◉Sheet ○Slides

Number

16

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Revision:

What are the basic types of neurons?

sensory (afferent), motor (efferent) and interneuron (equaled association neurons).

We classified the neurotransmitters to two types; can you figure them out? What about their subtypes?

1)small molecules, (rapid reacting neurotransmitters) and it has many classes (subtypes):

a) acetylcholine

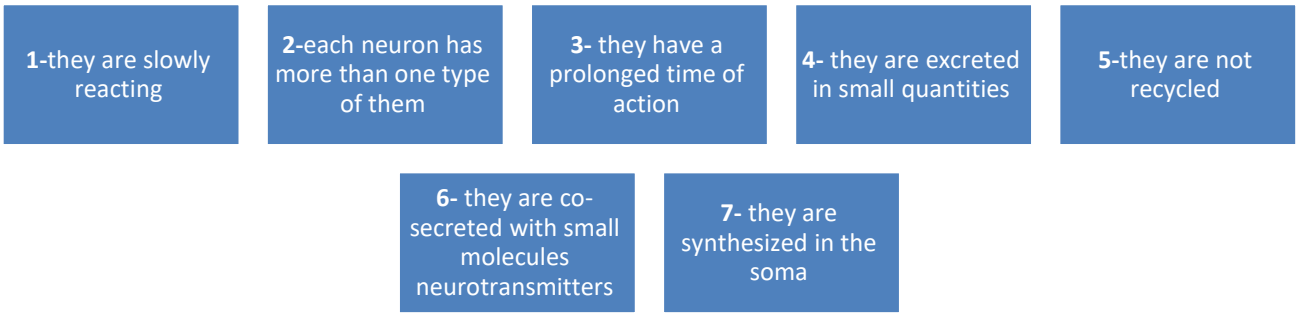
b) amines, which amino acid are they derived from? *

c)amino acids: Glycine, aspartate, glutamine, gamma-aminobutyric acid (GABA) which is an inhibitory neurotransmitter.

d)Gases: such as nitric oxide and carbon monoxide. What do you think is special about gases? #

Notice that their vesicles are recycled because some of them are reuptaken (both the vesicles and NT are reabsorbed) **plus that** the enzymatic machinery for the formation of the small molecules neurotransmitters are found in the presynaptic terminals.

2)polypeptides (neuropeptides or neuromodulators **because** they modulate the act of peptides) and their characteristics are:



***note**: any peptide in the nervous system can act as a neuromodulator.

neuropeptides are synthesized in the soma and are secreted from the presynaptic terminals, **how?** They are transported by axonal transport which is very slow (2 millimeters per day). Also, their formation needs a lot of energy that's why they are secreted in smaller quantities compared to small molecule neurotransmitters.

That's why vesicles of NP are not recycled, We don't have their enzymes in the terminals

*Tyrosine # lipid soluble and fast diffusion

HOW NEUROTRANSMITTERS ARE SECRETED?

By The process of NEUROTRANSMISSION:

1- When the action potential reaches the presynaptic terminals it causes voltage gated calcium channels to open, Ca^{2+} will move into the terminals according to the **electrochemical gradient** by diffusion**.**

2-The increase in the intracellular calcium causes movement of the vesicles (containing neurotransmitters) toward the membrane and fuse with it, after that, the vesicles release their content of neurotransmitters into the synaptic cleft.

3-Neurotransmitters move to the postsynaptic membrane where they bind to their receptors.

Binding of the neurotransmitters to the receptors changes the permeability of certain channels, **accordingly,** if the binding causes Na^+ channels to open, there will be a **depolarization** on the postsynaptic membrane, this state is called **excitation** (less negative=> closer to threshold). Since it occurs in the postsynaptic membrane we call it **excitatory post synaptic potential** (because it is on the postsynaptic membrane).

Similarly, if the receptors are bound to K^+ channels or Cl^- channels, what do you think will happen?
K^+ => efflux => hyperpolarization => **IPSP**
Cl^- => influx => inhibition **Why not hyperpolarization?**
Because the membrane potential is similar to Cl equilibrium potential, However, if we have Na^+ influx, Cl will inhibit any change in the potential.

Finally, the NT will be inactivated by:

1)diffusion: the neurotransmitter might diffuse into the interstitial fluid (moving down their concentration gradient).

2)Enzymatic degradation: every neurotransmitter has enzymes that break it down, these enzymes are found on the postsynaptic membrane **[they are peripheral membrane proteins]**, for example:

the acetylcholine => acetylcholinesterase.

Epinephrine and norepinephrine: catechol-O-methyl transferase(COMT) and monoamine oxidase (MAO).

3)Reuptake: by neurons terminals (to be reused in the vesicles) or glia cells (cells around the neurons).

Examples:

1-after acetylcholine is broken down by acetylcholinesterase into choline and acetyl CoA, choline is reuptaken and then reused.

2-peptides are broken by peptidases

Now you should be able to answer this, what would you do to prolong the effect of a neurotransmitter? You simply inhibit its enzyme by a drug (this is one of many ways).

For example:

1-Prozac (a drug used for psychiatric patients) is a selective serotonin reuptake inhibitor.

2- Or you might use a drug that breaks down the neurotransmitter to stop the cycle, stopping the cycle is very important such as in **Epilepsy**

الصرع= Epilepsy

Note: in **Epilepsy** (which causes contraction of the muscles due to stimulations from the brain) if the cyclic AMP remain in the brain the muscles will stay contracted and that causes death. So, we must break down the cycle, **HOW? acetylcholine is broken down by cholinesterase and the cycle is finished.** (the doctor didn't mention them in section 1, so it's an additional information)**.**

you didn't understand anything? watch this=> https://www.youtube.com/watch?v=e_Eb32Eq_fw

0:00-21:00 was a revision!!

Basic Concepts of Neurotransmitters and Receptors

Neuroreceptor: Proteins on the cell membrane or in the cytoplasm that could bind with specific neurotransmitters and alter the behavior of neurons of effector cells**.**

Neurotransmitters: Endogenous signaling molecules that alter the behavior of neurons or effector cells.

Endogenous: exist inside the body naturally.

NOTE: there are no receptors for a substance that does not exist naturally inside the body, **however,** a substance from outside the body **(not endogenous)** can bind to the receptor only if this substance is similar to another endogenous substance in morphology (shape).

Where does the receptor exist?

It depends on the type of the neurotransmitter

water soluble NT=> won't enter the cell => receptors are on the membrane.

lipid soluble NT => enter the cell => receptors are inside the cell (in the cytoplasm or on the nucleus).

Don't forget that receptors are specific…

Is acetyl choline neurotransmitter excitatory or inhibitory?

The receptor determines whether the neurotransmitter is excitatory in that area or inhibitory NOT the neurotransmitter itself, for example:

Acetylcholine receptors of the parasympathetic system **in the heart** is **inhibitory** because it lowers the heart rate [bradycardia].

In the gastrointestinal system (GI), it increases the GI movement (stomach, intestine) and it increases the secretion, so it is **excitatory** in the GI. *Although it is the same neurotransmitter but its receptors in the heart are different to its receptors in the GI.*

Neurotransmitter (a classical definition):

1-The neurotransmitter should be synthesized in the presynaptic terminals and after that it must enter the vesicles (it is important to protect it)

2-Neurotransmitters have the same effect whether they are synthesized internally or administrated externally and that is important in drugs, **for example:**

a- if someone suffers from colic (which result from increase movement in the GI) we give him a drug (Buscopan) which blocks acetylcholine receptors in the GI.

b-if we want to increase the movement in the GI we give the patient a drug that contains acetylcholine.

3-neurotransmitters must be blocked by same drugs that block synaptic transmission.

4-they must be removed in specific ways (we mentioned them earlier)

5-they must be found in the presynaptic terminals.

 Colic= مغص

Agonist and Antagonist:

Agonist: a substance that mimics a specific neurotransmitter, and it can attach to that to that neurotransmitter's receptor, and thereby produces the same action that the neurotransmitter usually produces.

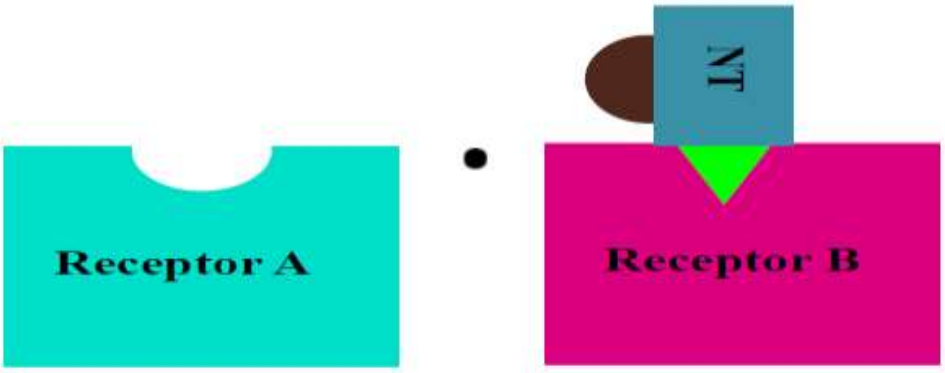
NOTE: drugs are often designed as receptor agonists to treat a variety of diseases and disorders when the original chemical substance is missing or depleted.

Example: when we give a patient a drug to increase the GI movement, its action is similar to acetylcholine, so we call it **parasympathomimetic** or **parasympathetic agonist [**it has the same action as acetylcholine or the parasympathetic system**]**

Antagonist: drugs that bind to but do not activate neuroreceptors, thereby blocking the actions of neurotransmitters or the neuroreceptor agonists.

Example: when someone is suffering from **hypertension** (high blood pressure), we give him alpha antagonist **[because alpha receptors causes vasoconstriction]** so we block the action of alpha neurotransmitters.

Note: the same neurotransmitter can bind to more than one receptor [In other words, a NT have more than one binding site for different receptors].

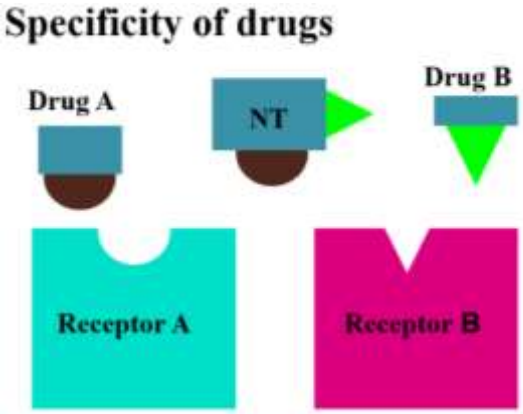


Accordingly, we might invent blockers (antagonists) for one of the receptors that bind to a specific binding site**.** In this case, we say that we have s**electively inhibited** that receptor.

Example: beta receptors (ADRENOGENIC sympathetic system receptors):

Beta-1 receptors are found in the heart,

beta-2 are found in the lungs, we sometimes may need drugs that work on the lungs and **not** on the heart, so we have **beta-2 agonist** [it is selective], **however,** we might use an antagonist that works on all beta receptor **[**in this case it is **not selective]**.



This slide shows:
1- Nt that bind to both receptors A and B
2- We can synthesize a blocker for receptor A only or receptor B only, So we can control the effect on specific organs.

Five Key Steps in Neurotransmission (what should NT have):

1-**Synthesis:** neurotransmitters are synthesized in cell body or terminals.

2-**Storage:** neurotransmitters are packaged into vesicles.

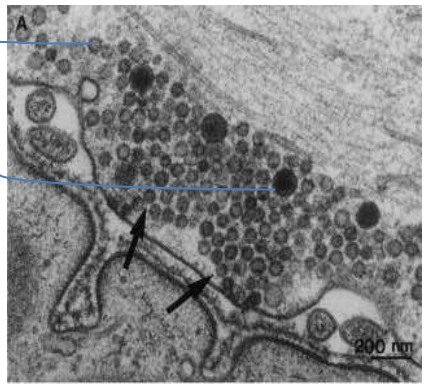
3-**Release:** neurotransmitters are released when the vesicles fuse.

4-**Receptor binding:** neurotransmitters bind to and activate post-synaptic receptors.

5-**Inactivation:** neurotransmitters diffuse away, are metabolized or transported back into terminals.

Synaptic vesicles:

*Vesicles of the small molecules neurotransmitters [small, clear-core] are different from the vesicles of neuropeptides neurotransmitters **[large, dense-core].**



*the importance of vesicles: they concentrate and protect neurotransmitters.

*vesicles can be docked at active zone.

Neurotransmitters Co-existence (Dale principle):

- Neurons in both the parasympathetic and sympathetic produce **1** classical neurotransmitter (ACh or a catecholamine) and **1 or more** polypeptide neurotransmitters.

*they are contained in different synaptic vesicles that can be distinguished using electron microscope (as previously shown).

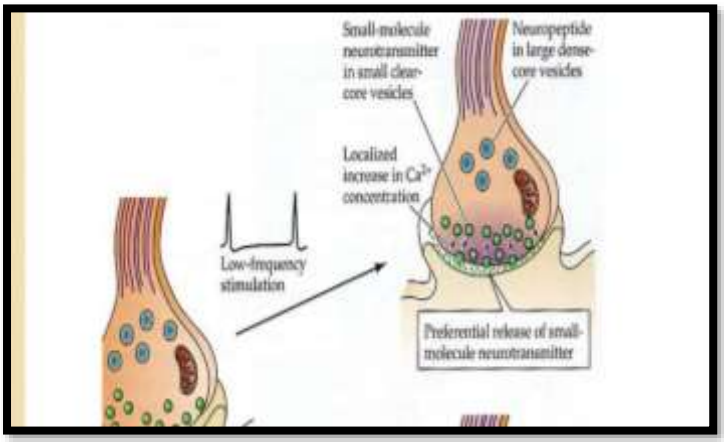
The neuron can thus release either the classical neurotransmitter or both the polypeptide and small molecule neurotransmitter under different conditions.

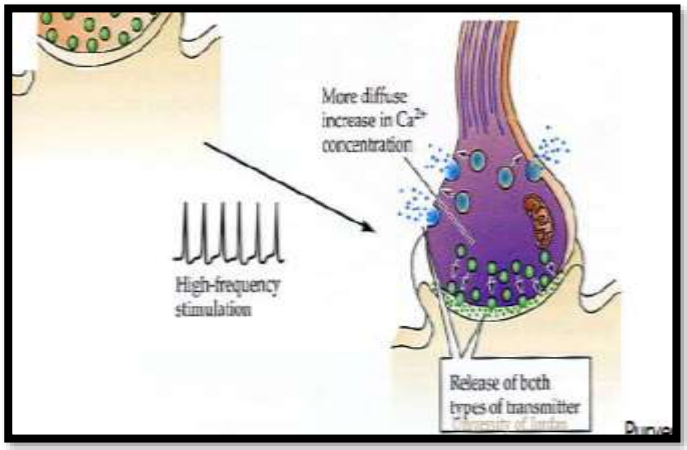
For the thousands time…… any neuron contains only <u>one type of classical neurotransmitters.</u> BUT it might have one or more <u>neuropeptide</u>

Neuropeptides are not secreted alone, they are <u>co-secreted</u> with the classical neurotransmitter.

Hmmm, when do you think neuropeptides are secreted?

It depends on the frequency of the stimulus and on the type of the stimulus , if the rate (frequency) of the stimulation is low (for example: if every 10 millisecond we have an action potential , the rate per second will equal 100 ⟹ [1000/10]) , then the neurotransmitter, which is secreted, is only the classical neurotransmitters <u>BUT</u> if the rate was 500 , classical **<u>plus</u>** polypeptide neurotransmitters are secreted.





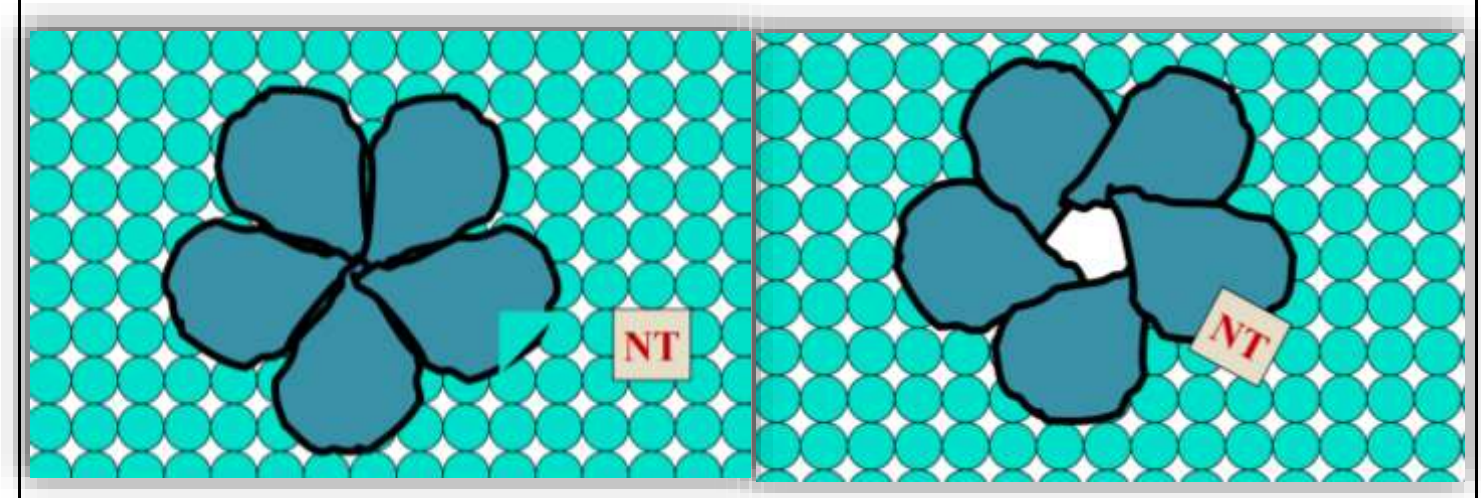
- Synapses are either excitatory or inhibitory
- that is determined by the **receptors** of the neurotransmitters (the type of channels) and there are two kinds of receptors:

1-**Ionotropic receptors:** receptors are connected **directly** to ion channels. **<u>They are fast</u>**.

2-**Metabotrobic 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.**

Receptor activation:

Ionotropic: directly and it is fast, when a neurotransmitter binds to the receptor, the channels inverses its conformation (if it was open, it becomes closed and vice versa). **So, the binding of the NT changes the permeability of the channel.**



Before binding (closed)

After binding (opened)

Metabotropic receptors: it uses G-protein system, G-protein uses a second messenger and it might be (c-AMP, c-GMP, calcium, calmodulin, phospholipids….)**.**

What is the first messenger? It's the Neurotransmitter.

Remember that:

adenylyl cyclase converts ATP into c-AMP/ Guanylate cyclase convert GTP into c-GMP.

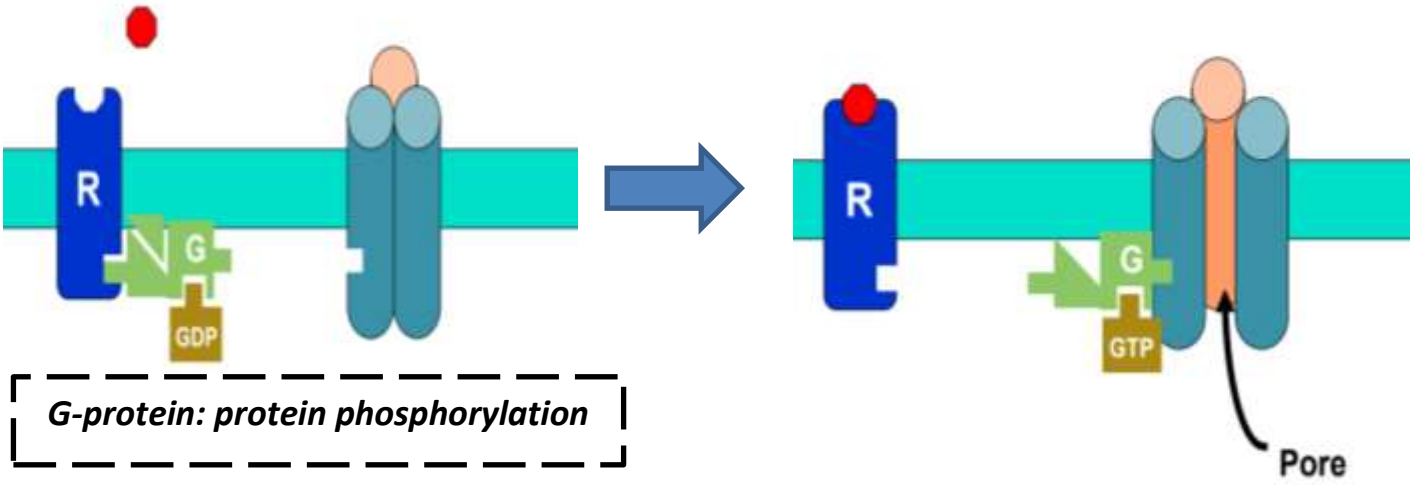
G-protein is a membrane protein and it consists or 3 subunits: **alpha, beta, gamma.** When there is no stimulation the three subunits are found together. **However**, when a neurotransmitter binds to a metabotropic receptor **alpha subunit dissociates.**

Effects of metabotropic (mentioned in the slides)

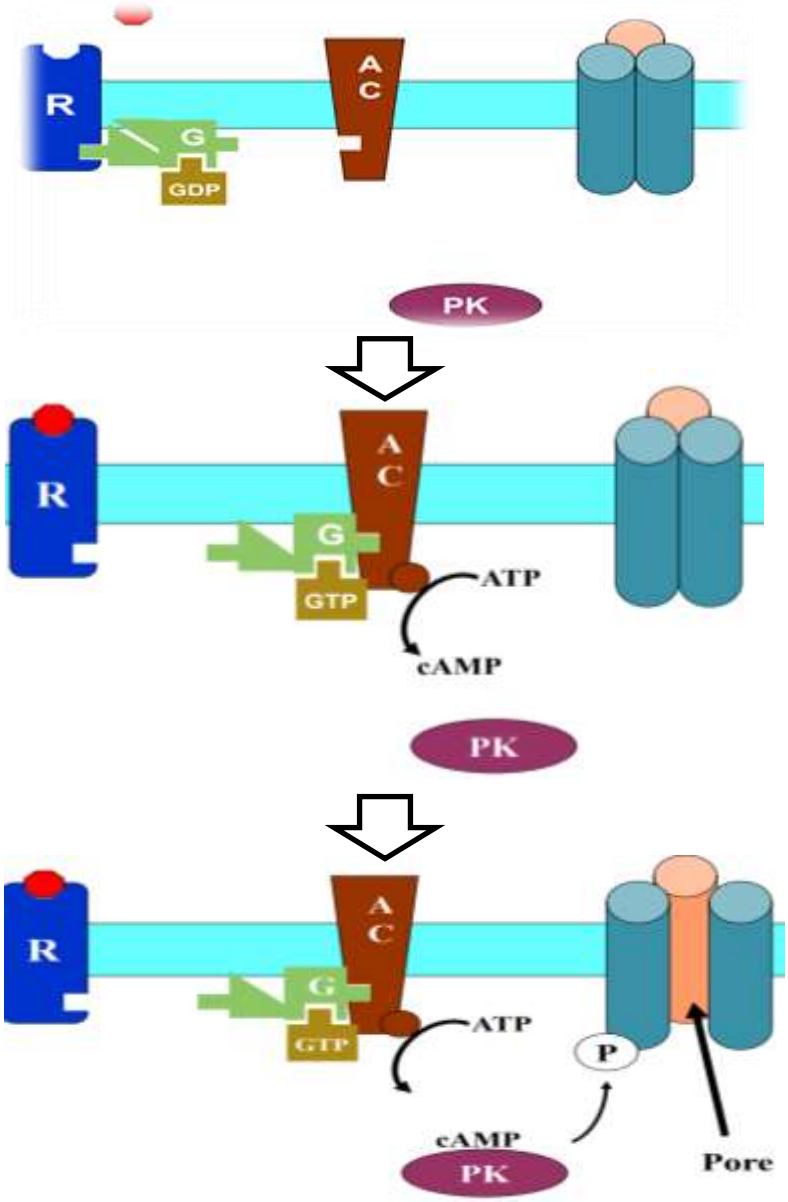
1-control channel. 2-alter properties of receptors. 3-regulation of gene expression

G-protein: direct control

Binding of the neurotransmitter to the receptor activated the G-protein, that causes the channel to open [direct control] (relatively fast)



G-protein: protein phosphorylation



1-Binding of the neurotransmitter to the receptor, causes dissociation of alpha subunit.

2- Alpha subunit activated enzyme <u>adenylyl cyclase</u>, the enzyme converted ATP to C-AMP

3- c-AMP stimulates the protein kinase (c-AMP dependent protein kinase) which is also called Protein kinase (A) which is a specific protein.

When the protein kinase gets activated, it opens the channel.

(slower than g-protein direct control)

(the slide shows only alpha subunit)