Lecture (7)

Receptor Families

pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

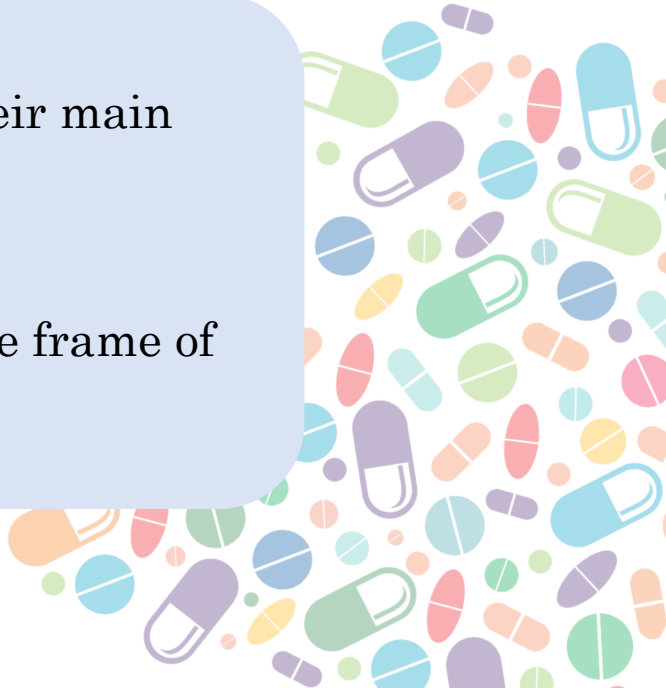
- Red : important
- Black : in male / female slides
- Pink : in girls slides only
- Blue : in male slides only
- Green : notes, Extra

Editing File:
https://docs.google.com/document/d/1WvdeC1atp7J-ZKWOUSukSLsEcosjZ0AqV4z2VcH2TA0/edit?usp=sharing

Reviewed by: Razan AlRabah & Khalid Alkhani

Objectives:

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

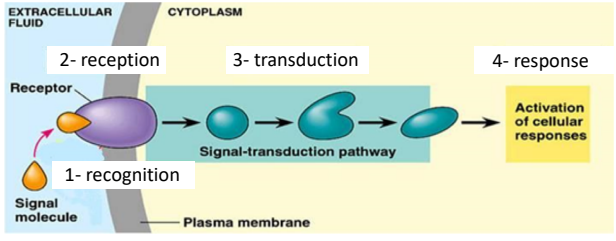


Main Receptor Classes (Receptor Families) :

- Effect Persistency of drugs
- Cellular mechanism of the drugs
- Selectivity of drugs
- Development of new drugs

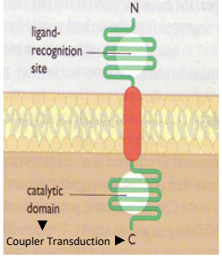
Receptor

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



A Receptor structure :

- Ligand recognition site
- Inner catalytic domain



Receptor 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

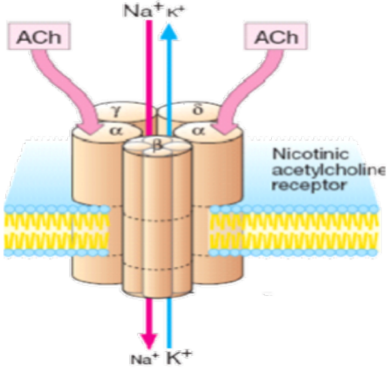
https://www.youtube.com/watch?v=WORIhbaRABg

https://www.youtube.com/watch?v=i7_VTkhR3UI

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

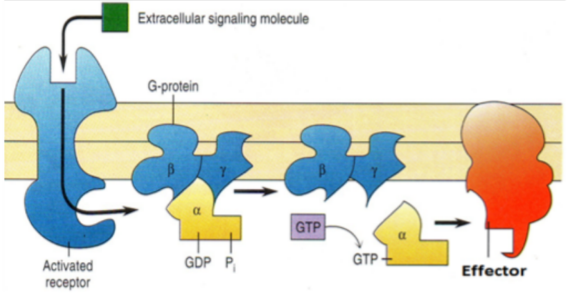
- Located at cell membrane.
- Directly activated by ligand binding.
- Involved in very fast synaptic transmission.
- Directly related to channels.
- Response occurs in milliseconds.
- *E.g. nicotinic receptors activated acetylcholine.*

  Nicotinic acetylcholine receptor is activated by occupancy of a ligand as Acetylcholine



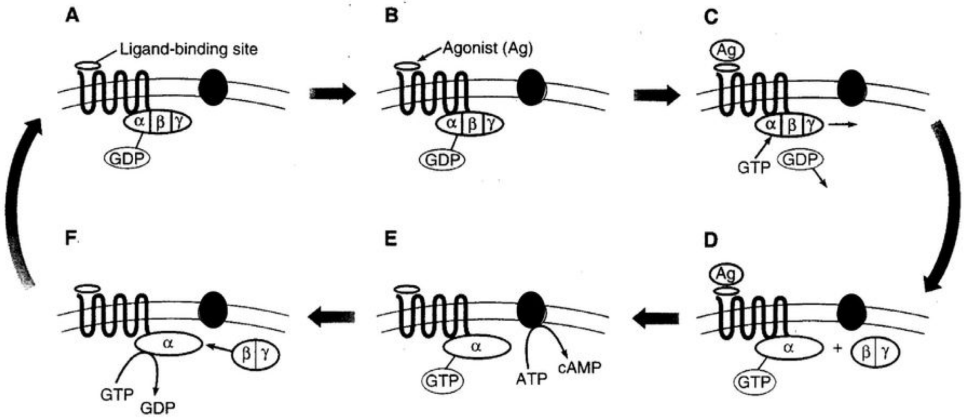
Type II : G-Protein coupled receptors (Metabotropic Receptor)

- 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.
- Involved in rapid transduction.
- Response occurs in seconds.
- *E.g. Muscarinic receptors of Ach (M)*
- *E.g. Adrenergic receptors of Noradrenaline (α and β receptors)*



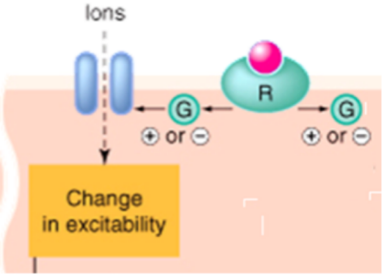
Type II : G-Protein coupled receptors

- GTP-binding Regulatory proteins.
- Regulates guanine nucleotides GDP,GTP.
- Comprise of 3 subunits (**α β γ**) , **α** subunit possess GTPase activity.
- When agonist binds to the receptor, G-protein is activated, the α-subunit dissociates & and is then free to activate an effector.
- Activation of the effector is terminated when the bound GTP molecule is hydrolyzed to GDP which allows **α**-subunit to recombine with (**β γ**) and return to its **inactive state**.



http://youtu.be/0nA2xhNiAow

Type II : G-Protein coupled receptors



Targets for G-Proteins:

1) Ion channels:

Can open or close ion channels causing change in the excitability
e.g. muscarinic receptors in heart (K-channel)
Ach acts on muscarinic receptors to produce a decrease in heart rate by opening of K channel and increasing K efflux **(hyper-polarization)**

Second Messengers (ENZYMES):

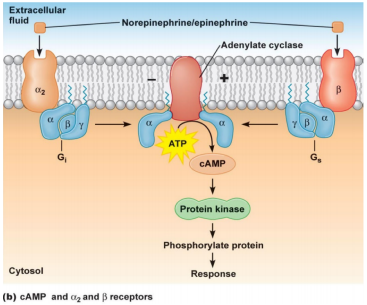
*cAMP = cyclic adenosine monophosphate

2) Adenyl cyclase enzyme (AC): Cyclic AMP system (cAMP)

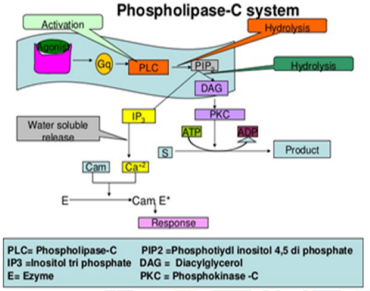
Activation of **Adenyl Cyclase** → **ATP** will be converted to → **cAMP** → **phosphorylation of protein kinase A (PKA)** → **Active PKA** →

⇧ Lipolysis ⇧ Glycogen breakdown to glucose ⇧ Ca^{+2} (force of contraction of heart)

⇩ Glycogen synthesis



(b) cAMP and α_2 and β receptors



3) Phospholipase C enzyme: Inositol phosphate system (IP3+DAG)

Once Phospholipase C is activated it will break **Phosphoinositol diphosphate (PIP2)** into:

- **Inositol triphosphate (IP3)** → ⇧ Intracellular Ca^{+2} → ⇧ Secretion of exocrine glands ⇧ Heart rate ⇧ Smooth muscle contraction.
- **Diacylglycerol (DAG)** → Stimulation of **Protein Kinase C (PKC)** → Ion Channels ⇧ Smooth muscle contraction.

Classes of G-Proteins

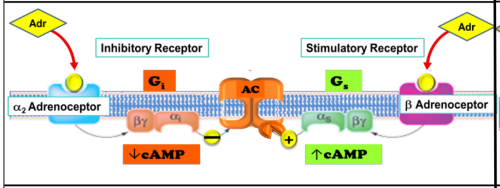
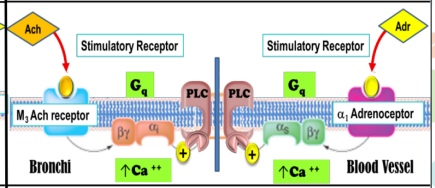
Divided according to their α-subunits into **Gs**, **Gi**, and **Gq**

1- Gs: stimulation of **Adenyl Cyclase**

2- **Gi: inhibition** of **Adenyl Cyclase**

3- **Gq: linked to activation** of **phospholipase C**
(PLC-IP3 - Ca^{++} CaM & PKC)

Classes of Receptors:

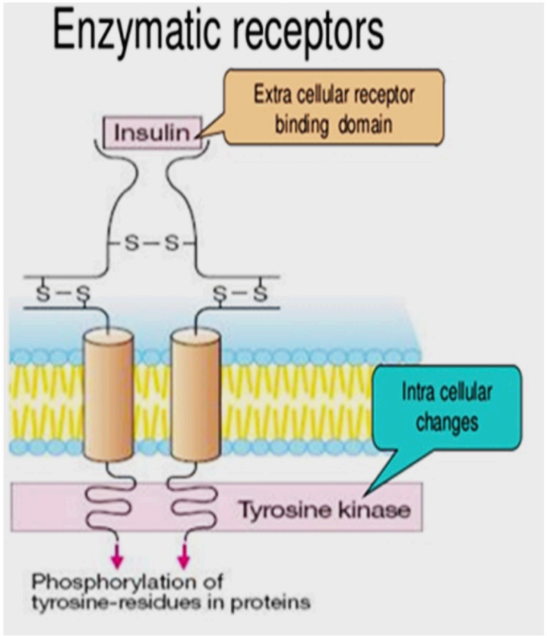
ADRENOCEPTORS	CHOLINERGIC RECEPTORS
α_1 Adrenoceptors couple to G_q to stimulate (PLC) (phospholipase c)	M_1 & M_3 Ach receptors couple to G_q to stimulate PLC (phospholipase c)
α_2 Adrenoceptors couple to G_i to inhibit AC (adenylyl cyclase)	M_2 & M_4 Ach receptors couple to G_i to inhibit AC (adenylyl 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 α_2 **Adrenoceptors** that will activate G_i **(Inhibitory)** protein. G_i protein will inhibit (AC) that will decrease cAMP Concentration. Decrease contraction Adrenaline bind to β **Adrenoceptors** that will activate G_s **(Stimulatory)** protein . G_s protein will activate (AC) that will increase cAMP Concentration. increase contraction	-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. Increase contraction -adrenaline work on **blood vessel** by α_1 receptor that will activate G_q proteins and G_q proteins will activate (PLC) that will increase ca Concentration. Increase contraction

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.

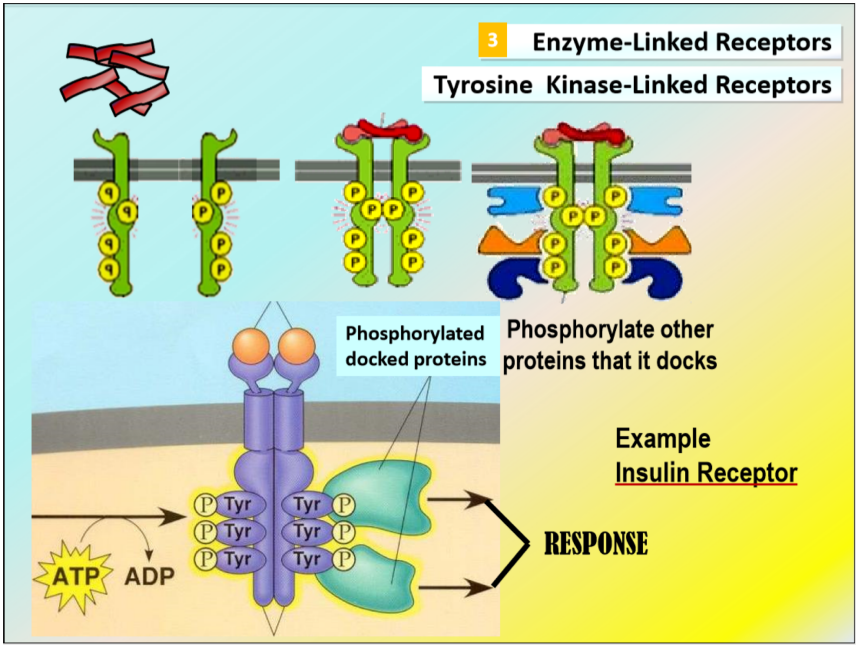
Activation of Type III receptors results in Activation of kinases as **tyrosine kinase** with **phosphorylation** of **tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

E.g. Insulin receptors



kinase (enzyme) does phosphorylation to other molecules & phosphorylation happens to it too.

الفوسفوريلاشين تحصل للكاينايز وايضا هو نفسه يعمل فوسفوريلاشين لحاجات ثانية.

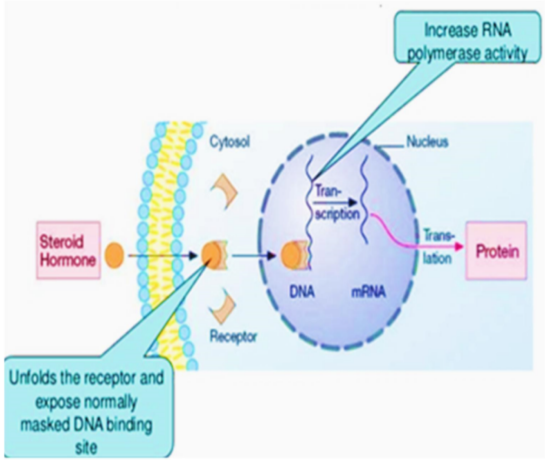


insulin (the drug) does dimerization to the receptor (brings the receptor closer so that it can combine the two parts of the receptor)

If there is any confusion, Check out this video to learn more about Enzyme-linked receptors https://www.khanacademy.org/test-prep/mcat/organ-systems/biosignaling/v/enzyme-linked-receptors

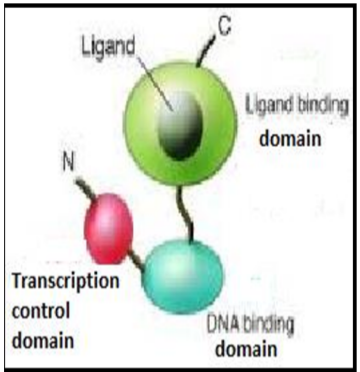
Type IV (GENE TRANSCRIPTION RECEPTORS; NUCLEAR RECEPTORS)

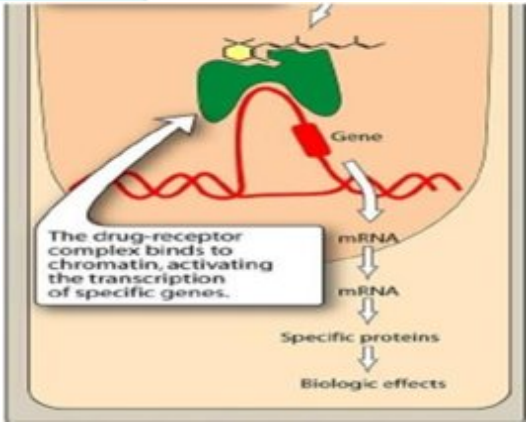
- Located **intracellularly**
- Directly related to DNA (Gene transcription).
- Activation of receptors either increase or decrease protein synthesis.
- Response occurs in hours or days and persists longer.
- Their natural ligands are lipophylic hormones; steroids, thyroids, estrogen.



Gene transcription receptors 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

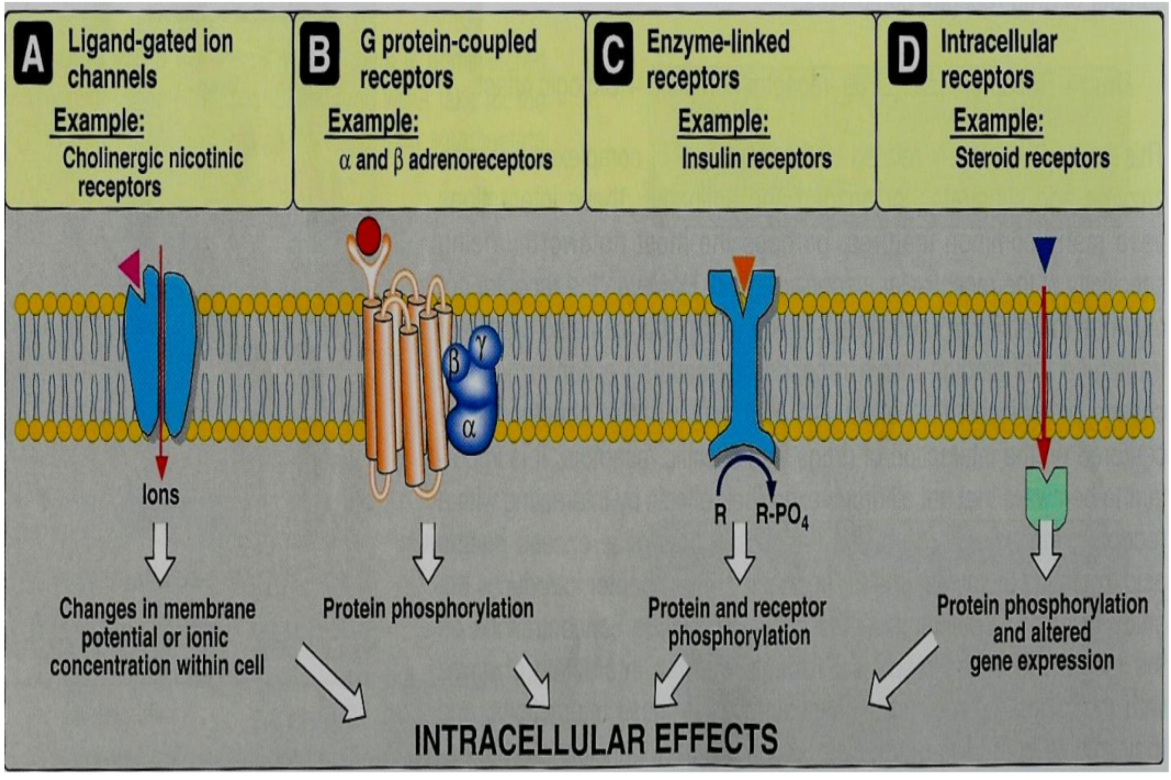


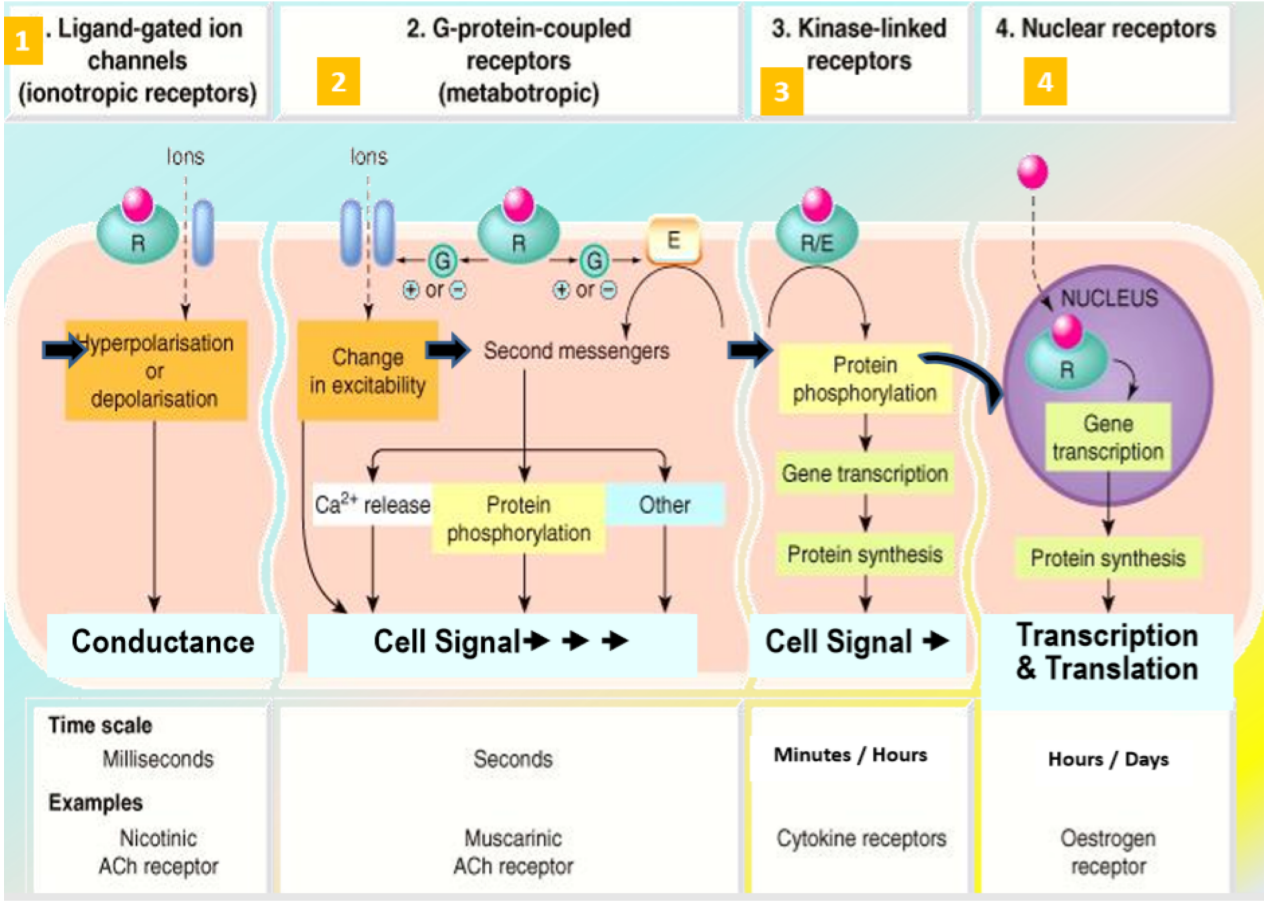


Receptor Families

	Type I	Type II	Type III	Type III
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

SIGNALING MECHANISMS




1. Ligand-gated ion channels (ionotropic receptors)
2. G-protein-coupled receptors (metabotropic)
3. Kinase-linked receptors
4. Nuclear receptors
Ions
Ions
R
R
G
G
E
⊕ or ⊖
⊕ or ⊖
R/E
NUCLEUS
R
Hyperpolarisation or depolarisation
Change in excitability
Second messengers
Protein phosphorylation
Gene transcription
Protein synthesis
Ca2+ release
Protein phosphorylation
Other
Conductance
Cell Signal
Cell Signal
Transcription & Translation
Time scale
Milliseconds
Seconds
Minutes / Hours
Hours / Days
Examples
Nicotinic ACh receptor
Muscarinic ACh receptor
Cytokine receptors
Oestrogen receptor

QUIZ

1-According to the receptor structure in the cell membrane , the ligand binding site of the receptor are in the ….

A-intracellular part of the receptor
B-Extracellular part of the receptor
C-transmembrane area (hydrophobic region of phospholipids)
D- catalytic domain of the receptor

2-What is the nature of the ligands that bind to type IV receptors ?

A-amphipathic
B-hydrophilic
C-hydrophobic
D-polar ,uncharged

3-Which one of these type of receptors gives the fastest response?

A-Nicotinic receptors
B-Muscarinic receptors
C-Insulin receptors
D-estrogen steroid receptor

4-Which one of these receptors is coupled with G_q protein ?

A-Alfa 1
B-Alfa 2
C-Beta 1
D-Beta 2

5-Which one of these receptors gives a direct response?

A- G-protein coupled receptor
B- Nuclear receptor
C- Intracellular receptor
D- Enzyme-linked receptor

6- Inositol phosphate system activate ……

A- Protein kinase A
B- Protein kinase C
C- Tyrosine kinase
D- Channel proteins

SAQ:

1-List the names of the four types of receptors ,and give examples for each one .

2- Describes the transduction process after activating the G-protein coupled receptors

3- List the main 2 targets for G-proteins ,and give examples for each one .

Answers : 1/B , 2/C , 3/A , 4/A ,5/D ,6/B

Good luck

Thanks to the pharma team 435

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