Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Receptor families

Objectives:

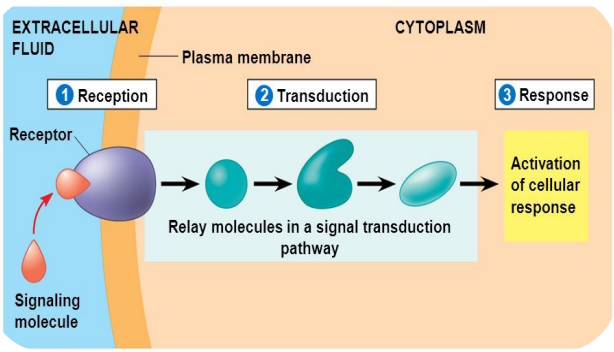
- Classify receptors into their main superfamilies.
- Recognize their different transduction mechanisms.
- Identify the nature & time frame of their respons.

Titles Very important Terms Extra informations

Success Doesn't Come To You, You Go To It!

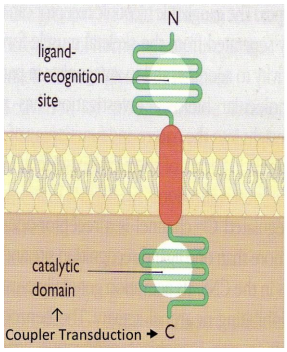
A Receptor:

1- Recognition → 2- Reception → 3- Transduction → 4- Response



A Receptor structure:

- Ligand recognition site
- Inner catalytic domain



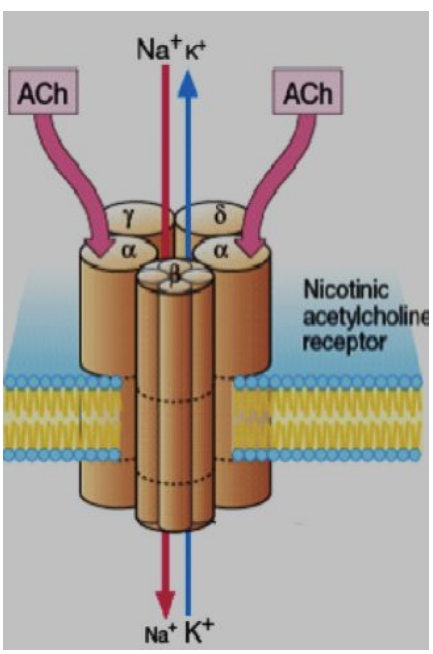
Receptor families

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

*type 1,2 and 3 are surface receptors. Type 4 is intracellular receptor

Type I : ion channel-linked receptor (ligand gated ion channel)-(ionotropic receptor)

- Located at cell membrane (as it's on the cell membrane, it doesn't require to be lipid soluble).
- Directly activated by ligand binding. (no second messenger needed)
- 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 acetylcholine** receptor that is activated by occupancy of a ligand as **acetycholine**.

notes from*436

Type II : G-Protein coupled receptor - (metabotropic receptor)

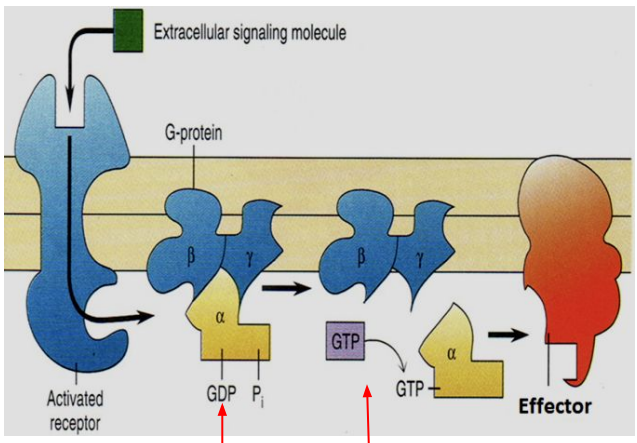
- **What is it?**

It's a receptor (located at cell membrane) cause changes in intracellular effector (especially in metabolic reaction) via G-protein.* درسناه بالبايوكمستري بتفهمونه افضل لو درستوا محاضرته *

- **Other names?**

It's also called "metabotropic receptor" while tropic means changes in ions.
سبب التسمية: لآنها تحدث تغيرات في الأيونات وهذه 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 on 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)



Inactive form Active form

E.g. **Muscarinic receptors of Ach**

E.g. **Adrenergic receptors of Noradrenaline** (alpha and beta receptors)

Targets for G-proteins

Its effector could be enzyme or ion channel :

Enzyme

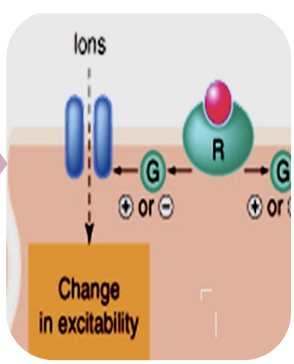
AC:
Adenyl cyclase enzyme. It acts on Cyclic AMP system (cAMP)*

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.

Adrenergic receptors



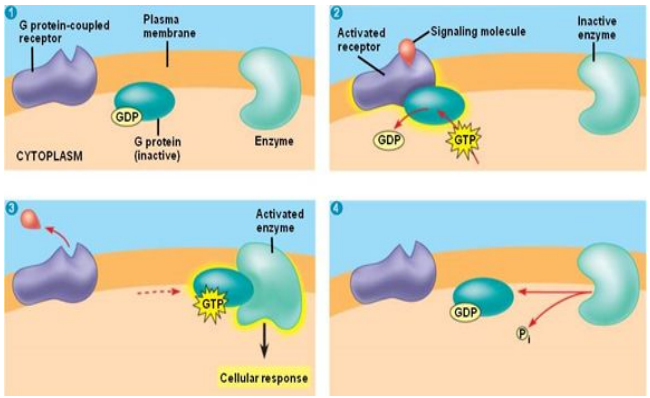
*cAMP: cyclic adenosine monophosphate
**IP3: inositol triphosphate
**DAG: diacylglycerol

notes from*436

G-protein

- Regulatory proteins.
- Regulate guanine nucleotides GDP,GTP.
- Comprise of three subunits (αβγ) ,α subunit possess GTPase activity.
- When the trimer binds to agonist-occupied receptor , the α-subunit dissociates & is then free to activate an effector .
- Activation of the effector is terminated when the bound GTP molecule is hydrolyzed the bound GTP to GDP which allow α-subunit to recemobion with βγ and return to its inactive state.

So 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 effctor.



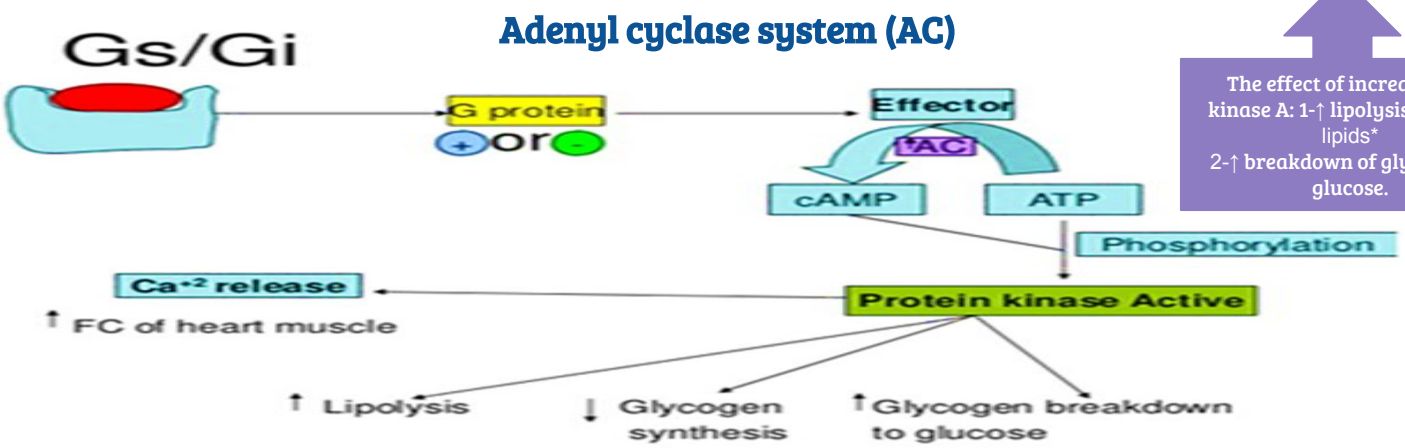
The story of G-protein:

*steps :نفس اللي فوق بس ب

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)
4) Then α subunit is free to activate an effector , by hydrolyzed the bound GTP to GDP
5) 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 → ATP>cAMP *الانزايم يحوله → Phosphorylation of Protein kinase A (PKA) → Active protein kinase A..



Adenyl cyclase system (AC)

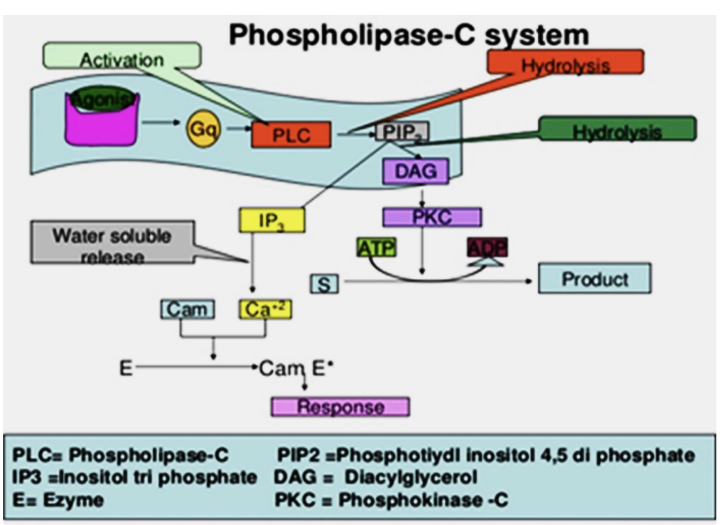
The effect of increasing of kinase A: 1-↑ lipolysis. *lysis of lipids*
2-↑ breakdown of glycogen to glucose.

Inositol phosphate system:

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

Inositol triphosphate IP3
↓
Increase intracellular calcium*.
↓
1-Secretion of exocrine gland.
2-Increase in heart rate.
3-Smooth muscle contraction**.

Diacylglycerol (DAG)
↓
Protein kinase C (PKC)
↓
1-Ion channels
2-Smooth muscle contraction



notes 436*:

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.

Classes of G protein

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

Gs and Gi produce, respective, stimulation and inhibition of AC. (Adenylyl cyclase)

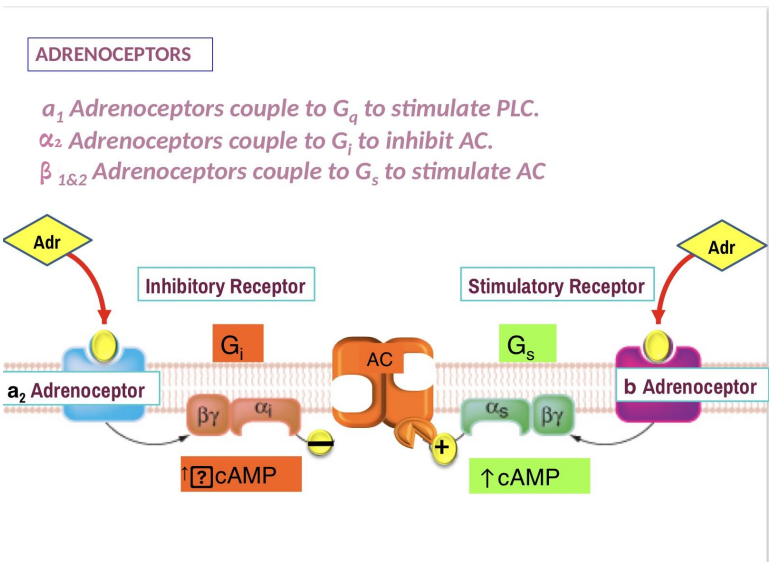
s= stimulation
i = inhibition

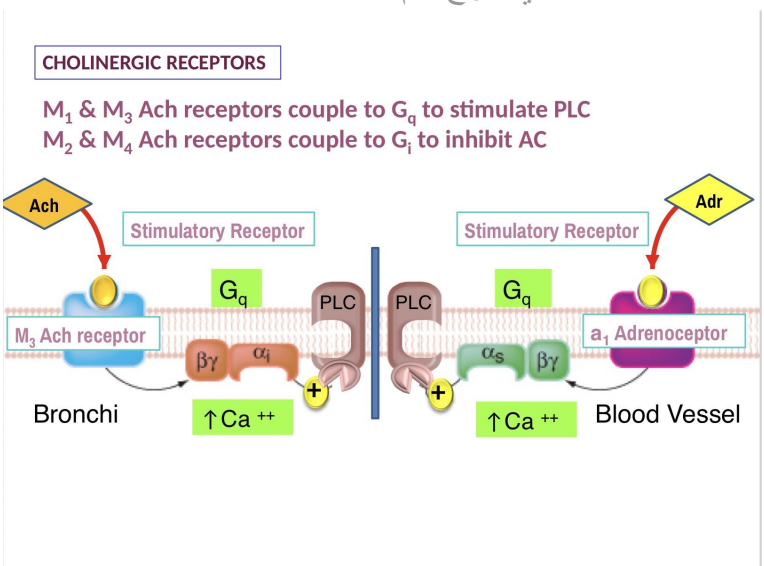
Gq is linked to activation of Phospholipase C system.

Receptors are selective to α subunit & effector with which they couple.

*When Ac (adenylyl cyclase) decreased, cAMP is decreased, calcium is decreased .

**السلايد الجاي شرح لهم





ITS IMPORTANT

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

G protein coupled receptors

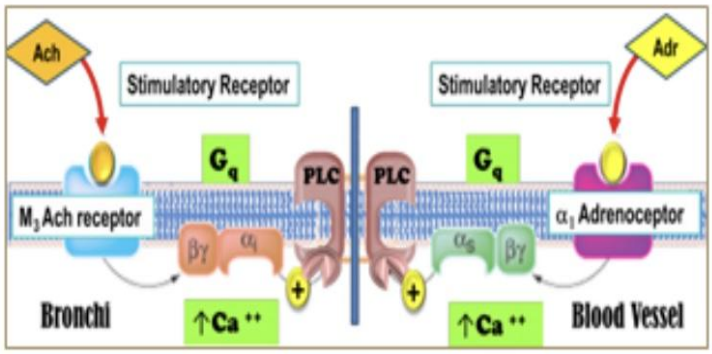
- Most abundant type.
- Receptors are selective to α subunit and effector with which they couple.

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

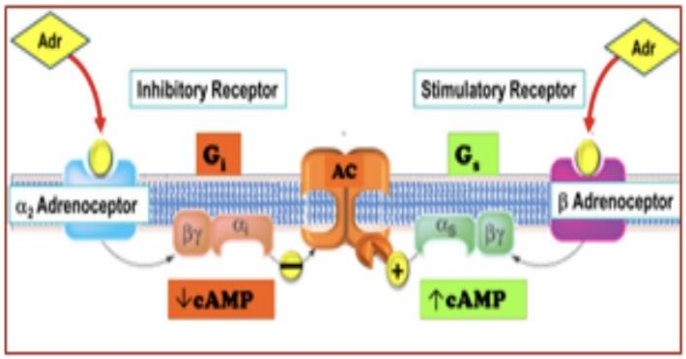


Ach works on the m_3 receptor in the bronchi which *activates* G_q which in turn *activates* PLC and *increases* Ca concentration

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)

436 team **

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

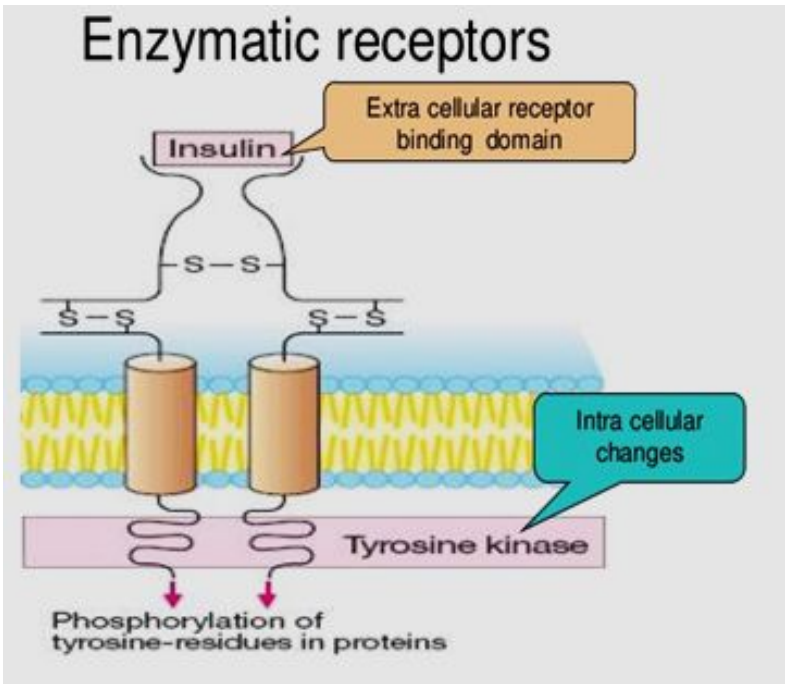
- Located at cell membrane.
- Linked to enzyme (with intrinsic enzymatic activity).
- Response occurs in minutes to hours.
- Involved in response to hormones, growth factors.
- They control many cellular functions as metabolism and growth.

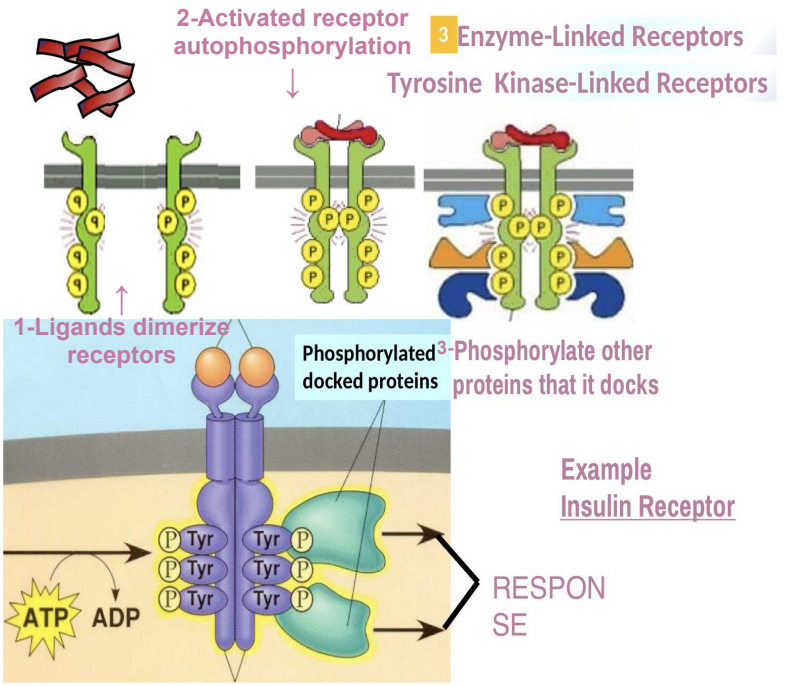
Activation of Type III receptors results in:

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.

Insulin receptors





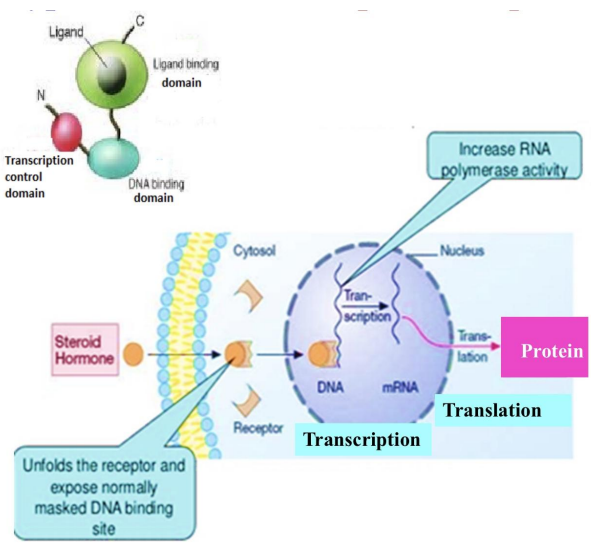
Type IV: Gene transcription receptors (Nuclear receptors)

o Located intracellularly
o Directly related to DNA (Gene transcription).
o Activation of receptors either increase or decrease protein synthesis
o Response occurs in hours or days and persists longer.
o Their natural ligands are lipophylic hormones; steroids, thyroids, estrogen.

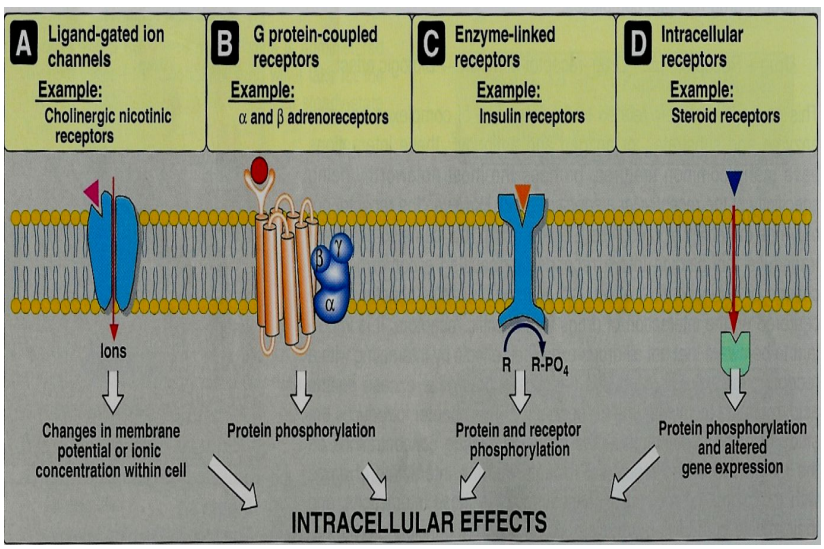
Type IV: Gene transcription receptors

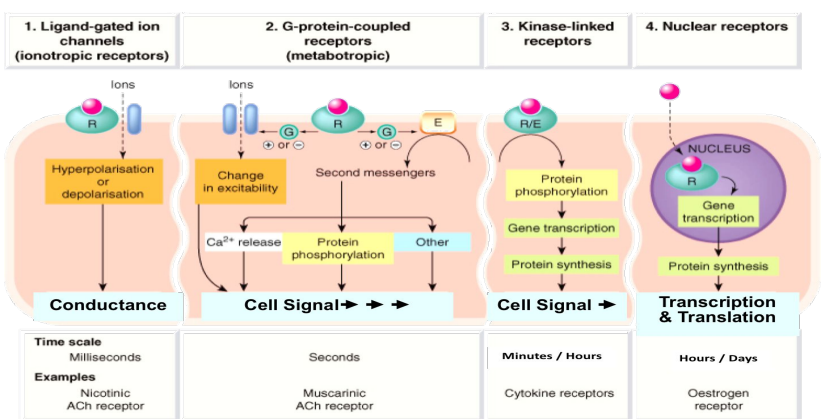
- They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE] .
- This means that the activated receptors are acting as TRANSCRIPTION FACTORS [TF] → expressing or repressing target genes.

Type IV: Gene transcription receptors

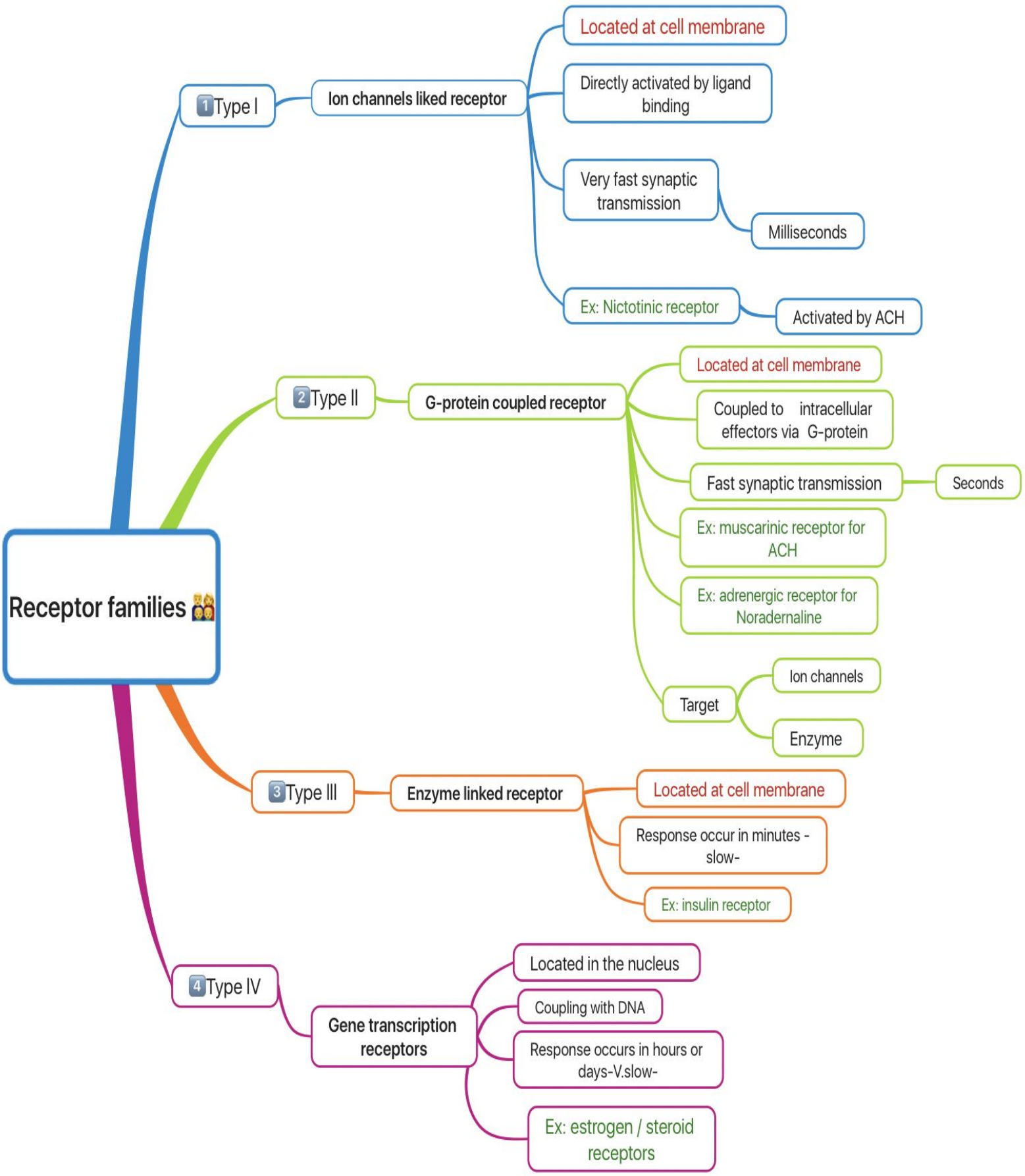


الصورتين اللي تحت بعض موجودة بآخر سلايدين من سلايدات الدكتورة.*





Summary


Receptor families
1 Type I
Ion channels liked receptor
Located at cell membrane
Directly activated by ligand binding
Very fast synaptic transmission
Milliseconds
Ex: Nictotinic receptor
Activated by ACH
2 Type II
G-protein coupled receptor
Located at cell membrane
Coupled to intracellular effectors via G-protein
Fast synaptic transmission
Seconds
Ex: muscarinic receptor for ACH
Ex: adrenergic receptor for Noradernaline
Target
Ion channels
Enzyme
3 Type III
Enzyme linked receptor
Located at cell membrane
Response occur in minutes - slow-
Ex: insulin receptor
4 Type IV
Gene transcription receptors
Located in the nucleus
Coupling with DNA
Response occurs in hours or days-V.slow-
Ex: estrogen / steroid receptors

MCQs

1-all of the following are a surface receptors except :

A-Type IV B-Type II
C-Type III D-Type I

2-Which one of the following receptorsoccurs in milliseconds (the fastest):

A- G-Protein B-IonChannel-Linked
C-Enzyme-Linked D-linked to gene transcription

3-Nicotinic receptors activated by acetylcholine is an example for:

A- G-Protein B-Enzyme-Linked
C-ion channel-Linked D-linked to gene transcription

4-Muscarinic receptors of Ach is an example for:

A- IonChannel-Linked B- G-protein
C-Enzyme-Linked D- gene transcription receptor

5-Increase intracellular calcium will cause:

A-Secretion of exocrine glands
B-Increase in heart rate
C-Smooth muscle contraction
D-all above

6-..... and ……..produce respective stimulation and inhibition of AC:

A- Gs &Gq
B- Gi &Gq
C- none of the above
D- Gs &Gi

7-which of the following is Directly related to DNA:

A- IonChannel-Linked B- G-protein
C-Enzyme-Linked D- gene transcription receptor

8-Gene transcription receptors usually occurs in:

A-seconds B-minutes
C-millisecond D- hours or days

Useful videos
https://www.youtube.com/watch?v=xT0mAQ4726s
https://youtu.be/i7_VTkhR3UI

Answers

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

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Team members:

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Rahaf AlShammari
Rahaf Althnayan
Reem Alqarni
Rinad Alghoraiby
Shaden AlOtay
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