PHARMACOLOGY
433

King Saud University
College of Medicine
Foundation Block

Pharmacodynamics III ; Receptor Families

7

Objectives :

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

Key Words :

Recognition, Reception, Transduction, Response, ligand, Conductance, Transcription, Translation, Adrenoseptors , Cholinergic receptors.

Abbreviations :

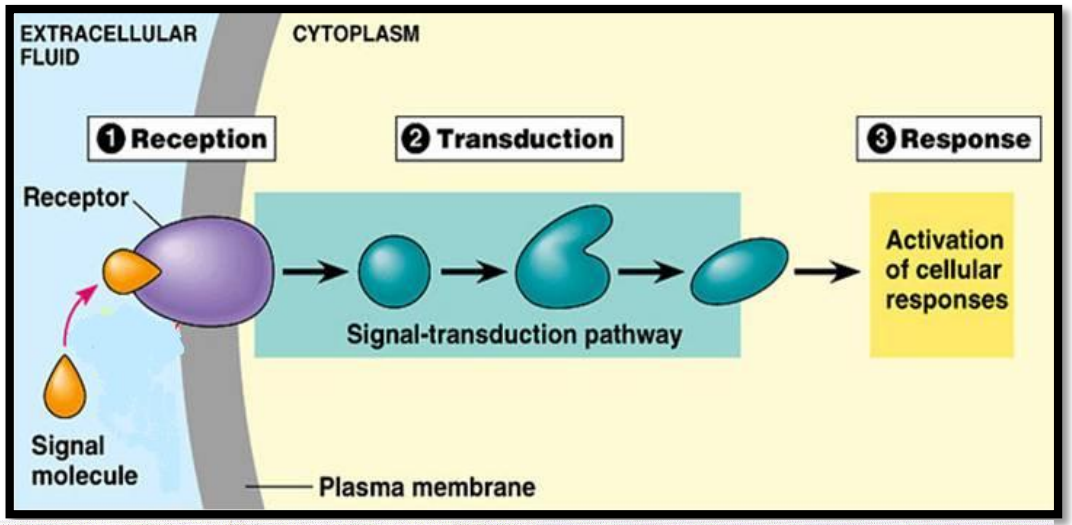
VSMC : Vascular Smooth Muscle Cells
PLC : Phospholipase C
AC : Adenyl Cyclase
cGMP : Cyclic Guanyl Mono-Phosphate
GC : Guanyl Cyclase
ANP : Atrial Natriuretic Peptide
Ach : Acetylcholine
PKA: Protein kinase A

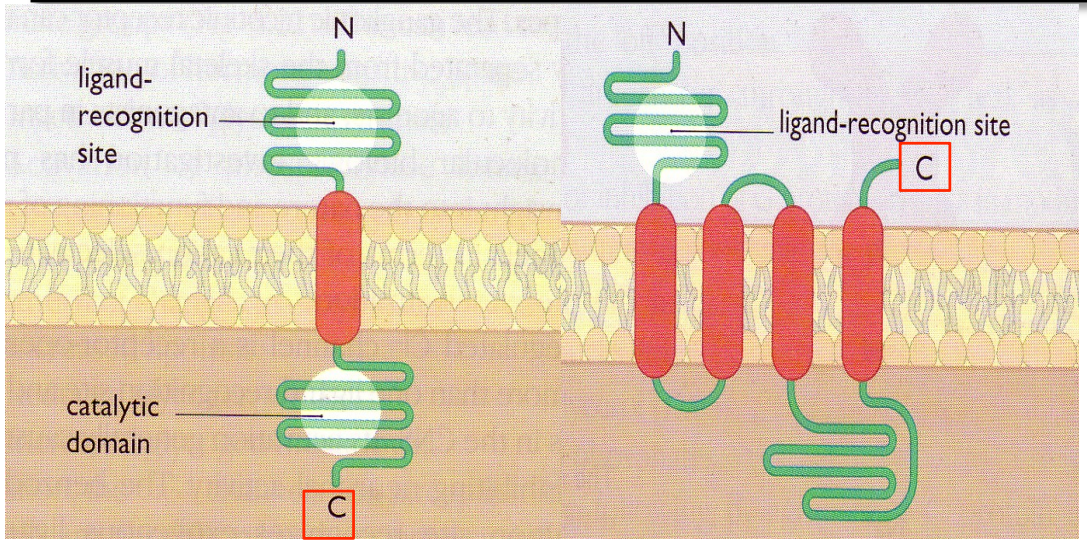
To understand this lecture properly; Study the 10th lecture of biochemistry (**Cell Signaling and Regulation of Metabolism**)
To download the Biochemistry-team's work on this lecture:
[http://www.ksums.net/files/1st/Foundation%20Block/433%20Teams%20Work/Biochemistry/Lecture%209%20&%2010%20important%20.pdf]

433 Biochemistry Team

What is a Receptor ?

Responsible for selectively sensing & binding of a stimulus (ligand) & its coupling to a response via a set of signal transduction machinery.





Receptors are classified according to :

*Location *Structure *Transduction Mechanism
*Nature of Response *Time Scale of Response

4 main Super-Families of receptors :

1. Channel-Linked Receptor
2. G-Protein Coupled Receptors
3. Enzyme-Linked Receptors

} On the cell membrane

4. Nuclear Receptors

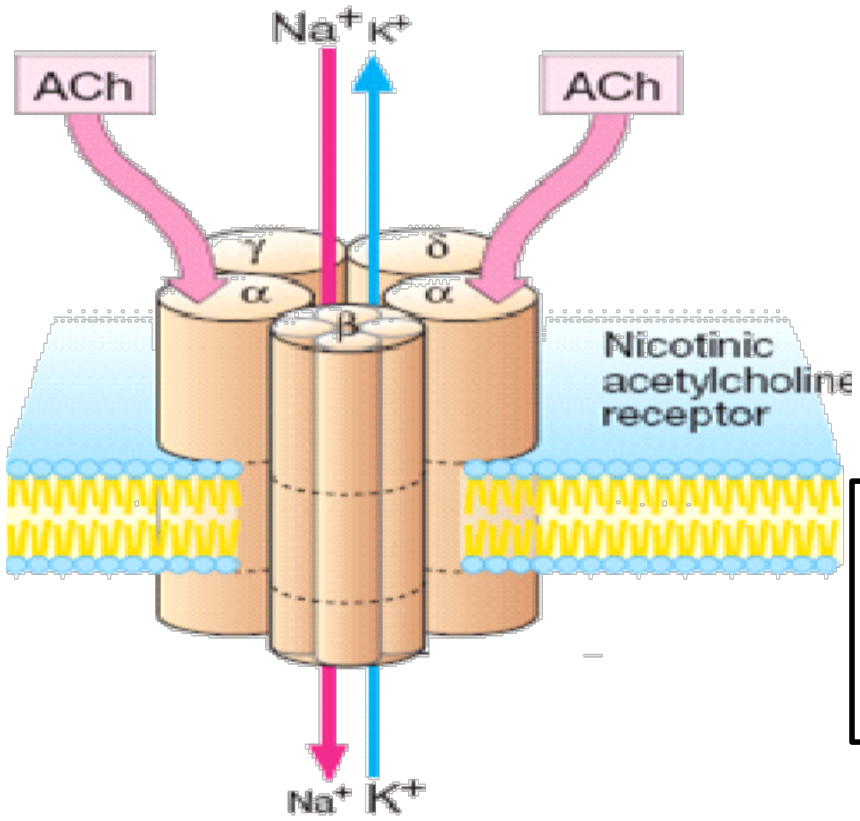
} In the Cytosol or Nucleus

Its Structure: 1\ N terminal 2\ C terminal

1. Channel-Linked Receptor

Involved in fast synaptic neurotransmission occurring over milliseconds
It is activated directly when a ligand binds to the receptor to open the channel causing influx of ions and it can cause either hyperpolarization or depolarization that is incorporated as part of its structure.

Examples; Nicotinic Ach receptor activated by Acetylcholine.



Influx Na ↓ (depolarization)

Efflux K ↑ (hyperpolarization)

This mechanism Different from Voltage-Gated Ion Channel , Is activated by a change in action potential not by occupancy of a ligand

2. G-Protein-Coupled Receptor

Are the Most Abundant Type

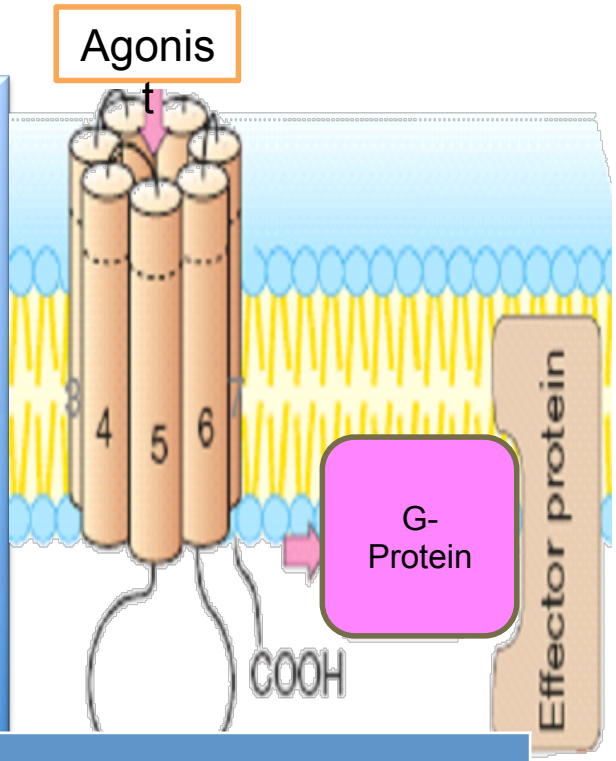
G-protein Composed of 3 subunits [α β g] & GDP

They Have Different G-Protein Classes

Divided according to their α-subunits into Gs, Gi and Gq

Gs and Gi produce, respective, stimulation and inhibition of AC

Gq is linked to activation of PLC-Ca^{++}



Activation of	Lead to activation of
G-protein	Adenyl cyclase (AC) Or Phospholipase C (PLC)
Adenyl cyclase (AC)	Protein kinase A (PKA)
Phospholipase C (PLC)	- Increase release of intracellular Ca^{++} ➔ calcium and calmodulin dependent protein kinase (CAM-PK) and - protein kinase C (PKC)

Phosphorylates a target protein → RESPONSE

3. Enzyme-Linked Receptors

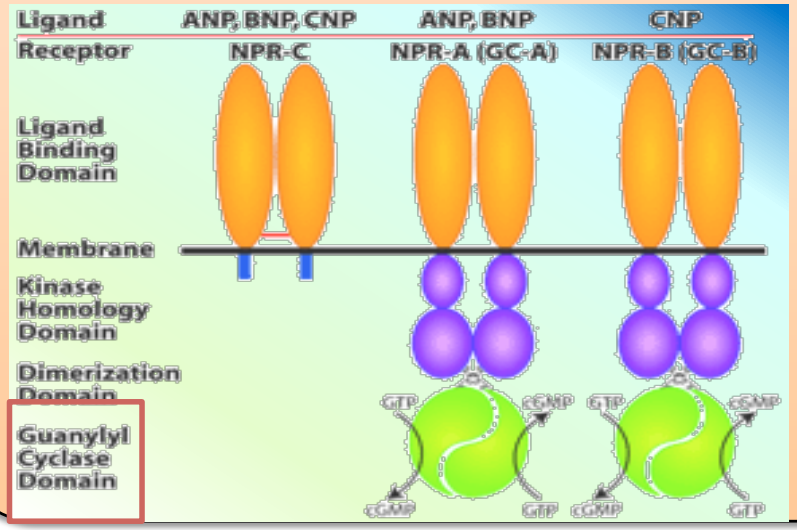
Involved in slow action of; hormones (insulin is the most common), growth factors, cytokines..ect. Cytosolic Domain either :

Associate directly with an enzyme :

e.g. guanyl cyclase [GC] as in [ANP] receptor.
*They have a single transmembrane spanning element.

*These have integral intrinsic Guanylate Cyclase activity.

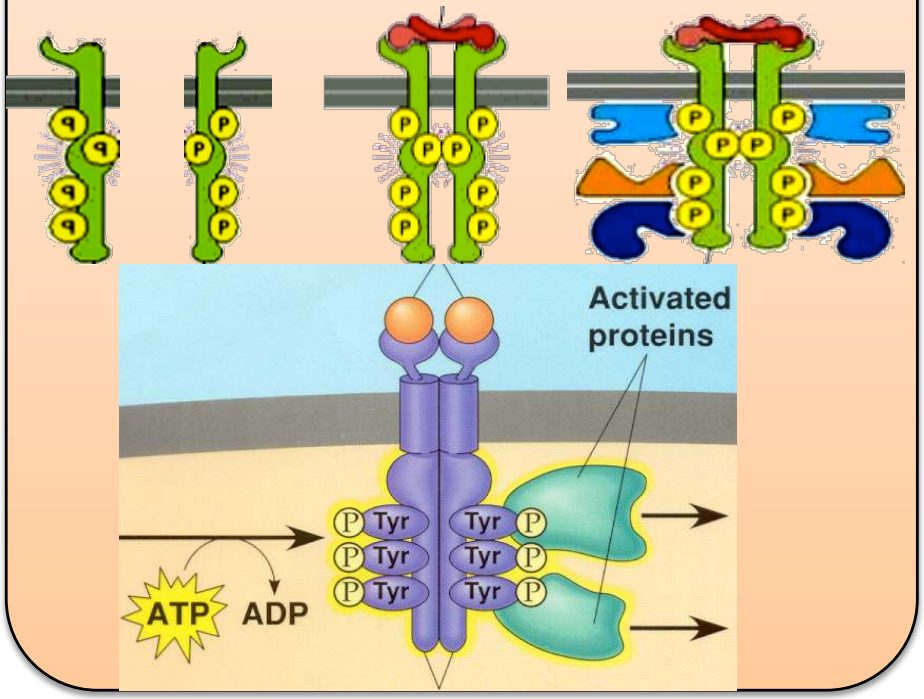
*Their 2nd messenger is cyclic guanyl mono-phosph. [cGMP]
→ activates PKG (protein kinase G)
→ to phosphorylate other
down stream protein signaling molecules.



Possess intrinsic Kinase activity (as tyrosine or serine/threonine kinase)

((2 receptors bind together to become one))
that can phosphorylate itself (autophosphorylation) and/or other proteins that dock or bind to it.

Example; insulin receptor



4. Nuclear Receptors

Are intra-cellularly located whether in cytosol or the nucleus.

Their Natural ligands are usually :

Extracellular lipophylic (hydrophobic, lipid soluble) hormones e.g. steroids, thyroids, …etc.

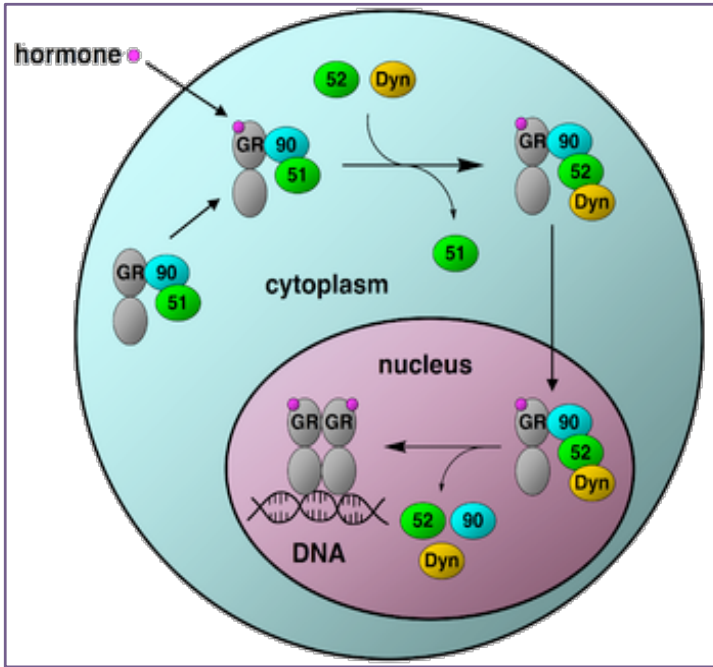
Have high lipid permeability to inter the cell.

- **Extracellular lipids; linolinic a., retinoic a.**

- Phosphorylated protein end product of 2nd messenger signaling

Involved in regulation of Protein synthesis "most slowest in action"

They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE] ⟶ these activated receptors are acting as Transcription Factors [TF] ⟶ expressing or repressing target genes sprite.



GLUCOCORTICOID [GC] RECEPTOR

"It is found in the cytosol"

The activated GC R complex

***Up-regulates expression of anti-inflammatory proteins.**

***Represses expression of pro-inflammatory proteins**

(by preventing the translocation of their transcription factors from the cytosol into the nucleus).

SUMMARY*

	Channel-Linked Receptor	G-Protein Coupled Receptor	Enzyme-Linked Receptor	Nuclear Receptor
Location	Cell membrane	Cell membrane	Cell membrane	Cytosol or Nucleus
Mechanism	Activation of this receptor lead to opening of ion gate and ion influx , this will lead to (**depolarization or hyperpolarization**) which produce a response.	*Activation of G protein lead to activation of adenyl cyclase (AC) or phospholipase C (PLC). *Activation of adenyl cyclase : lead to activated PKA (protein kinase A). *Activation of phospholipase C, will activate CaM-PK and PKC.	When agonist bind to receptor , it gets activated by two ways :- 1- activated guanyl cyclase enzyme to produce cGMP. example : **Atrial Natiueretic Peptide** receptor (ANP) 2- the receptor undergoes (autophosphorylation) which phosphorylates other protein that produce a response. example : **insulin receptor.**	The ligand (drug) has to cross the cell membrane either directly (If it is highly lipid-soluble) or through a carrier protein to act on the receptor. Once it is bound to the receptor, a translocation will happen for the complex to the nucleus. In the nucleus, it binds to a certain gene sequence and it will start the process.
Function	Nervous conduction	Cell signaling	Cell signaling	Transcription → Translation → Protein synthesis
Time Scale	Milliseconds	Seconds	Minutes-Hours	Hours-Days
Example	Nicotine Ach receptor	Muscarinic ACh receptor	Cytokine receptor	Oestrogen receptor

*This table is very important, check it for revising after you finish studying

MCQs

1 **Glucocorticoid [GC] is :**

A. Nuclear receptor in the Cytosol
B. G-protein receptor
C. Nuclear receptor in the Nucleus
D. Enzyme-Linked receptor

2 **An Example of Ligand-Gated-Ion Channel**

A. Nicotinic ACh receptor
B. Muscarinic ACh receptor
C. Cytokine receptor
D. Oestrogen receptor

3 **α_2 Adrenoceptor couple to Gi results in :**

A. stimulate AC
B. Inhibit PLC
C. decrease in cAMP
D. Increase in cAMP

4 **Those control many cellular functions as motility, growth factors, differentiation, division, morphogenesis :**

A. Channel-Linked receptors
B. G-protein Coupled receptors
B. Enzyme-Linked receptors
C. Nuclear receptors

5 **The slowest receptors are**

A. Channel-Linked receptors
B. G-protein Coupled receptors
C. Enzyme-Linked receptors
D. Nuclear receptors

6 **Nuclear receptors exist in :**

A. Only in the Nucleus
B. The Nucleus or the Cytoplasmic membrane
C. The Nucleus or the Cytosol
D. The Nucleus or the Enzymes

7 **An example for Channel-Linked (Hyperpolarization and depolarization):**

A. Nicotinic Ach receptor.
B. Nicotinic Ach receptor.
C. Metabotropic receptor.
D. Cytokine receptor.

8 **How long do Hyperpolarization and depolarization take ?**

A. Second
B. Days
C. Hour
D. Millisecond

9 **Cytokine Receptor is an example for……. And it takes …….. long.**

A. Enzyme-Linked-minutes to hours
B. G-Protein Coupled-Hour to Days
C. Channel-Linked – Millisecond
D. Enzyme-Linked- Hour to Days.

10 **Where does change in excitability occur?**

A. Enzyme-Linked
B. G-Protein Coupled
C. Channel-Linked
D. Nucleus

1-A 4-C 7-A
2-A 5-D 8-D
3-C 6-C 9-A
10-B

We hope we made this lecture easier for you
Contact us for any questions or comments
Good Luck !

Nada Dammas
Layan Al Taweel
Budoor Alsalman
Sara AlKharashi
Nada Bin Dawood
Latifa AlAnazi
Norah Alnaeim
Maha Alrajhi

Ahmed Aldakhil
Faris Almoammarie
Mohammed Alnafisah
Abdulmalek Alnujidi
Khalid Alanazi

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Summary of the lecture:
(http://www.youtube.com/watch?v=GPoDNQhP0Mg&feature=youtu.be)
G-Protein Signaling
(http://www.youtube.com/watch?v=V_0EcUr_txk)

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