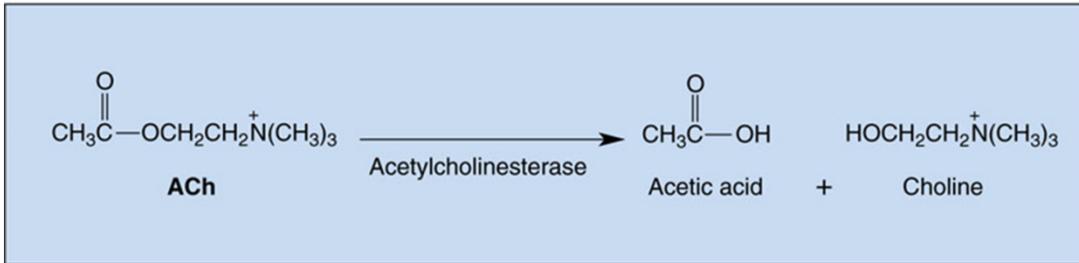
-When the vesicles release the acetylcholine into the synaptic cleft during neuronal transmission, the acetylcholine is rapidly split again to acetate and choline by the enzyme “acetylcholinesterase (AChE)” which presents on postsynaptic membrane or immediately outside the membrane (it prevents continued stimulation).

-Then once again, inside the presynaptic terminal, the vesicles are recycled, and choline is actively transported through transporters on the presynaptic membrane -through co-transporters (secondary active transport)-back into the terminal to be used again for synthesizing acetylcholine.





(a)



(b)

****Drugs Specificity:***

- ❖ *Same NT can bind to different receptors, because they have different binding domains.*
- ❖ *Drugs act selectively.*
 - *For clarification, beta adrenergic agonists or beta agonists are medications (drugs) that result in easier breathing. They are a class of sympathomimetic agents which act upon the beta adrenoreceptors in the heart, lungs, and smooth muscles.*
 - *For example, a patient with low heart rate is given beta agonist treatment that is "cardio-selective" (Beta 2 agonist) which increases the force of contraction of the heart muscle.*

Again, the example above shouldn't be learnt by heart but is for clarification ONLY.

