# PHARMACOLOGY

## Receptor Families – Pharmacodynamics III

**OBJECTIVE:**

- Classify receptors into their main families
- Recognize their different transduction mechanism
- Identify the nature & time frame of their response

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# Receptors

## Classification of Receptors

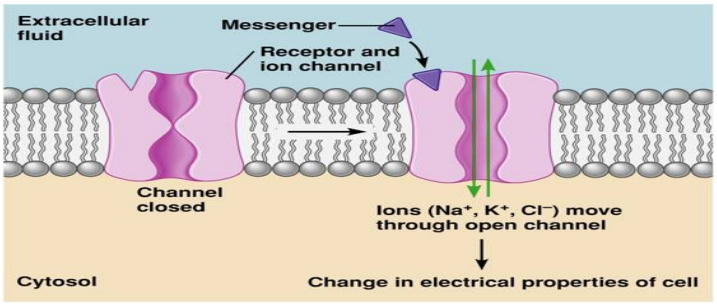
**1-Channel-Linked Receptor** e.g. Nicotinic Acetyl Choline
**2-G-Protein Coupled Receptors** e.g. Muscarinic Acetyl Choline
**3-Enzyme-Linked Receptors** e.g. Insulin
**4-Nuclear Receptors** e.g. Steroid hormones

### They are classified based on their:

- Location
- Structure
- Transduction Mechanism
- Nature of Response
- Time scale of Response

### Receptor Structure:

- Ligand recognition Site
- Inner domain site




## 1-Channel-Linked Receptor:

**Involved in fast synaptic neurotransmission, ligand binding & opening occur in milliseconds. (**The ligand binds to the receptor which is incorporated as a part of the ionic channel, thus it is activated as long as the ligand is bound to the receptor. (Ionotropic receptor; Membrane receptors coupled directly to ion channels)).

- **e.g. Nicotinic Ach receptor is activated by Ach**

(Nicotinic Acetyl choline receptor is a pentamer (consists of 5 subunits); it's a sodium/ potassium channel.

When the cell is activated (open or close the receptor) it is depolarized, i.e. the intracellular part is positively charged (e.g. influx of Na+).

When it is inactive, it is repolarized or hyperpolarized, since the intracellular part is negatively charged.

- The receptor is activated by the occupancy of the ligand and not by a change in the action potential as in the voltage-gated ion channel.

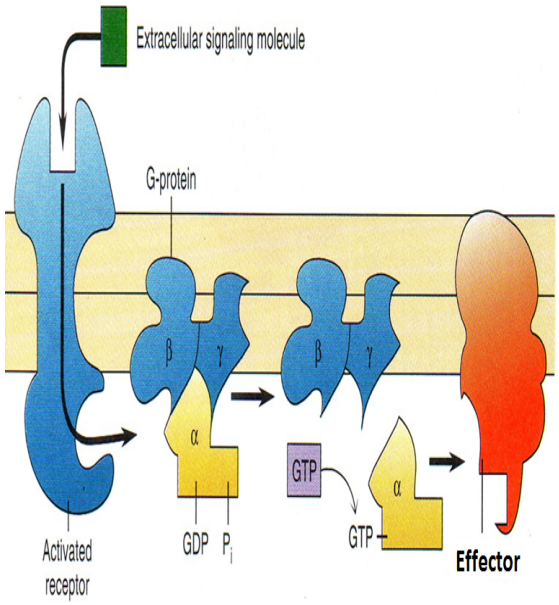
## 2- G-Protein Coupled Receptors:

**(**Receptors for many hormones & slow transmitters (takes seconds)
e.g. mAch & adrenergic receptors**)**

### Mechanism:

- The G- protein consist of 3 subunits [αβχ] ,the α- subunit has a GDP bind to it .
- When the receptor is activated by the ligand the trimer G protein will bind to the receptor .
- Once the trimer bind to the receptor the the α- subunit will dissociate and the GDP will be displaced by GTP, In this form it will be able to activate the effector .
- Activation of the effector is terminated when the bound GTP molecule is hydrolysed , which allows the α-subunit to recombine with βχ .
- There are several types of G- proteins ,which interact with receptors & control different effectors.

**Effector:** the effector is a macromolecule that mediate the effect of the receptor.



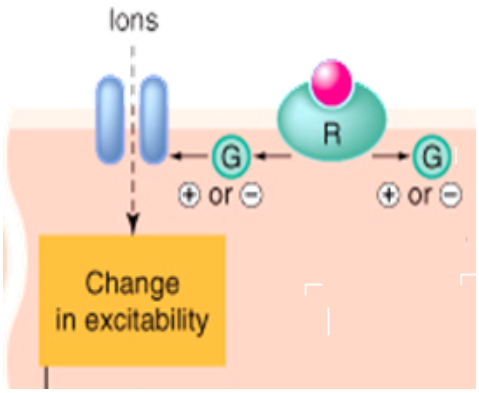
# G-Protein Coupled Receptors:

## 1-Ion channels: (Effector)

the receptor will either activate or inactivate the ion channel via G-protein.

when the ion channel is activated the cell membrane excitability will be changed.

e.g. K+, Ca++thus affecting membrane excitability, transmitter release.

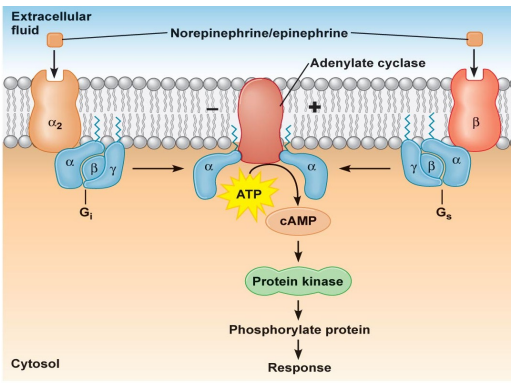



## 2-Adenylate cyclase: (Effector)

once the Adenylate cyclase is activated it will convert the ATP into cAMP (secondmessenger)

The cAMP will act on protein kinase which will lead to phosphorylation of proteins and trigger a response .

- ⬆Lipolysis
- ⬇Glycogen synthesis
- ⬆Glycogen breakdown
- ⬆Fc of heart muscle




(b) cAMP and $\alpha_2$ and $\beta$ receptors

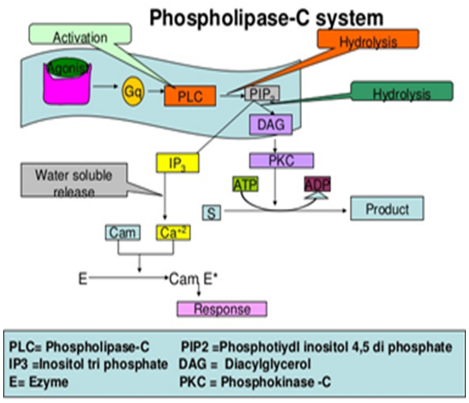
## 3-Phospholipase C: (Effector)

When pip (phosphatidylinositol) hydrolysis it will give two second messenger.

1- well active (IP3):

Ip3(inositol tri phosphate). IP3 goes to the endoplasmic reticulum and releases the stored calcium and so it increases the intracellular calcium. which will lead to(Ca + cam) will activate the enzyme Release of neurotransmitter or contraction of muscle.

2-Diacylglycerol (DAG): will activate Phosphokinase and it well activate other enzymes.



# G-Protein Coupled Receptors:

## -Classes of G proteins:

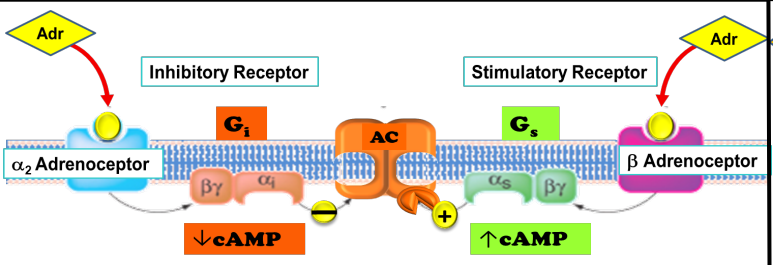
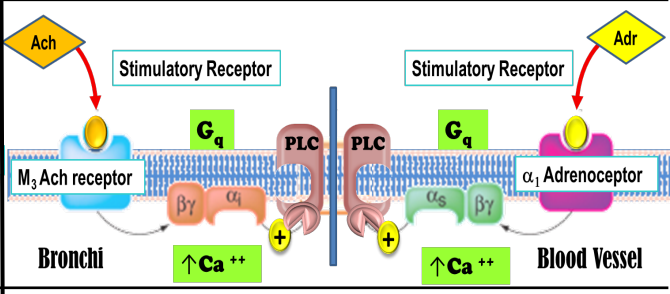
Divided according to their α-subunits into $G_s$, $G_i$ and $G_q$

($G_s$)stimulation and ($G_i$)inhibition of adenylyl cyclase (AC)

($G_q$)is linked to activation of Phospholipase C system

Receptors are selective to a subunit and effector with which they couple

## -Classes of receptors:

| ADRENOCEPTORS | CHOLINERGIC RECEPTORS |
|---|---|
| $\alpha_1$ Adrenoceptors couple to $G_q$ to stimulate (PLC) (phospholipase c) | $M_1$ & $M_3$ Ach receptors couple to $G_q$ to stimulate PLC (phospholipase c) |
| $\alpha_2$ Adrenoceptors couple to $G_i$ to inhibit AC (adenylyl cyclase) | $M_2$ & $M_4$ Ach receptors couple to $G_i$ to inhibit AC (adenylyl cyclase) |
| $\beta_{1\&2}$ Adrenoceptors couple to $G_s$ to stimulate (AC) | |
|   |   |
| same drug different receptor opposite effect the same effector by different g proteins | different drugs different receptor same effect same effector same g proteins |
| Adrenaline bind to $\alpha_2$ **Adrenoceptors** that will activate $G_i$ **(Inhibitory)** protein.<br>$G_i$ protein will inhibit (AC) that will decrease cAMP Concentration.<br>Adrenaline bind to β **Adrenoceptors** that will activate $G_s$ **(Stimulatory)** protein .<br>$G_s$ protein will activate (AC) that will increase cAMP Concentration. | -acetylcholine work on **bronchi** by $M_3$ Ach receptor that will activate $G_q$ proteins and $G_q$ proteins will activate (PLC)phospholipase c that will increase ca Concentration.<br>-adrenaline work on **blood vessel** by $\alpha_1$ receptor that will activate $G_q$ proteins and $G_q$ proteins will activate (PLC) that will increase ca Concentration. |

## Enzyme linked receptors:

- Located at the cellular membrane
- The receptors have a **large extracellular ligand binding domain** connect via **α-helix** to the **intracellular domain**
- some have intrinsic tyrosine kinase activity
- Receptors for hormones such as : **insulin and growth factors** , so they are controlling cell growth and differentiation.

## Signal transduction:

- **Autophosphorylation** of tyrosine residue acts as acceptor of **SH2***domain of various protein , as a result of allowing control of various **cell function .**
- This usually require many intracellular signaling steps that take time to process (minutes to hours) . SH2*= Src homology 2

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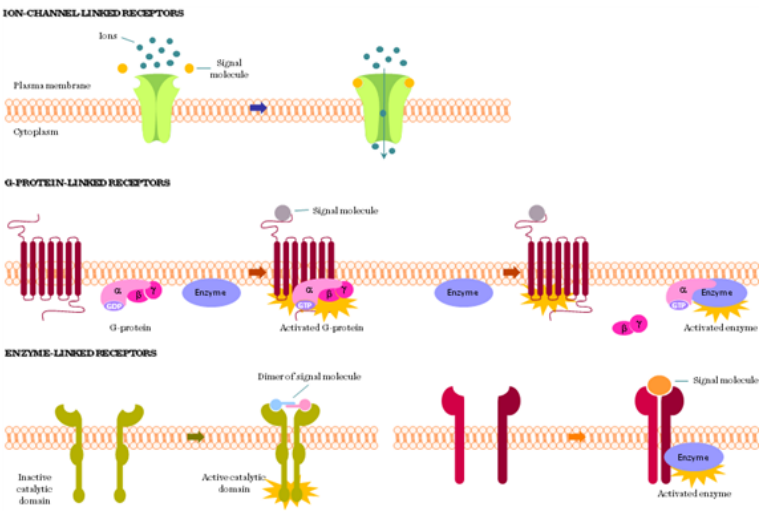
## Nuclear Receptors (Intercellular Receptors):

### Characteristics :

- The Receptor entirely **Intercellular**.
- The Ligand must have sufficient **lipid solubility**.
- Receptors consist of **3 Domains** : a conserved **DNA-binding** domain attached to variable **ligand–binding & transcription** control domains.
- DNA-binding domain recognizes specific base sequences (response element) , thus **promoting or repressing** particular genes.
- They react as **TRANSCRIPTION FACTORS** expressing or repressing target genes.
- Effects are produced as a result of **protein synthesis**, thus they are **Slow In Onset** (hours & days).
- Pattern of gene activation depends on both **cell type & nature of ligands.**
- ligands include **steroid hormones , vitamin D & thyroid hormone.**

## Mechanism:

Activation of these factors causes transcription of DNA into RNA and translation of RNA into proteins. The time course of activation and response of receptors from hours to days.




## Synopsis:

Characteristics of Receptor families :

| | Ligand Gated | G-protein coupled | Enzymatic | Nuclear |
|---|---|---|---|---|
| **Location** | Membrane | Membrane | Membrane | Intercellular |
| **Effector** | Ion Channel | Ion Channel Or Enzyme | Enzyme | Gene |
| **coupling** | Direct | G-protein | Direct | Via DNA |
| **Example** | Nicotinic | Muscarinic | Insulin | Steroid, Hormone |
| **Time scale** | Milli Seconds | Seconds | Min/Hours | Hours/Days |

# THANK YOU FOR CHECKING OUR WORK

## THE PHARMACOLOGY TEAM

مريم سعيدان
كيان كعكي
نورة الطويل
اسرار باطرفي
كوثر الموسى
نوف العبدالكريم
لمى الزامل
رفان هاشم
ديمة الفارس
ياسمين الفارسي

ساره الخليفه
رنيم الدبيخي
منيرة الحسن
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هديل الغرير
ريم العقيل
سارا الحسين
نوف الرشيد
نورة العقيل

عبدالرحمن السياري
خالد الزهراني
عبدالله الجنيدل
أحمد المصعبي
مهند الزيد
عبدالرحمن الشمري
معاذ باعشن
عبدالعزيز الشعلان

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology.med435@gmail.com

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