MEDICINE
KING SAUD UNIVERSITY

7- Receptors families

Objectives:

- Classify receptors into their main super families
- Recognize their different transduc5on mechanism
- Iden5fy the nature & 5me frame of their response

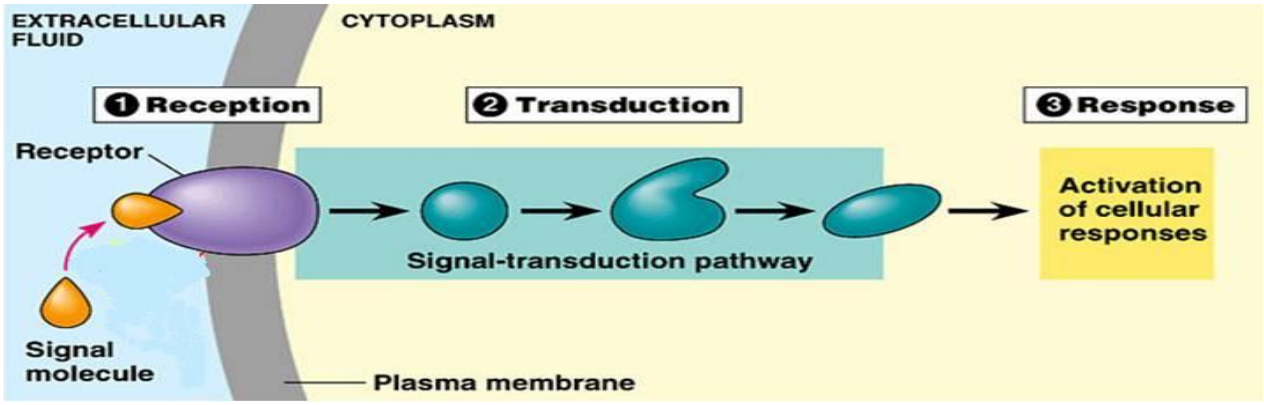
Success is falling nine times and getting up ten

Titles
Very important
Extra information
Terms

Pharmacology team 436

Receptors:

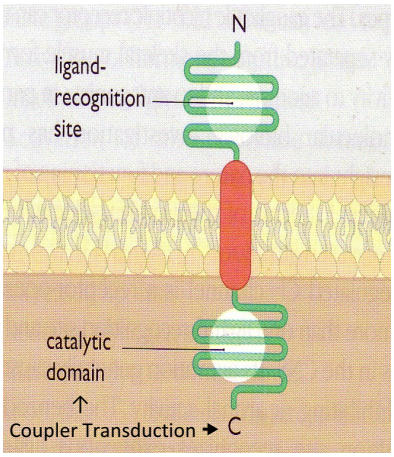
1. Recognition 2. Reception 3. Transduction 4. Response



Receptor structure:

1- Ligand recognition site

2- Inner catalytic domain



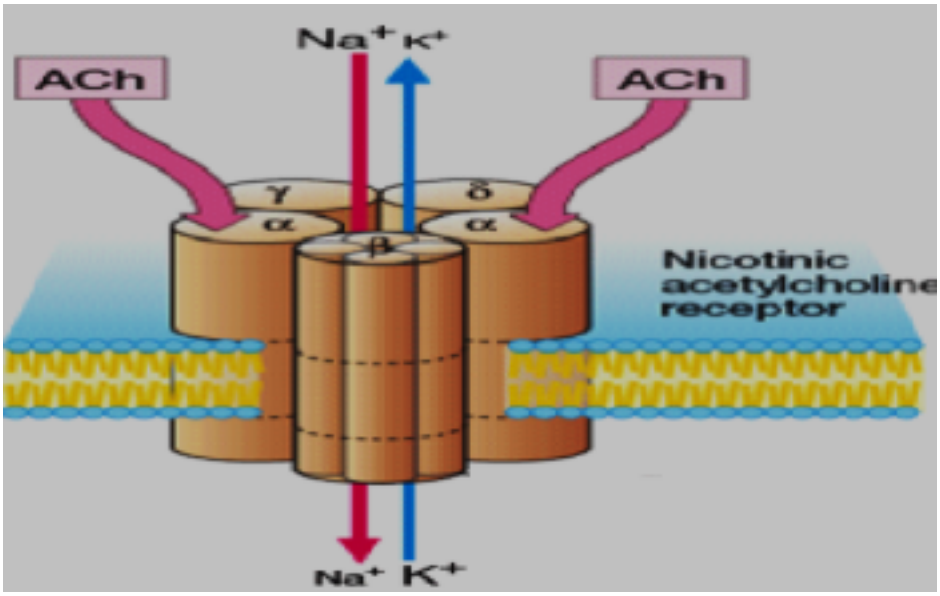
Receptors families

- **Type I** (Ion Channel-Linked **receptors)**
- **Type II** (G-Protein coupled receptors)
- **Type III** (Enzyme-Linked receptors)
- **Type IV** (Receptors linked to gene transcription)

Type I: Ion channel-Linked receptor – (Ligand gated ion channel) – (Ionotropic receptor)

- Located at cell membrane (as it is on the cell membrane, it does not require to be lipid soluble)
- Directly activated by ligand binding
- Directly related to ion channels. (when the drug starts produce its effect, the effect will directly change the ion channel 'open or close the channel)
- Involved in very fast synaptic transmission.
- Response occurs in milliseconds

- e.g. **nicotinic acetycholine** receptor that is activated by occupancy of a ligand as **acetycholine**.



Type II: G-Protein coupled receptors - Metabotropic Receptor

- What is it ?

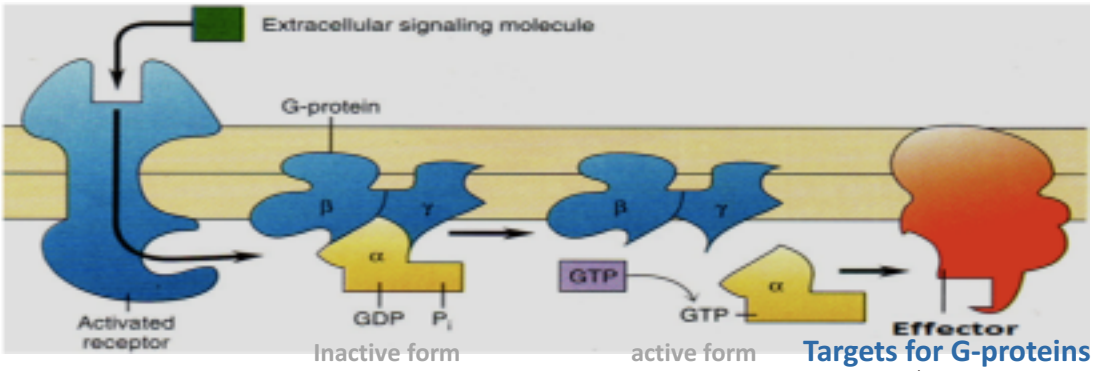
It is a receptor (Located at cell membrane) Cause changes in intracellular effector (especially in metabolic reaction) via G protein.

- Other name ?

it's also called Metabotropic Receptor :while tropic = changes in ions
^ سبب التسمية: لأنها تُحدث تغيرات في الأيونات و هذه التغيرات تسبب تغير في الأيض

- The largest family that accounts for many known drug targets
- Located at cell membrane
- Coupled to intracellular effectors via G-protein
- Response through ion channels or enzymes. (the effect is not direct, first the drug binds with the receptor, then G protein take the drug then go to the ion channel or enzyme, 'the drug will not effect the ion channel or the enzyme')
- Involved in rapid transduction
- Response occurs in seconds. (it is not in milliseconds so that it is not very rapid)
- E.g. Muscarinic receptors of Ach
- E.g. Adrenergic receptors of Noradrenaline (alpha and beta receptors)

-Its effector could be enzyme or ion channel :



Targets for G-proteins

- **enzyme**
  - **AC**: Adenyl cyclase enzyme. It acts on Cyclic AMP system (cAMP)*
  - **PLC**: Phospholipase C enzyme. It acts on Inositol phosphate system (IP3+DAG)**
- **Ion channel**
  - **Ach** e.g.: muscarinic receptors in heart. Ach acts upon muscarinic receptors by opening of K-channel and increase K efflux (hyper-polarization) to produce decrease in heart rate
  - e.g.: Adrenergic receptors

*cAMP= cyclic adenosine monophosphate
** IP3 = inositol triphosphate
DAG= diacylglycerol

G protein: it is a Regulatory protein found in the cell membrane , Comprise of three subunits (αβγ) (where α subunits possess (يمتلك) GTPase activity) , It is an intermediary (وسيط) between the receptor and the effector.

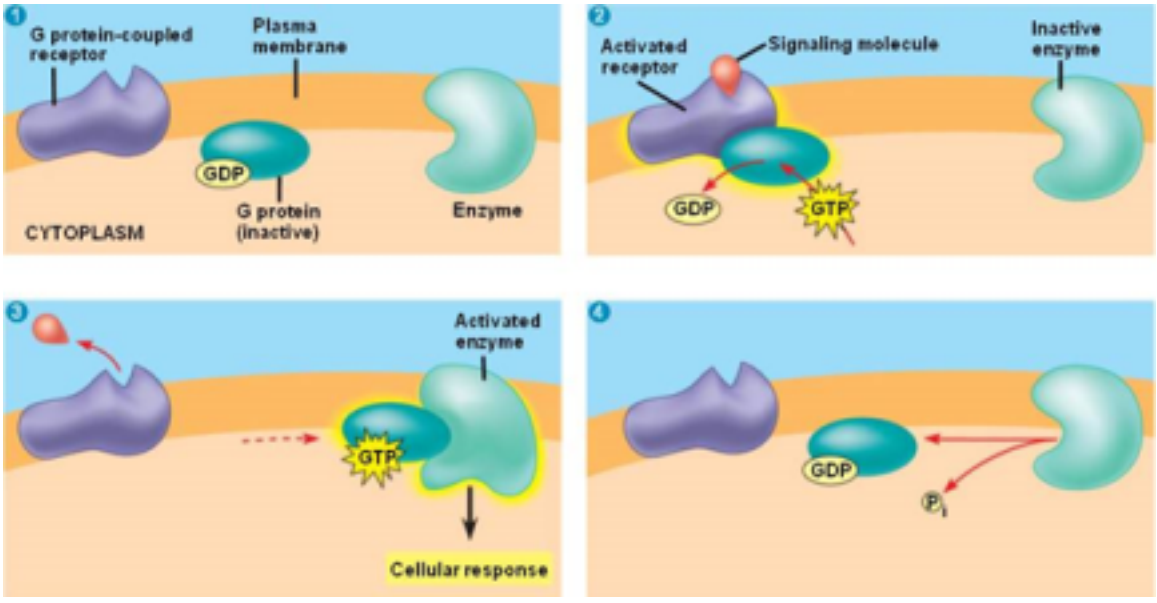
The story is:

1) the ligand bind to the receptor
2) the receptor undergo conformational change
3) G-protein bind to the receptor

+ α subunit become active(has GTP molecule) & dissociates (تنفصل) from βγ

<before step.1 α subunit was inactive(has GDP molecule)

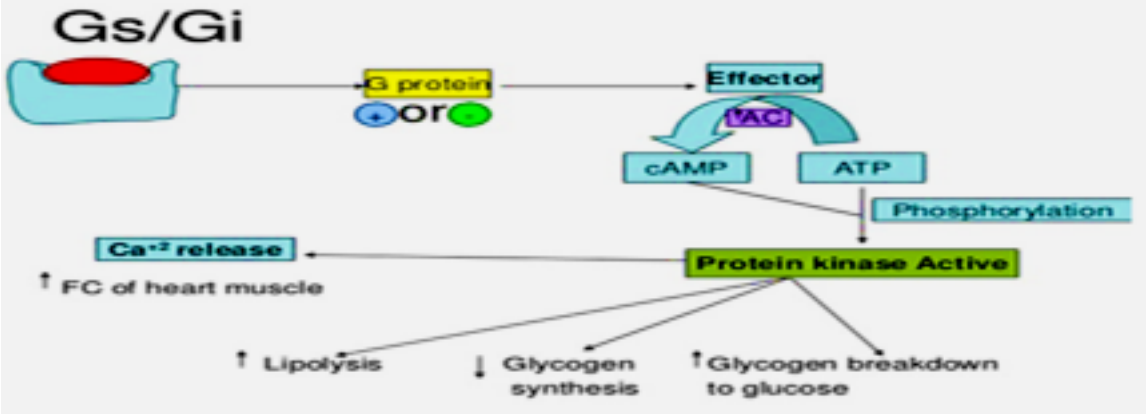
1) then α subunit is free to activate an effector , by hydrolyzed the bound GTP to GDP
2) hydrolyzation of GTP to GDP also allow α-subunit to recombine with (βγ) and returns to its inactive state.



Cyclic AMP system (cAMP):

G-protein → Adenyl cyclase enzyme → cAMP → Phosphorylation of Protein kinase A (PKA) → Active protein kinase A

The effect of increasing of kinase A:
↑ lipolysis
↑ breakdown of glycogen to glucose



Inositol phosphate system:

G-protein → Phospholipase C → Phosphoinositol diphosphate (PIP2)

Inosito triphosphate IP3 → Increase intracellular calcium* → Secretion of endocrine gland
Increase in heart rate
Smooth muscle contraction**

Diacylglycerol (DAG) → Protein kinase C (PKC) → Ion channels
Smooth muscle contraction

The G-protein will affect on the Phospholipase C and produce 2 substances: IP3 AND DAG, and both of these substances will increase the calcium level in the cell

* The endothelium reticulum storage the calcium, and the IP3 will affect on the endothelium reticulum and make it release the calcium, that will increase the Ca level inside the cell

** stick with this rule: whenever there is increasing in the Ca level inside the cell, there will be contraction

AC = Adenylyl cyclase
PLC = Phospholipase C
Ach = Acetylcholine
M= muscarinic
NA= noradrenaline
Adr= adrenaline

Classes of G protein

According to their α subunits they are divided into

- G_s = stimulates AC
- G_i = inhibits AC
- G_q = activates PLC

G protein coupled receptors

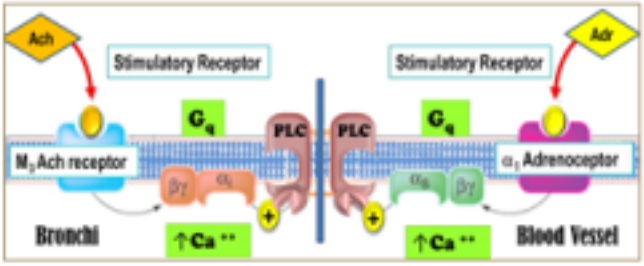
- Most abundant type.
- Receptors are selective to α subunit and effector with which they couple.

Classes of receptors

Receptor subtypes

Cholinergic (Ach) M				Adrenergic (NA) α & β				
m_1	m_2	m_3	m_4	α_1	α_2	β_1	β_2	β_3

m_1 & m_3 couple to G_q to stimulate PLC
m_2 & m_4 couple to G_i to inhibit AC
odd # > stimulate even # > inhibit

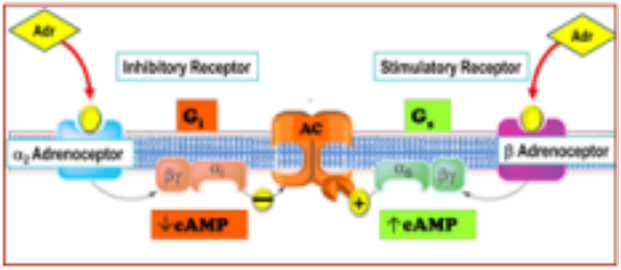


Ach works on the m_3 receptor in the bronchi which *activates* G_q which in turn *activates* PLC and *increases* Ca concentration

Adr works on the α_1 receptor in the blood vessel which *activates* G_q which in turn *activates* PLC and *increases* Ca concentration

different drugs (Ach / Adr)
different receptor (m_3 / α_1)
same effect (↑Ca)
same effector (PLC)
same G proteins (G_q)

α_1 couple to G_q to stimulate PLC
α_2 couple to G_i to inhibit AC
β_1 & β_2 couple to G_s to stimulate AC



Adr binds to the α_2 receptor which *activates* G_i which *inhibits* AC and *decreases* cAMP concentration

Adr binds to the β receptor which *activates* G_s which *stimulates* AC and *increases* cAMP concentration

same drug (Adr)
different receptor (α_2 / β)
opposite effect (↓/↑cAMP)
same effector (AC)
different G proteins (G_i / G_s)

Type III (Enzyme-Linked receptors) – (Tyrosine Kinase-linked receptor):

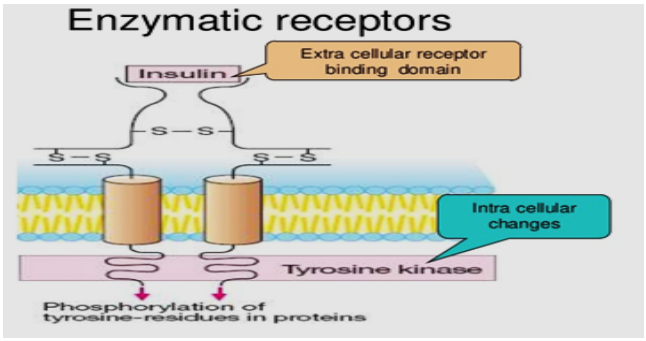
- Located at cell membrane
- Linked to enzyme (with intrinsic enzymatic activity)
- Response occurs in minutes to hours.
- Involved in response to hormones, growth factors.
- They control many cellular functions as metabolism and growth.

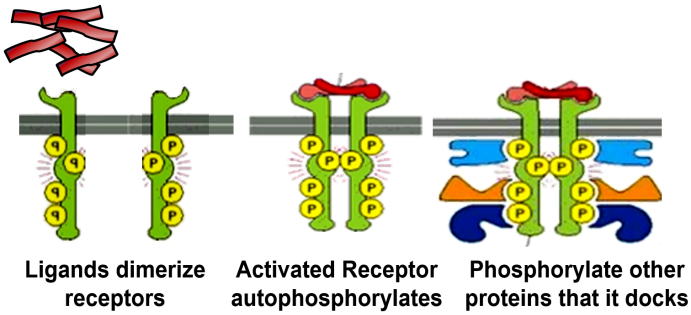
Activation of Type III receptors results in :

Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell*

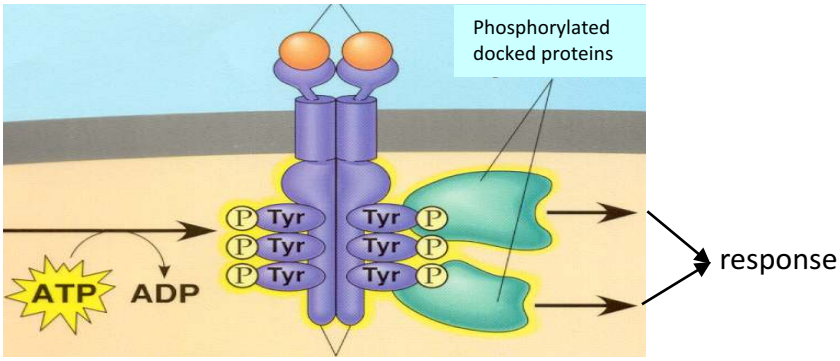
E.g. Insulin receptors

* Kinase enzyme make **phosphorylation (adding phosphate) to the tyrosine. Tyrosine located in the intracellular protein, like enzyme**





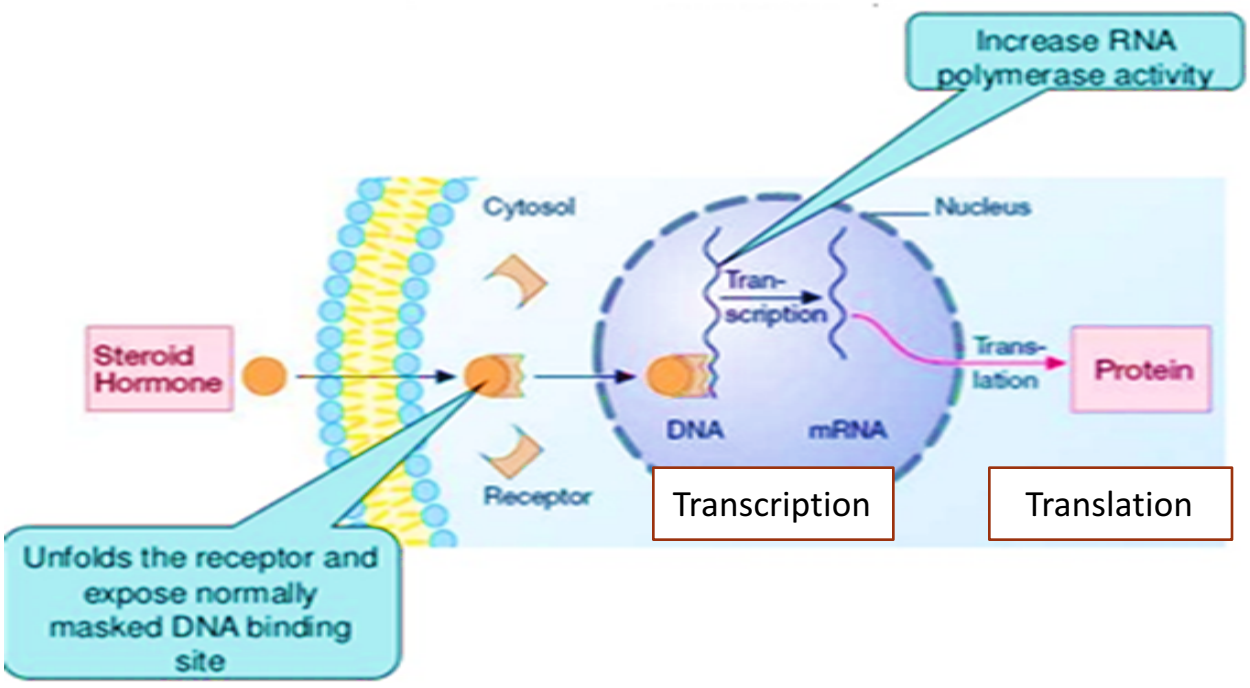
Example: Insulin receptors



Type IV: Gene transcrip5on receptors – (Nuclear receptors):

- Located intracellularly (so that the drug has to be lipid soluble)
- Directly related to DNA (Gene transcription).
- Activation of receptors either increase or decrease protein synthesis
- Response occurs in hours or days and persists longer.
- Their natural ligands are lipophylic hormones; steroids, thyroids, estrogen.

They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE] . (the place where the drug will bind is the DNA, especially in some sequence of the DNA which we called it Responsive Element)
This means that the activated receptors are acting as TRANSCRIPTION FACTORS [TF] →
expressing or repressing target genes.



Summary:

	Type I	Type II	Type III	Type VI
Location	Membrane	Membrane	Membrane	Nucleus
Coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	Muscarinic receptors Adrenergic receptors	Insulin receptors	Estrogen Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	DNA

Quick exam

https://www.onlineexambuilder.com/pharmacology-l9/exam-110846

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