Receptor Families

Lecture no. 7

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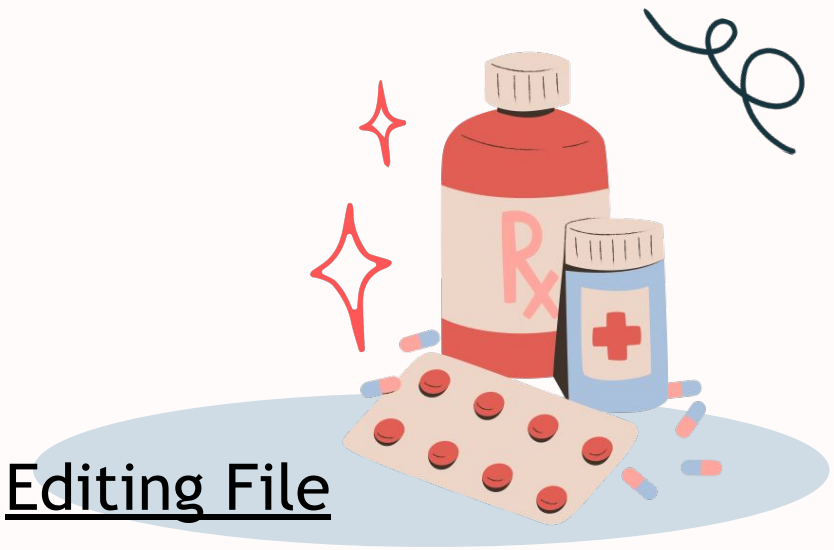
- Extra info.



Editing File

(اللَّهُمَّ انفَعْنِي بِمَا عَلَّمْتَنِي، وَعَلِّمْنِي مَا يَنْفَعُنِي وَزِدْنِي عِلمًا)

Objectives

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

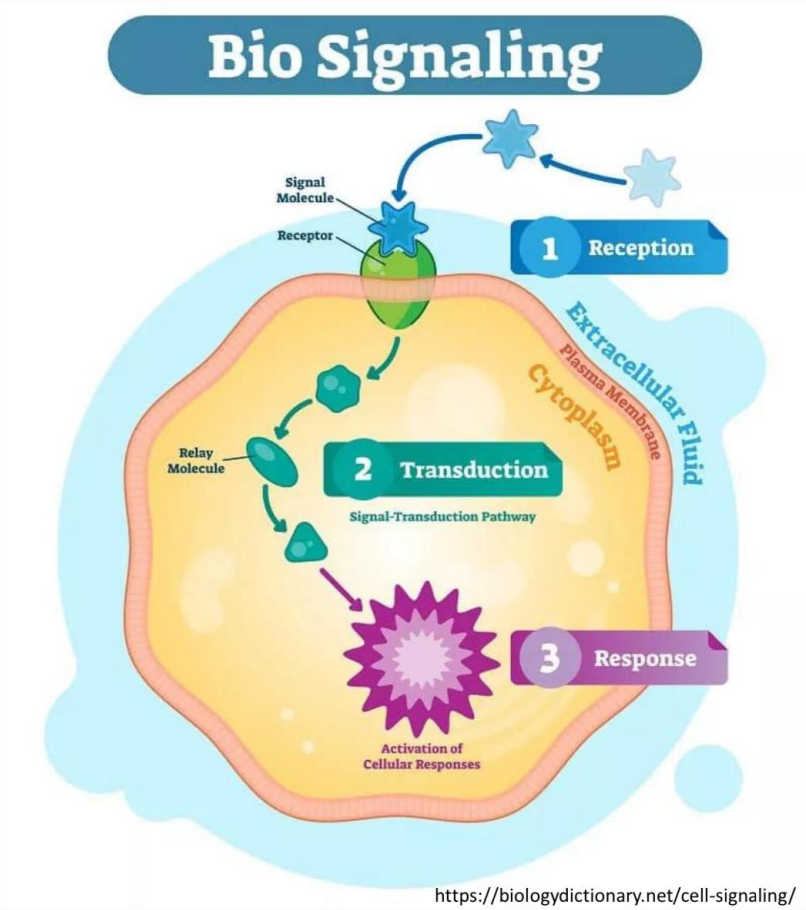
Cell Signaling/Transduction

Recognition
(When ligand attaches to a receptor)

Reception
(When ligand activates a receptor)

Transduction
(Signal transduction pathway)

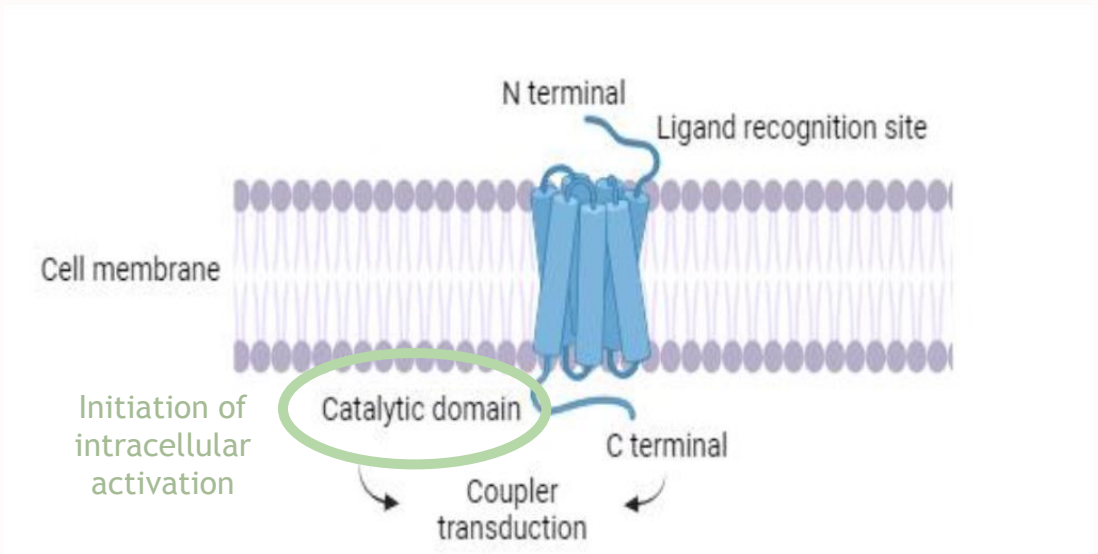
Response



https://biologydictionary.net/cell-signaling/

Receptor Structure

1. Ligand (Drug, hormone, neurotransmitter…) recognition site
2. Inner catalytic domain (catalysis>break cell)



Receptor Families-Type I

Ion channel-linked receptors

Synonyms

- Ion channel-linked receptors
- Ligand-gated ion channels (common name)
- Ionotropic receptors

Example

Nicotinic receptors that are activated by occupancy of a ligand as **acetylcholine**

- Located at the **cell membrane.**

(as it's on the cell membrane, it doesn't require to be lipid soluble)

- **Directly** activated by ligand binding.

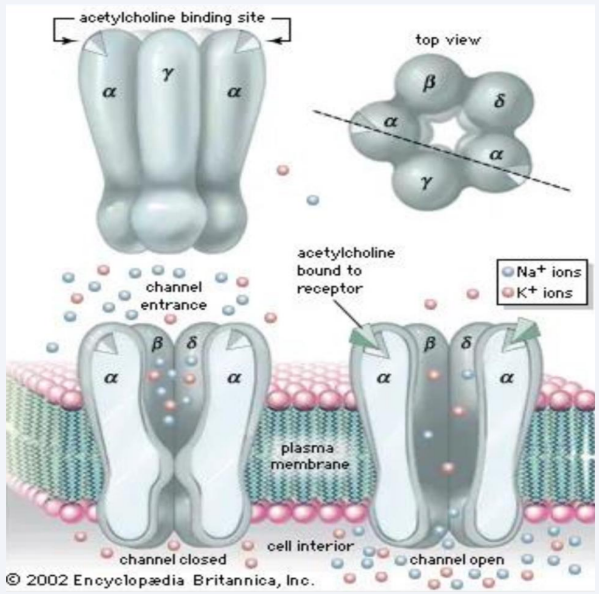
(no second messenger needed)

- **Directly** related to **ion channels.**

(when the drug starts producing 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.**



Extra explanation from 442:
Nicotinic receptors are only found inside ganglia for parasympathetic so it could activate any action related to parasympathetic system.The process simply will be:
Neuron transmission (Ach) is a ligand -> bind to the receptor ->the receptor will open channel-> High Na intracellular ->depolarisation ->parasympathetic response such as heart relaxation

Receptor Families-Type II

G-protein coupled receptors

Synonyms

- G-protein coupled receptors (GPCRs)
- Metabotropic Receptor

Examples

- **Muscarinic** receptors of **Ach**
- **Adrenergic** receptors of **Noradrenaline**

- 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. (not direct)
- Involved in **rapid** transduction.
- Response occurs in **seconds.**

Receptor Families-Type II

G-protein coupled receptors

- Guanosine triphosphate (GTP)
- Guanosine diphosphate (GDP)

G-proteins

- Regulatory proteins (regulation for intracellular events).
- Comprise of three subunits (αβγ), **α** subunits possess GTPase activity.
- G proteins belong to the larger group of enzymes called GTPases.
- Regulate guanine nucleotides GDP, GTP.
- They bind and hydrolyse guanosine triphosphate (**GTP**) to guanosine diphosphate (**GDP**).
- They are **active** 'on'→when they are bound to **GTP**.
- They are **inactive** 'off'→when they are bound to **GDP**.

Has different classes of receptors:	Has different receptors subtypes:
- Cholinergic R (Ach)→M Rs - Adrenergic R (NA)→α & Β	- m Ach; m1, m2, m3, m4 - Β Adrenergic receptors; Β1, Β2 , Β3

Has differences in their related G-protein classes

special thanks to 441 & 442

Extra Info for understanding

It's also recommended to study biochem lecture 10-Cell signaling & regulation before this for a better understanding.

Receptor Families-Type II

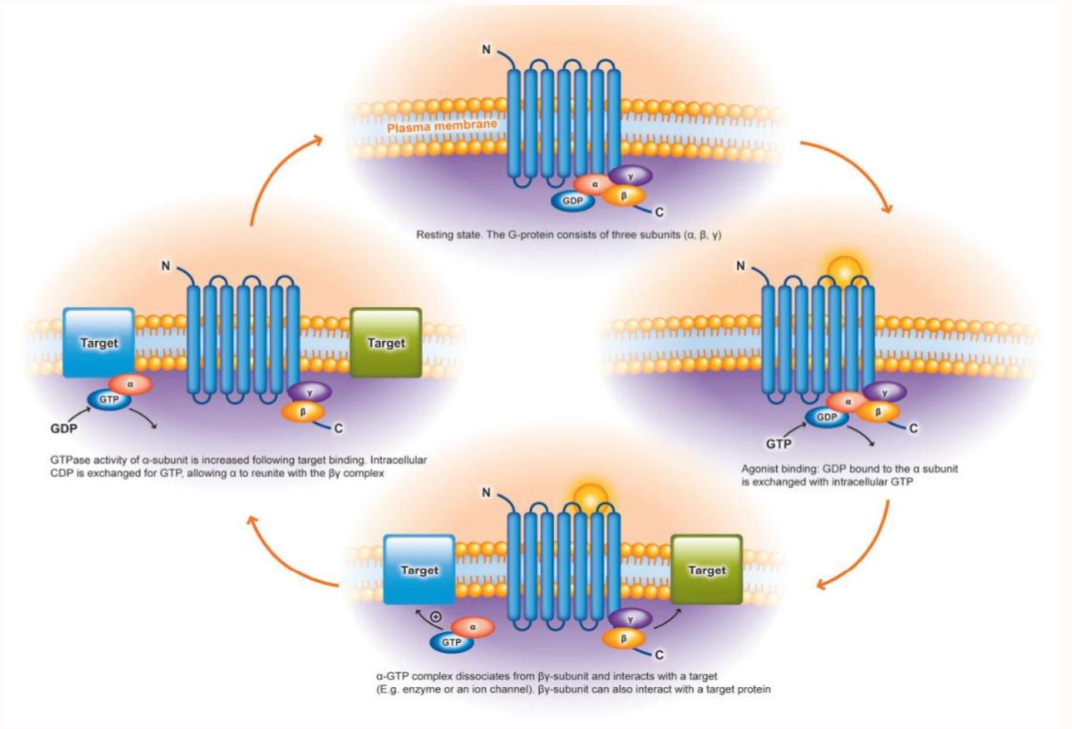
G-protein coupled receptors

Receptors of this family respond to agonists by:

1	2	3
promoting the binding of **GTP** to the **G protein alpha (α) subunit.**	GTP activates the G protein and allows it, in turn, to activate the effector protein.	The G protein remains active until it hydrolyzes the bound GTP to GDP and returns to its ground (inactive) state.

When the G-protein trimer (αβγ), 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 to GDP which allow α-subunit to recombine with (βγ) and returns to its inactive state.



GPCRs response to agonist

Receptor Families-Type II

G-protein coupled receptors

Targets for G-proteins

Ion channels

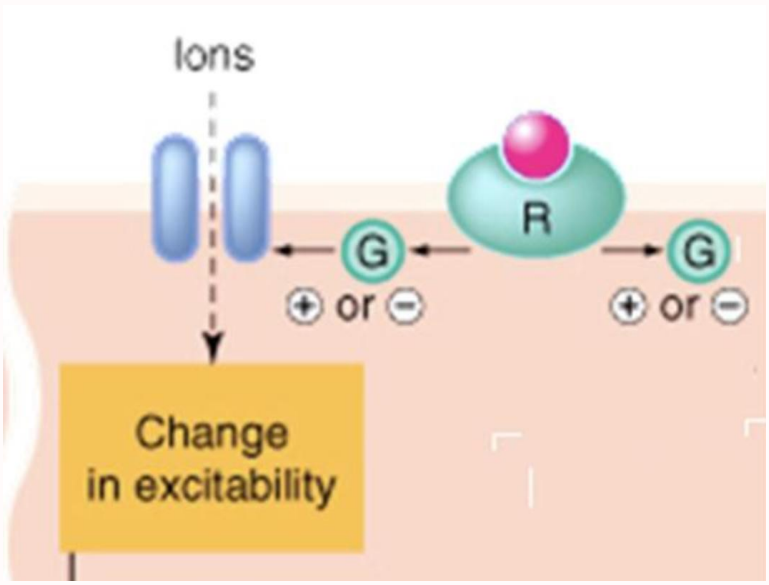
e.g. **Ach** acts on **muscarinic** receptors in the heart (opening of K-channel) to **decrease heart rate**

Enzymes

To give second messengers

Adenylyl cyclase enzyme→Cyclic AMP system (cAMP)

Phospholipase C enzyme→Inositol phosphate system (IP3+DAG)



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

special thanks to 443
Extra Info about exact mechanism for understanding

Receptor Families-Type II
G-protein coupled receptors

Second messenger
Cyclic AMP system (cAMP)

G-protein → Activates Adenylyl cyclase enzyme

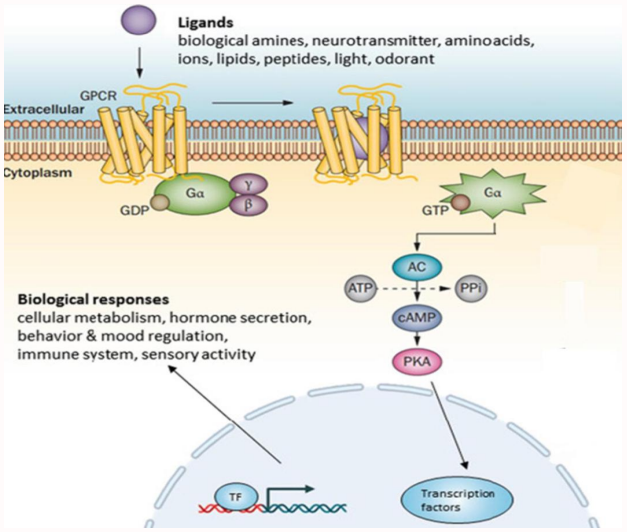
ATP

cAMP

Phosphorylation of Protein kinase A (PKA)

Active protein kinase A

Activation or inhibition of ion channels or enzymes:
↑Ca2+ , ↑ lipolysis &
↑ breakdown of glycogen to glucose



cAMP: Cyclic AMP
AC: Adenyl cyclase enzyme
PKA: Protein kinase A

Second messenger
Inositol phosphate system

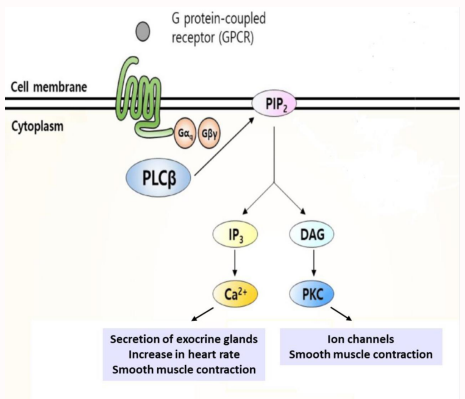
G-protein → Activates Phospholipase C

Inositol triphosphate (IP3) → Increase intracellular calcium

- Secretion of exocrine glands
- Increase in heart rate
- Smooth muscle contraction

Diacylglycerol (DAG) → Protein kinase C (PKC)

- Ion channels
- Smooth muscle contraction



PLC: Phospholipase C
PIP2: Phosphoinositol diphosphate
IP3: Inositol triphosphate
DAG: Diacylglycerol
PKC: Protein kinase C

Important

Types of G-protein according to their α-subunits :

	Gs	Gi	Gq
Effect of the effector	Stimulation	Inhibition	Stimulation
Pathway	cAMP-dependent pathway	cAMP-dependent pathway	Inositol phosphate system
Examples	β1&2 Adrenoceptors	• M2 &M4 Ach • α2 Adrenoceptors	• M1 & M3Ach • α1 Adrenoceptors

Example of GPCRs:

Receptor	G-protein	Effect	Pharmacological activity
β1&2 Adrenoceptors	Gs	Stimulate AC	• β1→Stimulation (tachycardia) • β2 → Vasodilatation
• M2&M4Ach • α2 Adrenoceptors	Gi	Inhibit AC→Dec cAMP→ Opening of K-channels	• M2 → Heart (Bradycardia) • M4→Analgesia • α2 → Inhibit transmitters release
• M1&M3Ach • α1 Adrenoceptors	Gq	Stimulate PLC	• M1 → Enhance cognitive function • M3 & α1→Contraction of Smooth muscles

Receptor Families-Type III

Enzyme-Linked receptors

Example

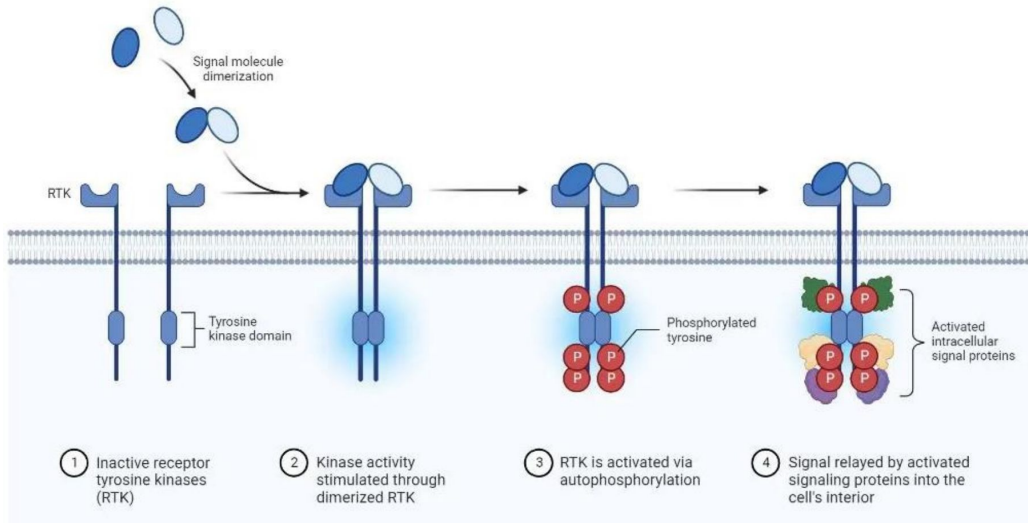
Tyrosine Kinase-linked receptor

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

Activation of Type III receptors results in:

- Activation of kinases as tyrosine kinase →
- Phosphorylation of tyrosine residue on their substrates →
- Activation of many intracellular signalling pathways in the cell.

E.g. Insulin receptors



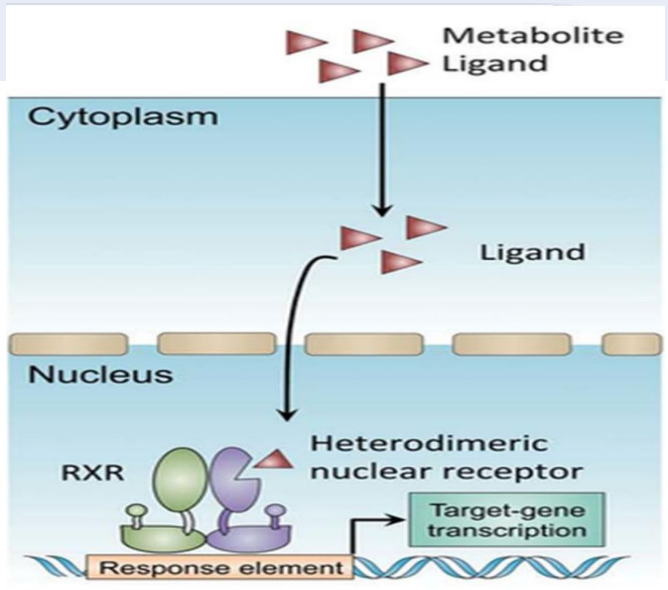
Receptor Families-Type IV

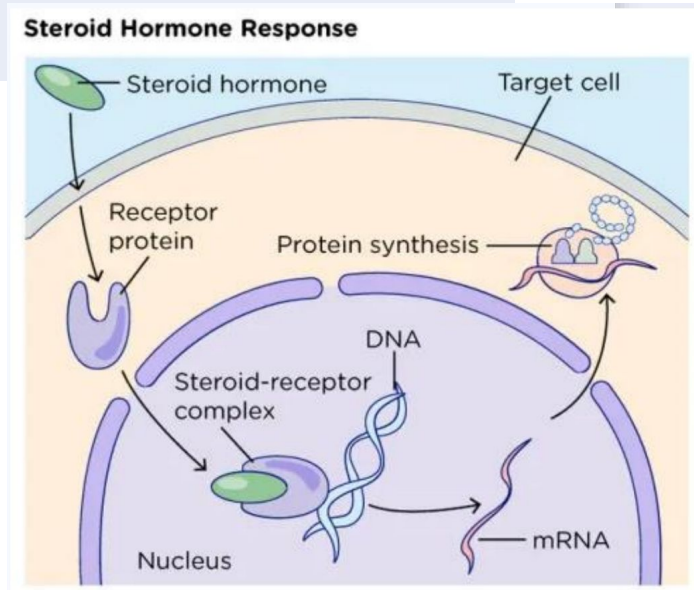
Nuclear receptors

Synonyms

- Nuclear Receptors
- Gene Transcription 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 **lipophilic** hormones; steroids, thyroids, and estrogenic.
- They possess an area that recognises specific DNA sequences in the nucleus which can bind it. This sequence is called a **Responsive Element [RE]**.
- The activated receptors are **acting as TRANSCRIPTION FACTORS [TF]** → expressing or repressing target genes.





Receptor Families

	Type I ion channel-linked	Type II G-protein coupled R (G-PCR)	Type III Enzyme-linked R	Type IV Receptors linked to gene transcription
Location	Membrane	Membrane	Membrane	Nucleus Must be lipid soluble
Coupling	Direct	G-protein	Direct	Via DNA
Synaptic Transmission	Very fast	Fast	Slow	Very Slow Because human body take a long time to synthesize proteins
Response	Milliseconds	seconds	Minutes to hours	Hours to days
Example	Nicotinic receptors	Muscarinic receptor Adrenergic receptor	Insulin Receptors	Estrogen steroid receptors
Effectors	Channels	Channels (1st message)/Enzymes (2nd message)	Enzymes	DNA (in a specific sequence of a gene)

MCQs

Q1)Which GTP protein subunit has enzymatic activity ?			
a) α	b)β	c)γ	d)all

Q2) Another name for a Metabotropic Receptor is :			
a)Nuclear receptors	b)G-protein coupled receptors	c)Ion channel linked receptors	d)IEnzyme Linked receptors

Q3) All receptors are found on cell membrane except?			
a)Type I	b)Type IV	c)Type III	d)Type II

Q4) An example of Type II receptor is :			
a)Insulin receptors	b)Nicotinic acetylcholine receptor	c)Muscarinic & Adrenergic receptors	d)Estrogen Steroid receptors

Q5) Function of Gq protein is :			
a) stimulates Inosotol phosphate system	b)inhibits cAMP dependent pathways	c)inhibits Inosotol phosphate system	d)stimulates cAMP dependent pathway

Answers:
1)A
2)B
3)B
4)C
5)A

SAQS

Q1.What are the Targets for G-proteins?

slide 8

Q2. Which of the receptor families can act as a transcription factor?

type IV receptors (Nuclear receptors)

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