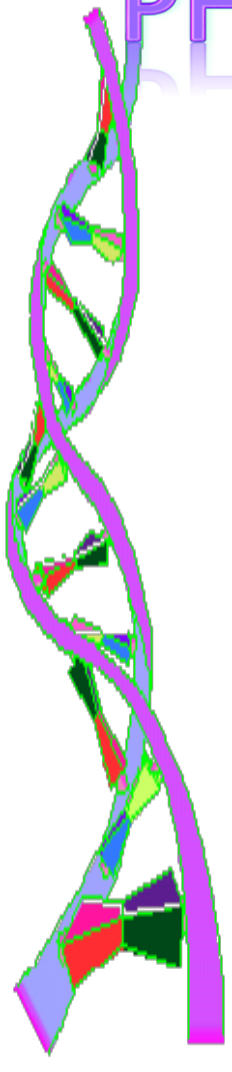
PHARMACODYNAMICS III



RECEPTOR FAMILIES

Prof. Hanan Hagar

ilos *the end of this lecture you will be able to :*

➢**Classify receptors into their main superfamilies**

➢**Recognize their different transduction mechanisms**

➢ **Identify the nature & time frame of their response**

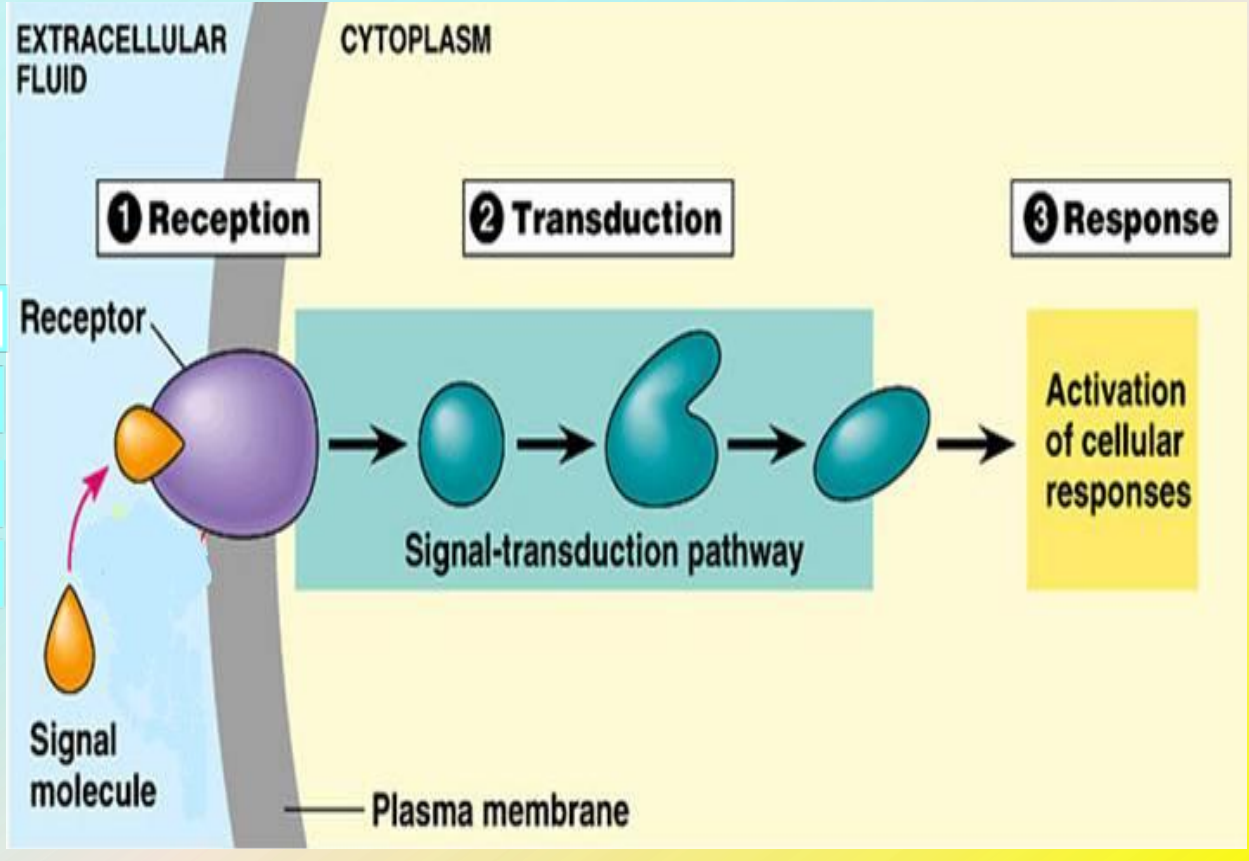
A RECEPTOR

Recognition

Reception

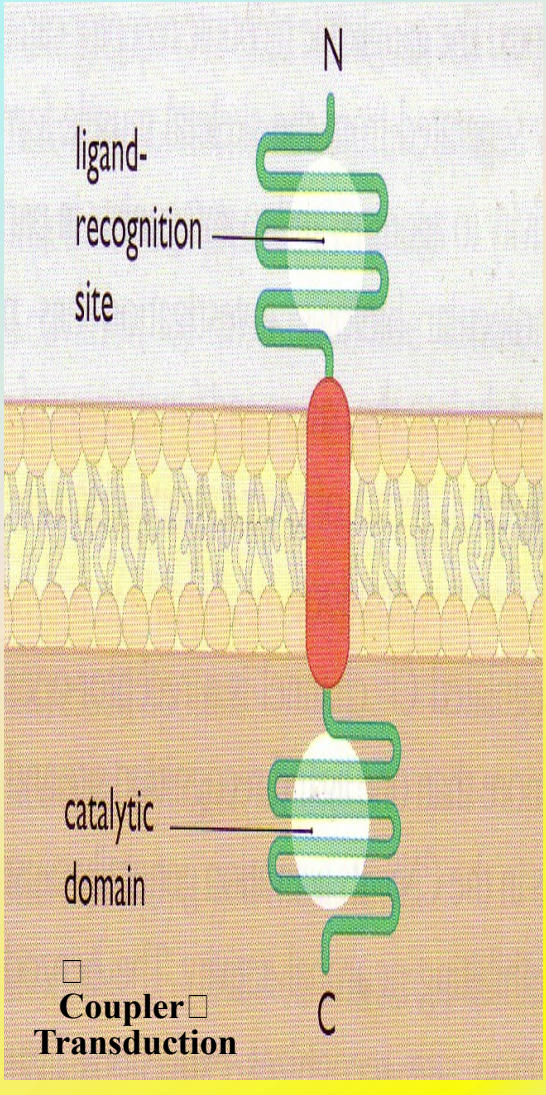
Transduction

Response



A RECEPTOR structure

- Ligand recognition site
- Inner catalytic domain



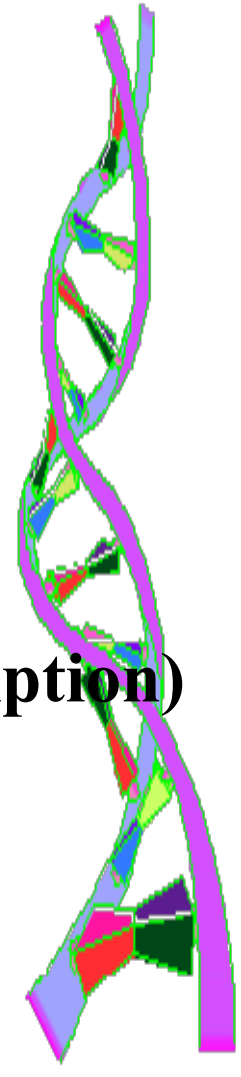
RECEPTOR FAMILIES

Type I (Ion Channel-Linked receptors)

Type II (G-Protein coupled receptors)

Type III (Enzyme-Linked receptors)

Type IV (Receptors linked to gene transcription)



RECEPTOR FAMILIES

	Type I	Type II	Type III	Type IV
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 e.g. nicotine	muscarinic receptors adrenergic receptors	Insulin receptors	estrogen receptors Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	DNA

TYPE I : Ion Channel-Linked receptors

Ligand gated ion channels

Ionotropic receptors

Located at cell membrane

Directly activated by ligand binding

Directly related to ion channels.

Involved in very fast synaptic transmission.

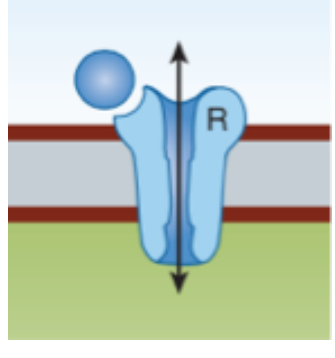
Response occurs in milliseconds.

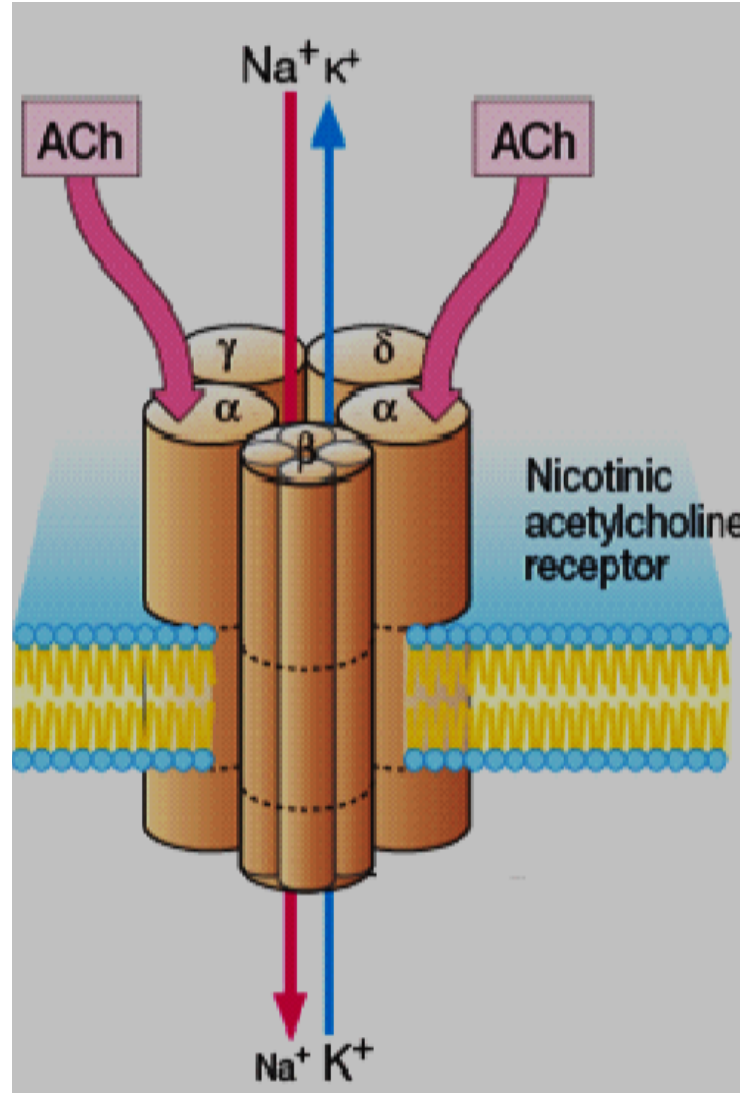
1 **Channel-Linked Receptor**

Ionotropic Receptor

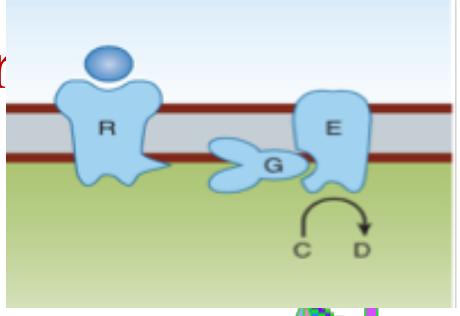
Ligand-Gated-Ion Channel

e.g. nicotinic receptors that are activated by occupancy of a ligand as acetylcholine.





Type II: G-Protein coupled receptor
Metabotropic Receptor



The largest family that accounts for many known drug targets

Located at cell membrane

Coupled to intracellular effectors via **G-protein**

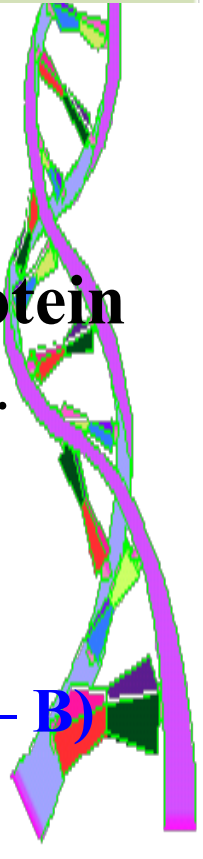
Response through ion channels or enzymes.

Involved in rapid transduction

Response αβoccurs in seconds.

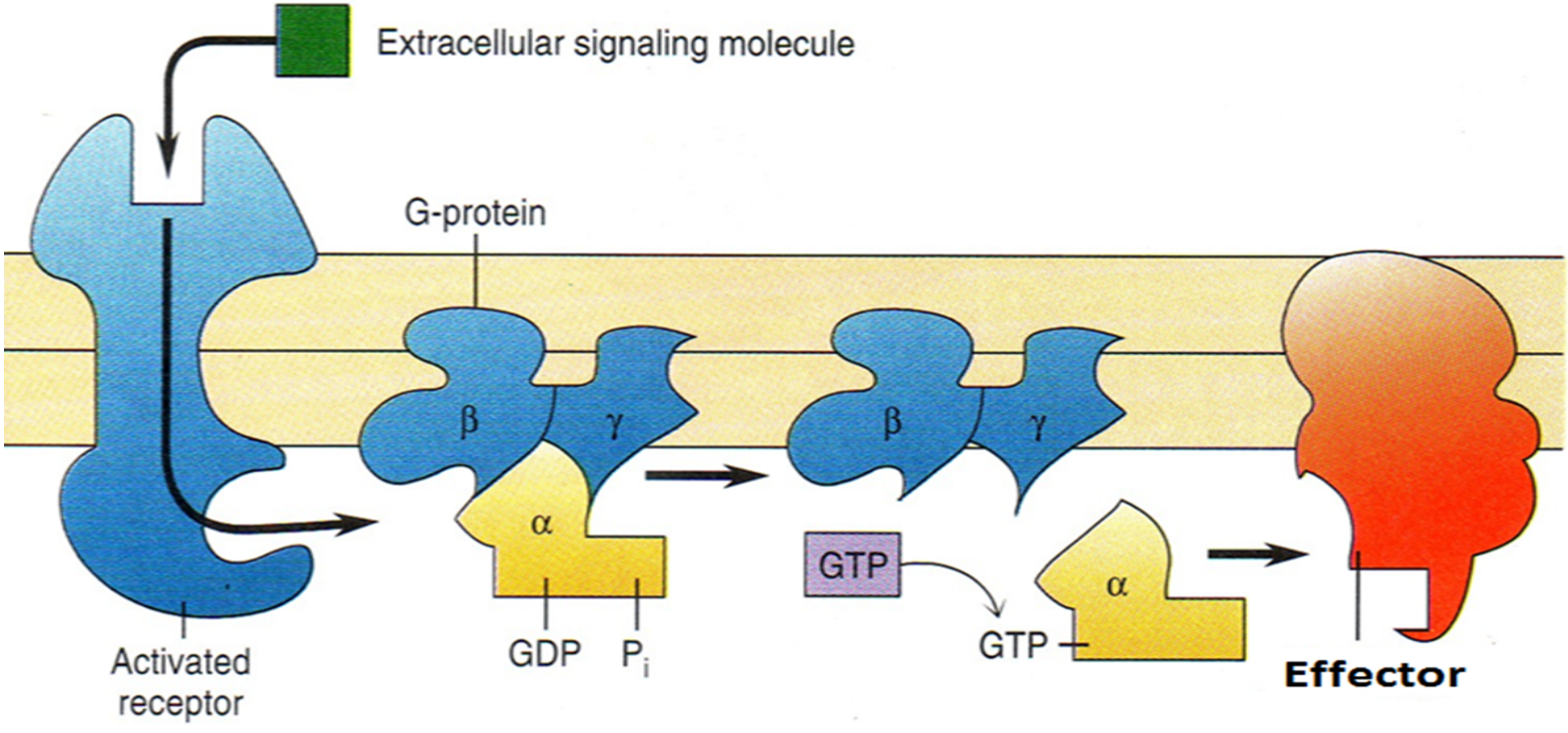
E.g. Muscarinic receptors of Ach

E.g. Adrenergic receptors of Noradrenaline(α – B)



G-protein (Guanine nucleotide-binding proteins)

- Regulatory proteins
- Comprise of three subunits (□□γ), □ subunits possess GTPase activity.
- G proteins belong to the larger group of enzymes called GTPases.
- Regulate guanine nucleotides GDP, GTP.
- They bind and hydrolyze 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



Receptors in this family respond to agonists

•by 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.

G-protein

- When the G-protein **trimer** (□□γ), binds to agonist-occupied receptor , **the □-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 □-subunit to recombine with **(□γ)** and returns to its inactive state.

Targets for G-proteins

Ion channels

e.g. Ach acts upon muscarinic receptors in heart (opening of K-channel), to decrease heart rate

Enzymes

To give Second messengers

Cyclic AMP system (cAMP)

Inositol phosphate system (IP3+DAG)

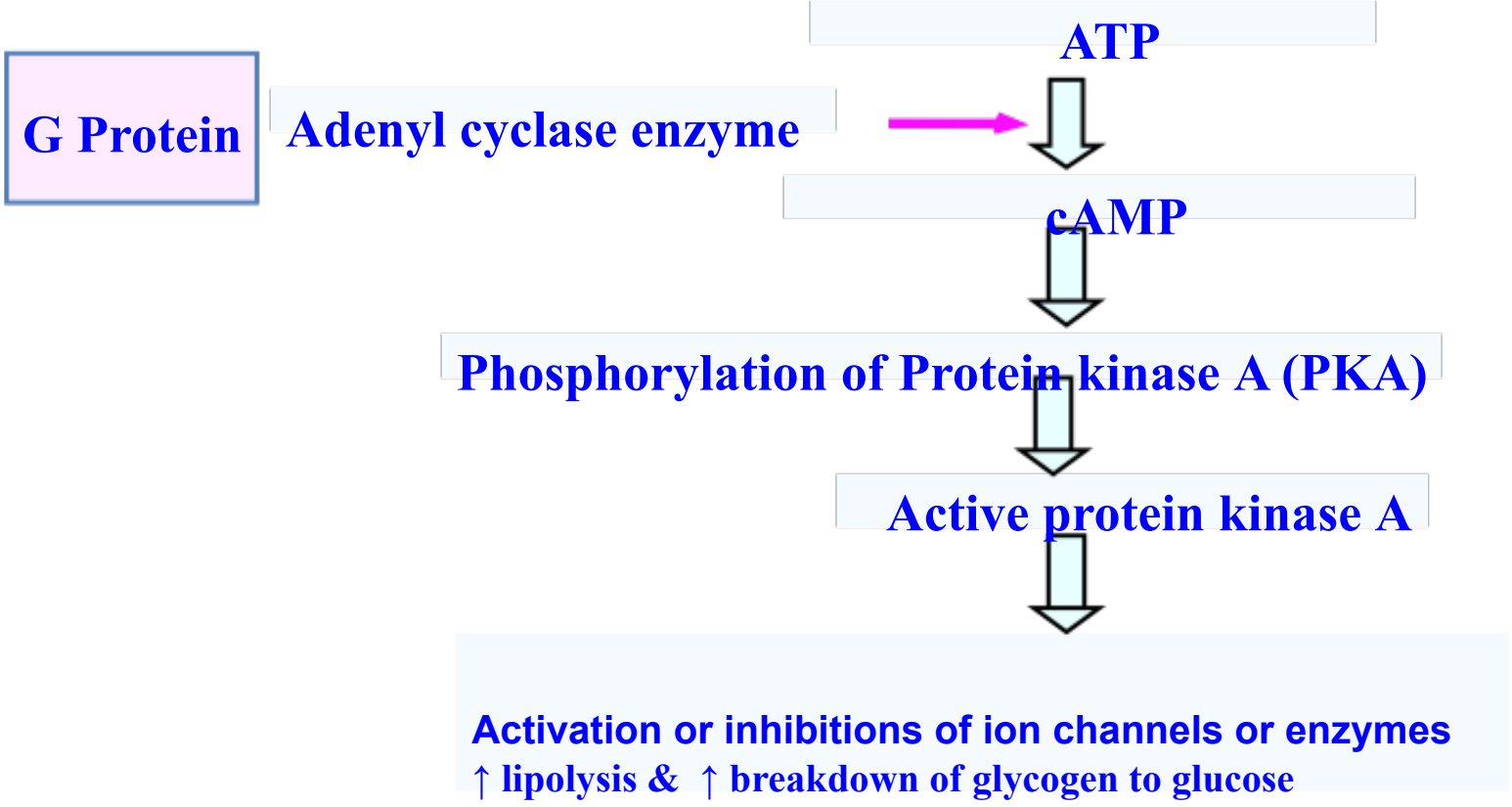
cAMP= cyclic adenosine monophosphate
IP3 = inositol triphosphate DAG= diacylglycerol

Type II receptors (G-Protein coupled receptors)

Targets for G-proteins

- Second messengers

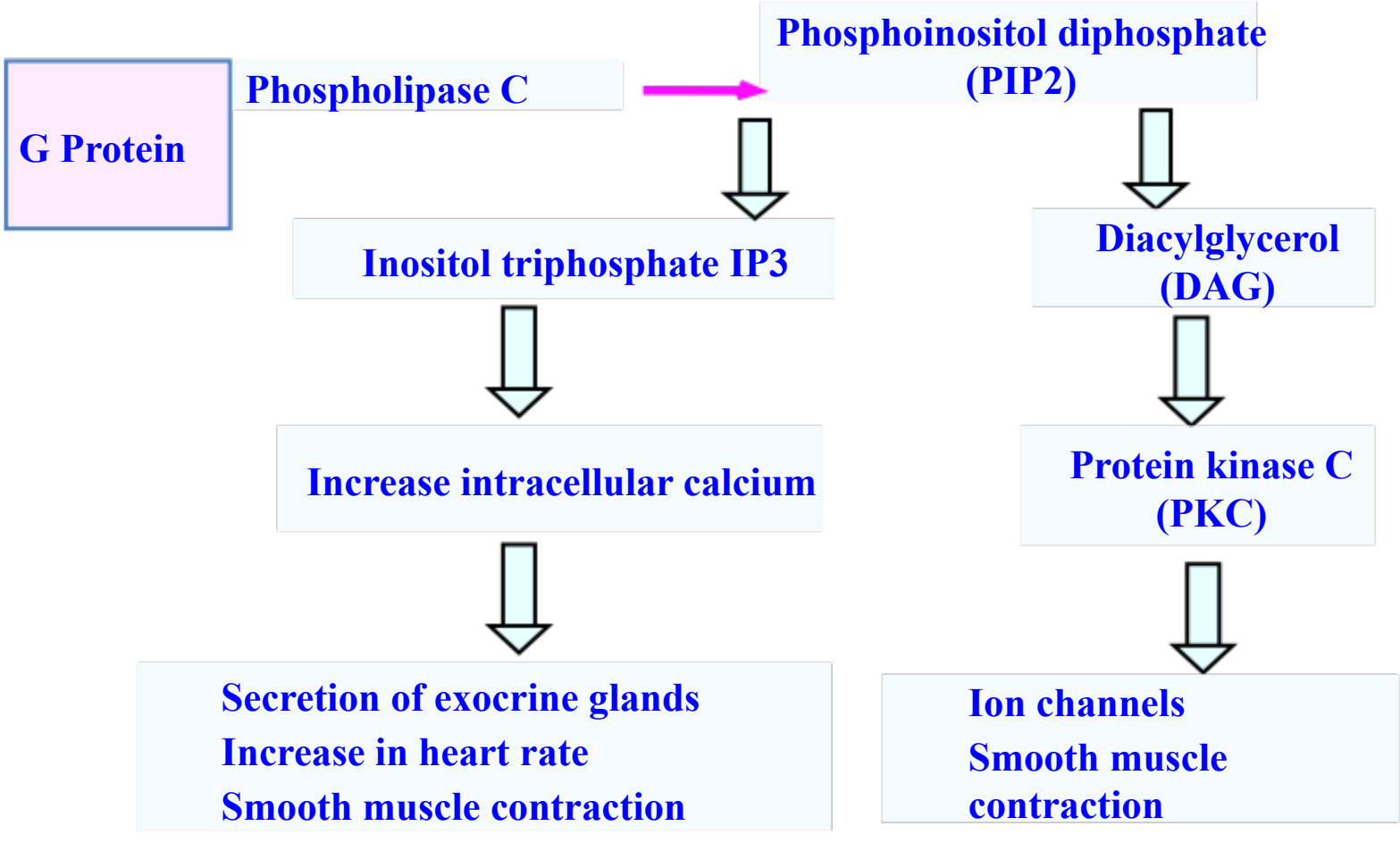
Cyclic AMP system (cAMP)



Type II receptors

Targets for G-proteins

Inositol phosphate system



Type II receptrs (G-Protein-Coupled Receptors)

Are the Most Abundant Type

Different Classes of Receptors

cholinergic R (Ach) □ m **Adrenergic R (NA) □ a & b**

Different Receptors Subtypes

m Ach; m1, m2, m3, m4
b Adrenergic receptors; b1, b2 , b3

Difference in their related G-Protein Classes

G-protein

(Guanine nucleotide-binding proteins)

are divided according to their α-subunits into:

Gs: stimulation of the effector
Linked to the **cAMP-dependent pathway**

Gi: Inhibition of the effector
Linked to the **cAMP-dependent pathway**

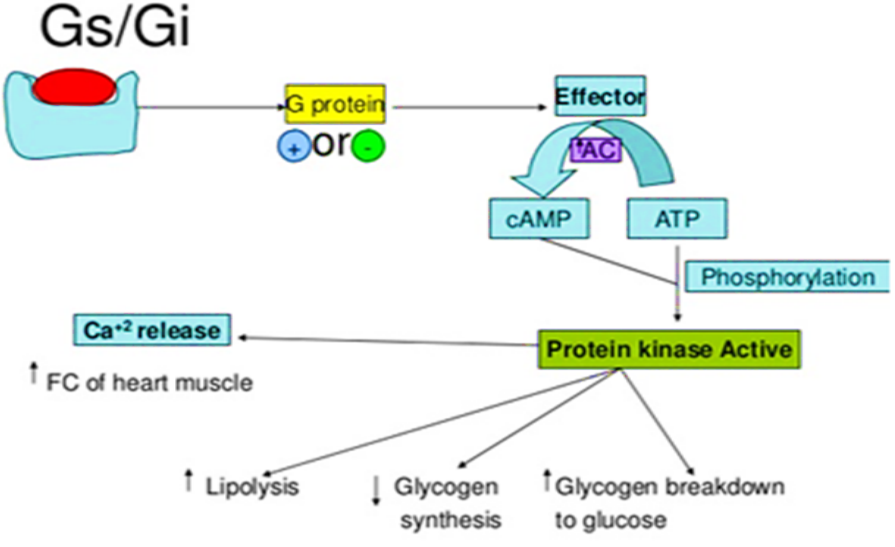
Gq (activation, linked to **Inositol phosphate system**).

Type II receptors (G-Protein coupled receptors)

Targets for G-proteins

Second messengers

- Cyclic AMP system (cAMP)
  - 1&2 Adrenoceptors couple to Gs to stimulate AC
  - M2 & M4 Ach receptors couple to Gi to inhibit AC
  - 2 Adrenoceptors couple to Gi to inhibit AC.

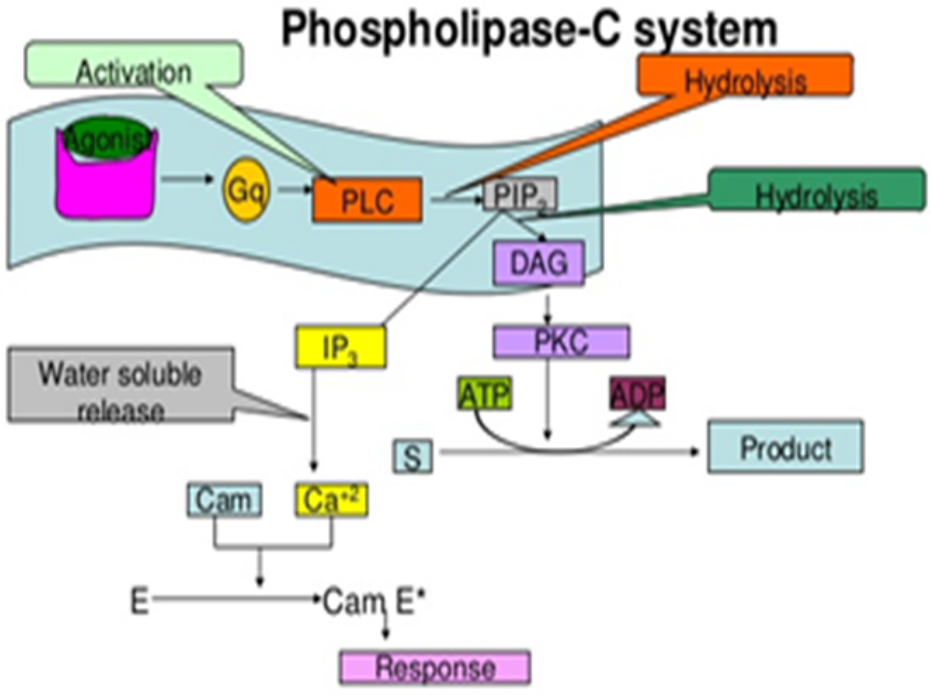


Type II receptors (G-Protein coupled receptors)

Targets for G-proteins

Second messengers

- Inositol phosphate system (IP3+DAG)
- **M1 & M3** Ach receptors couple to **Gq** to **stimulate** PLC
- **1** Adrenocepto



Ach receptors	Couple to	Intracellular mechanisms	Response
M1 stimulatory	Gq	stimulate PLC	stimulation
M2 inhibitory	Gi	Inhibit AC (↓ cAMP) Opening of K-channels	Heart (Bradycardia)
M3 stimulatory	Gq	stimulate PLC	Contraction of Smooth muscles (brocnchoconstriction)
M4 inhibitory	Gi	Inhibit AC (↓ cAMP)	Inhibition

Adrenoceptors	Couple to	Intracellular mechanisms	Response
1 stimulatory	Gs	stimulate AC	Stimulation (tachycardia)
1 stimulatory	Gq	stimulate PLC	Contraction of smooth muscles

Type III (Enzyme-Linked receptors)

(Tyrosine Kinase-linked receptor)

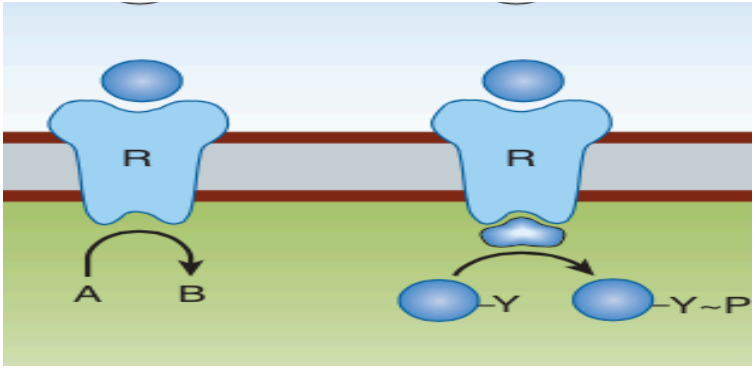
Located at cell membrane

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.



Type III (Enzyme-Linked receptors)

(Tyrosine Kinase-linked receptor)

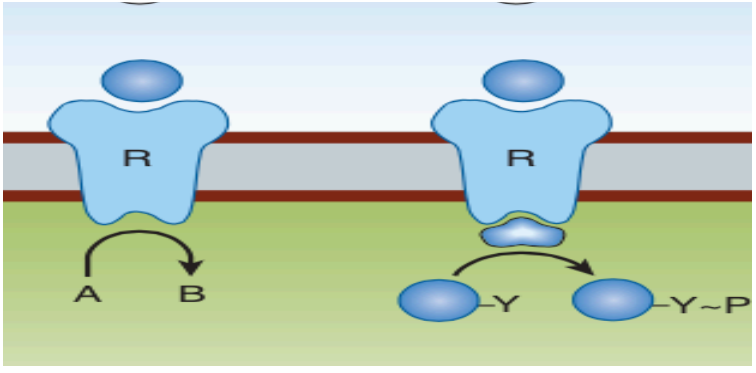
Activation of Type III receptors results in

Dimerization of receptors

Auto-phosphorylation

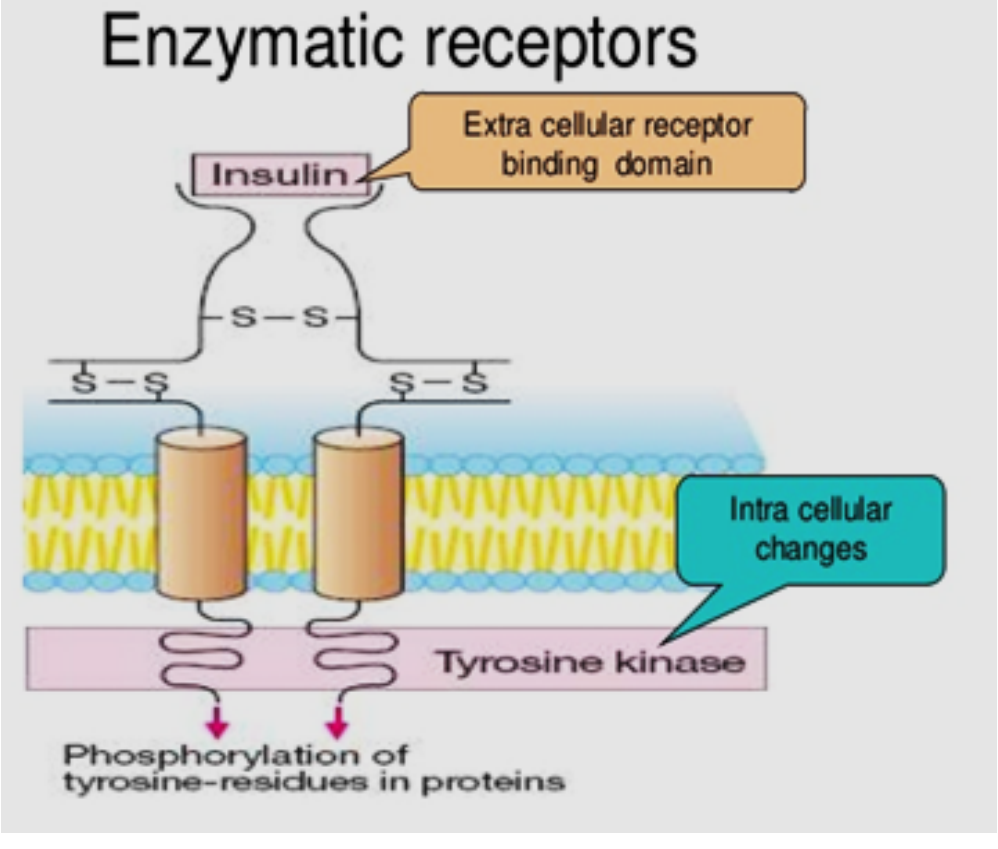
Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

E.g. Insulin receptors



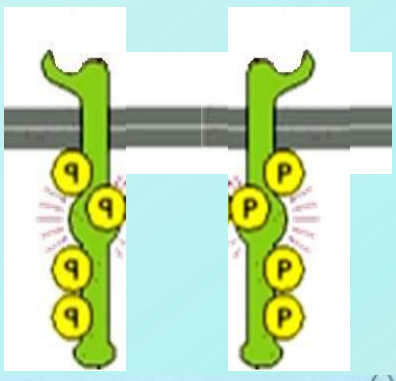
Type III (tyrosine kinase-Linked receptors)

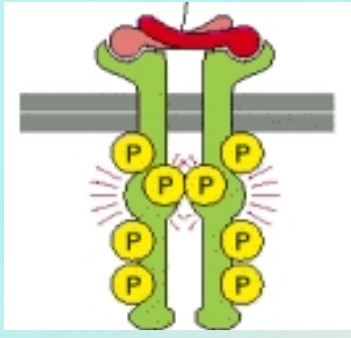
Insulin receptors

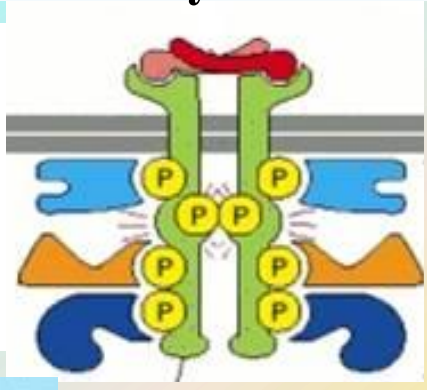


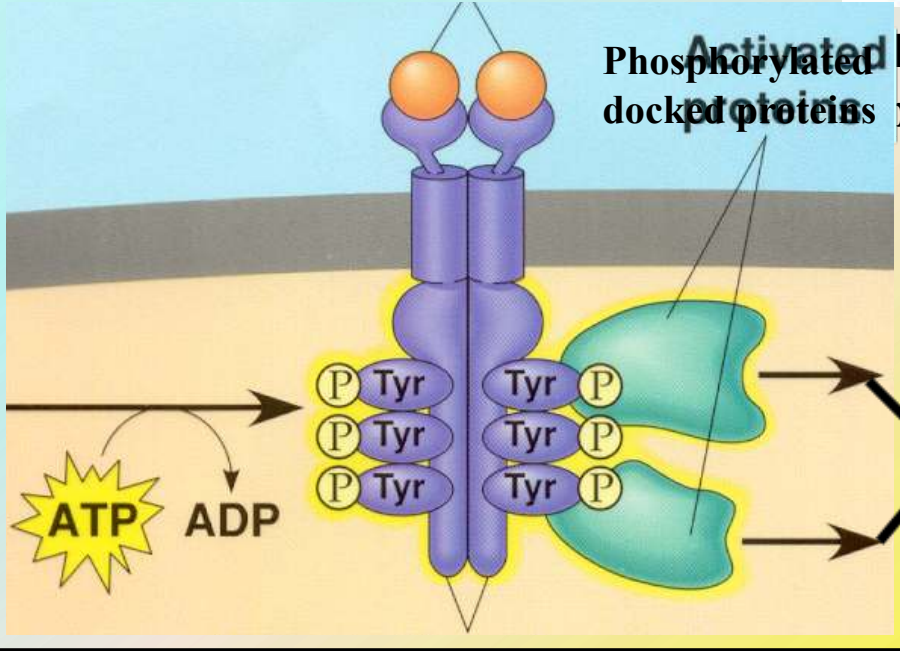
3 Enzyme-Linked Receptors

Tyrosine Kinase-Linked Receptors









Phosphorylate other proteins that it docks

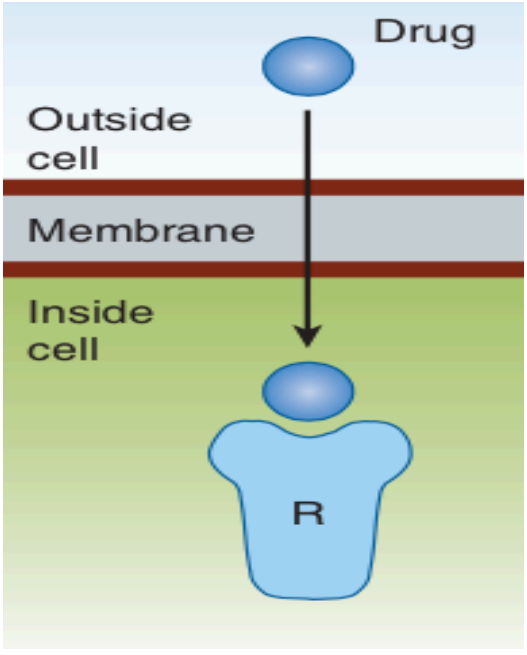
Example

Insulin Receptor

RESPONSE

Type IV: 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 lipophylic hormones; steroids, thyroids, estrogen.

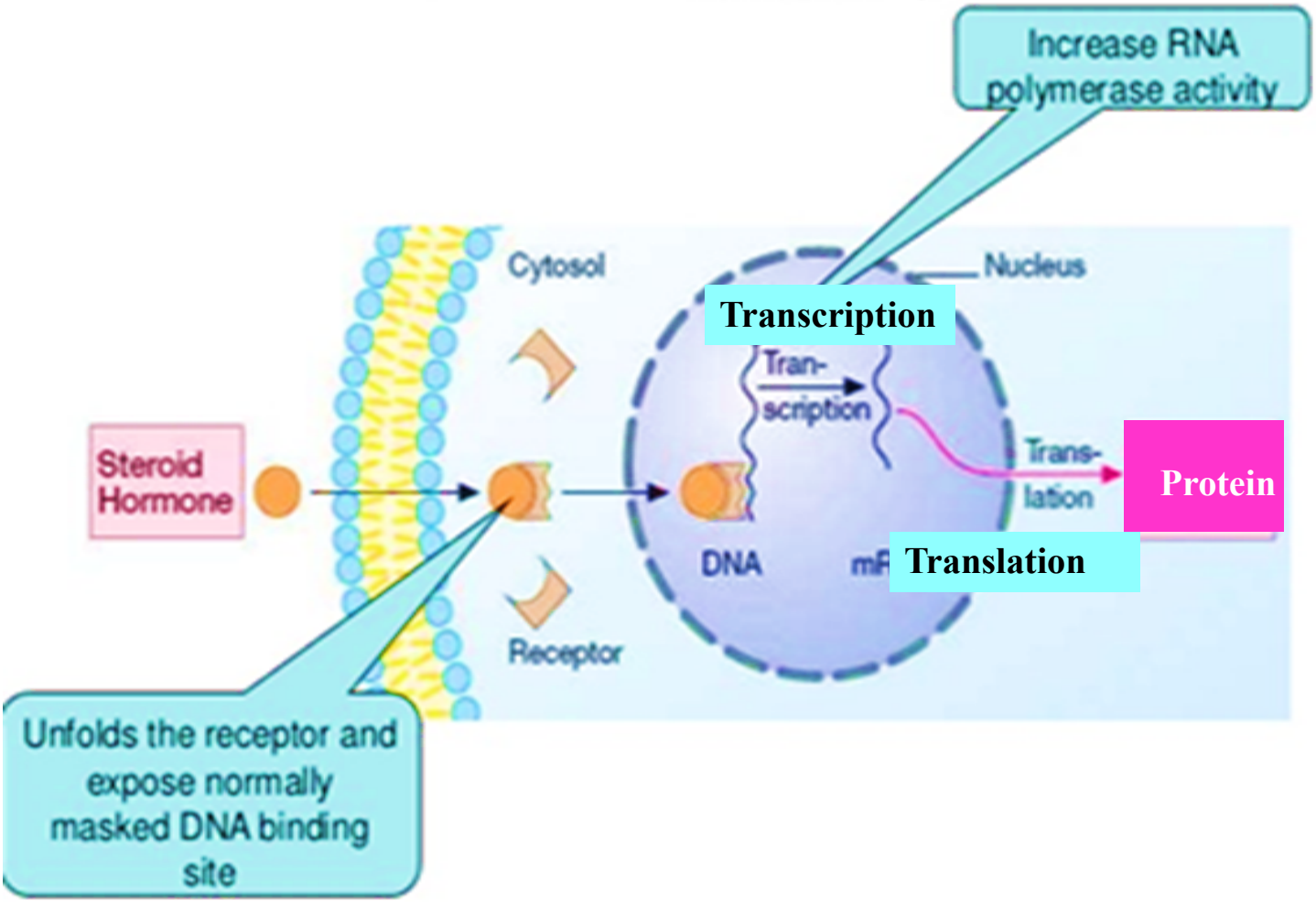


Type IV: Gene transcription receptors

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



RECEPTOR FAMILIES

	Type I	Type II	Type III	Type IV
Location	Membrane	Membrane	Membrane	Nucleus
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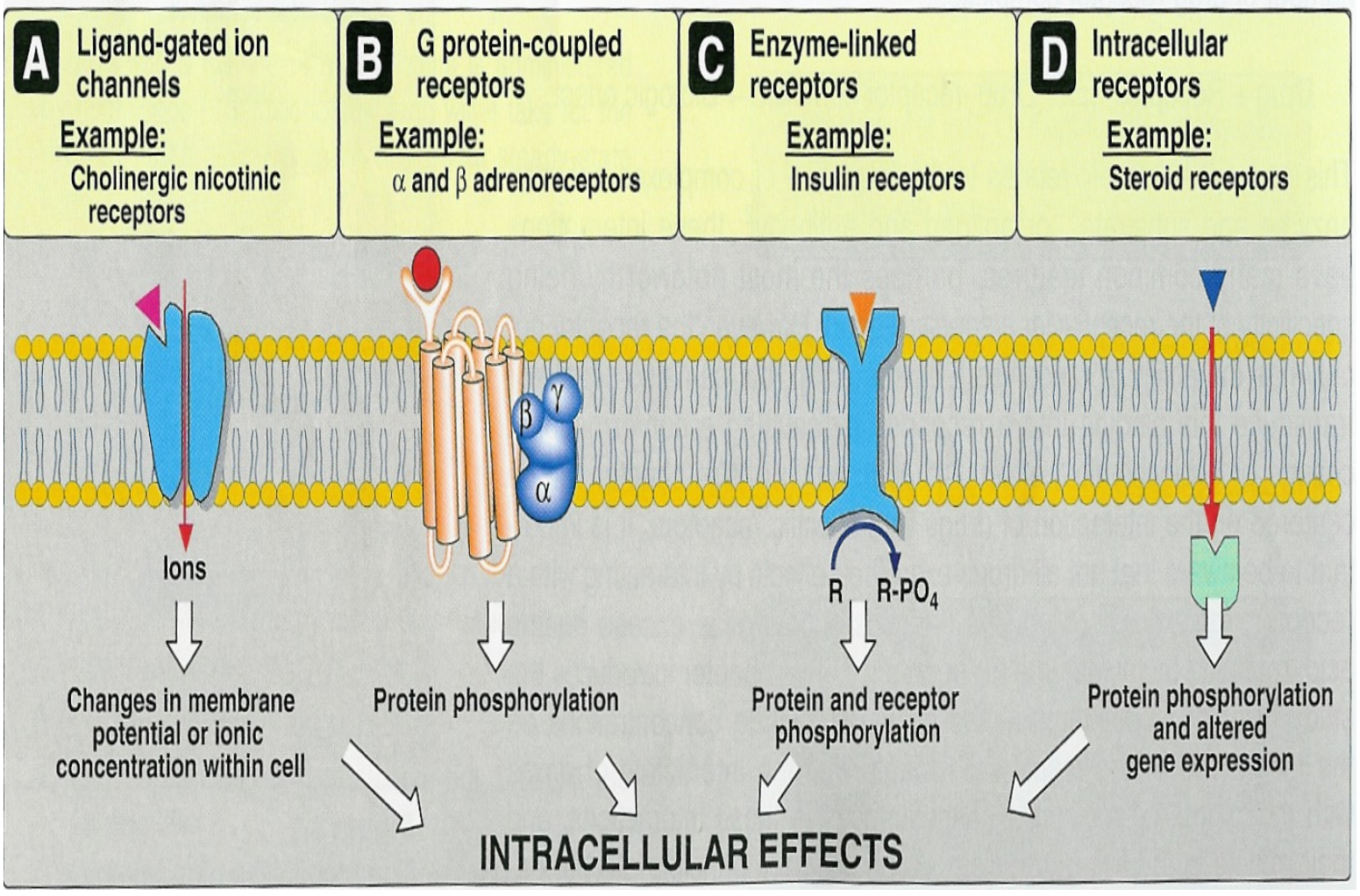
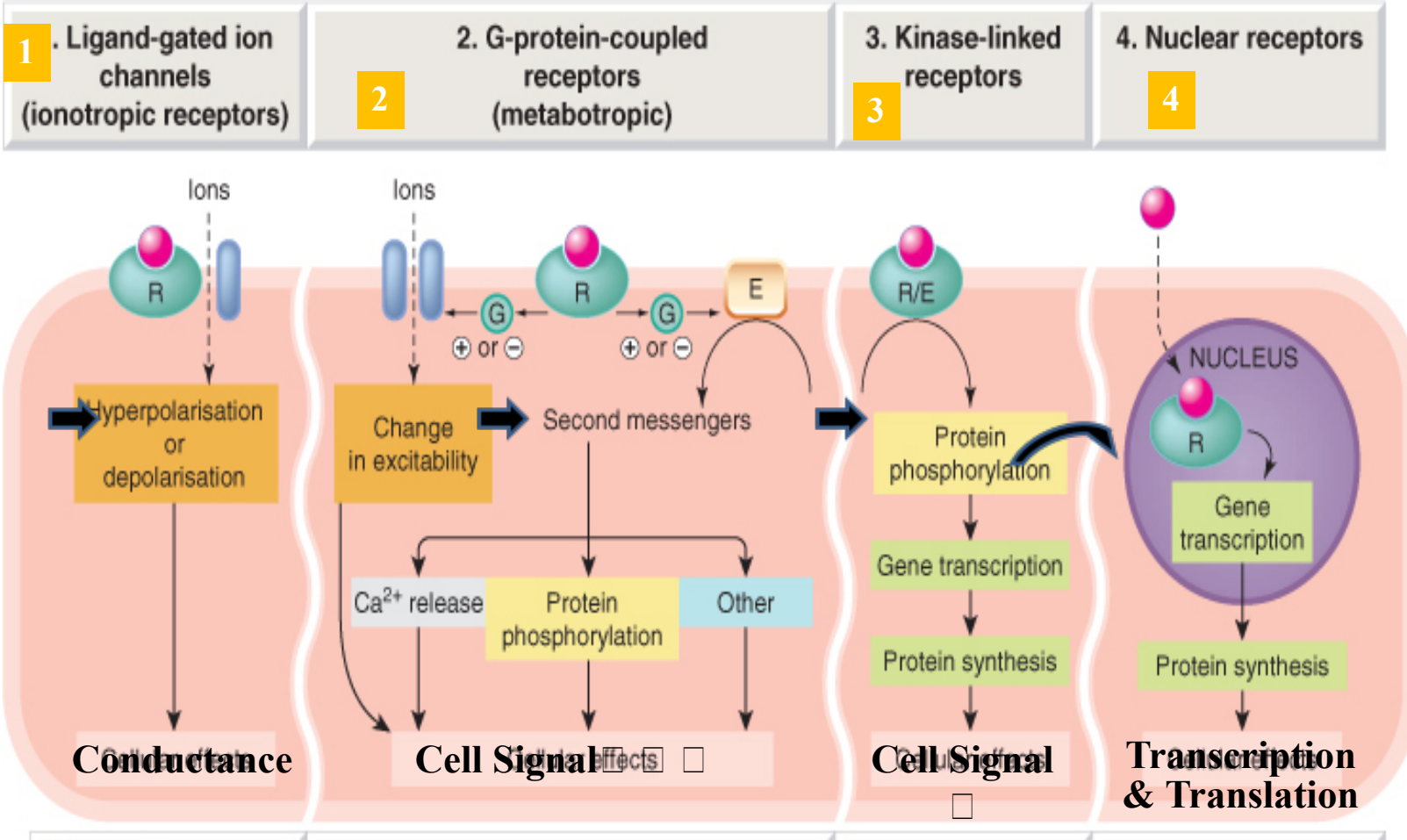
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors e.g. nicotine	**muscarinic receptors (M)** **adrenergic receptors** (α -β)	Insulin receptors	estrogen receptors Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	

SIGNALING MECHANISMS




1. Ligand-gated ion channels (ionotropic receptors)
2
2. G-protein-coupled receptors (metabotropic)
3
3. Kinase-linked receptors
4
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
Gene transcription
Protein synthesis
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