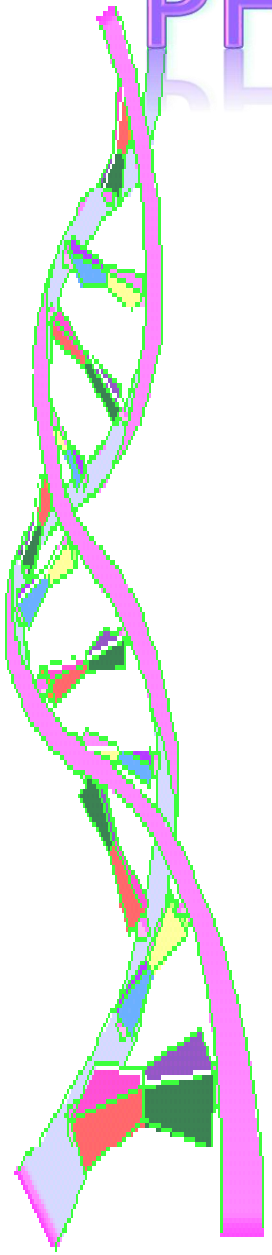
PHARMACODYNAMICS III



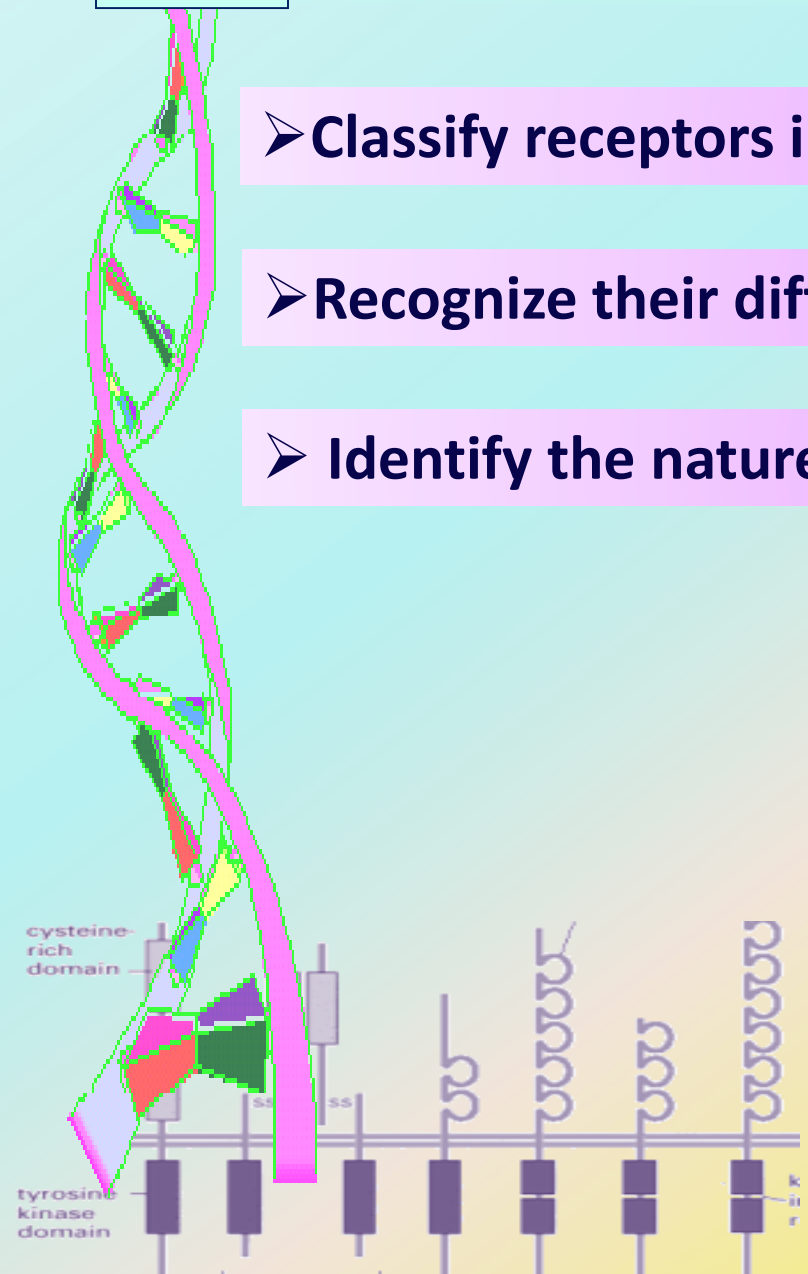
RECEPTOR FAMILIES

Prof. Hanan Hagar

ILOs

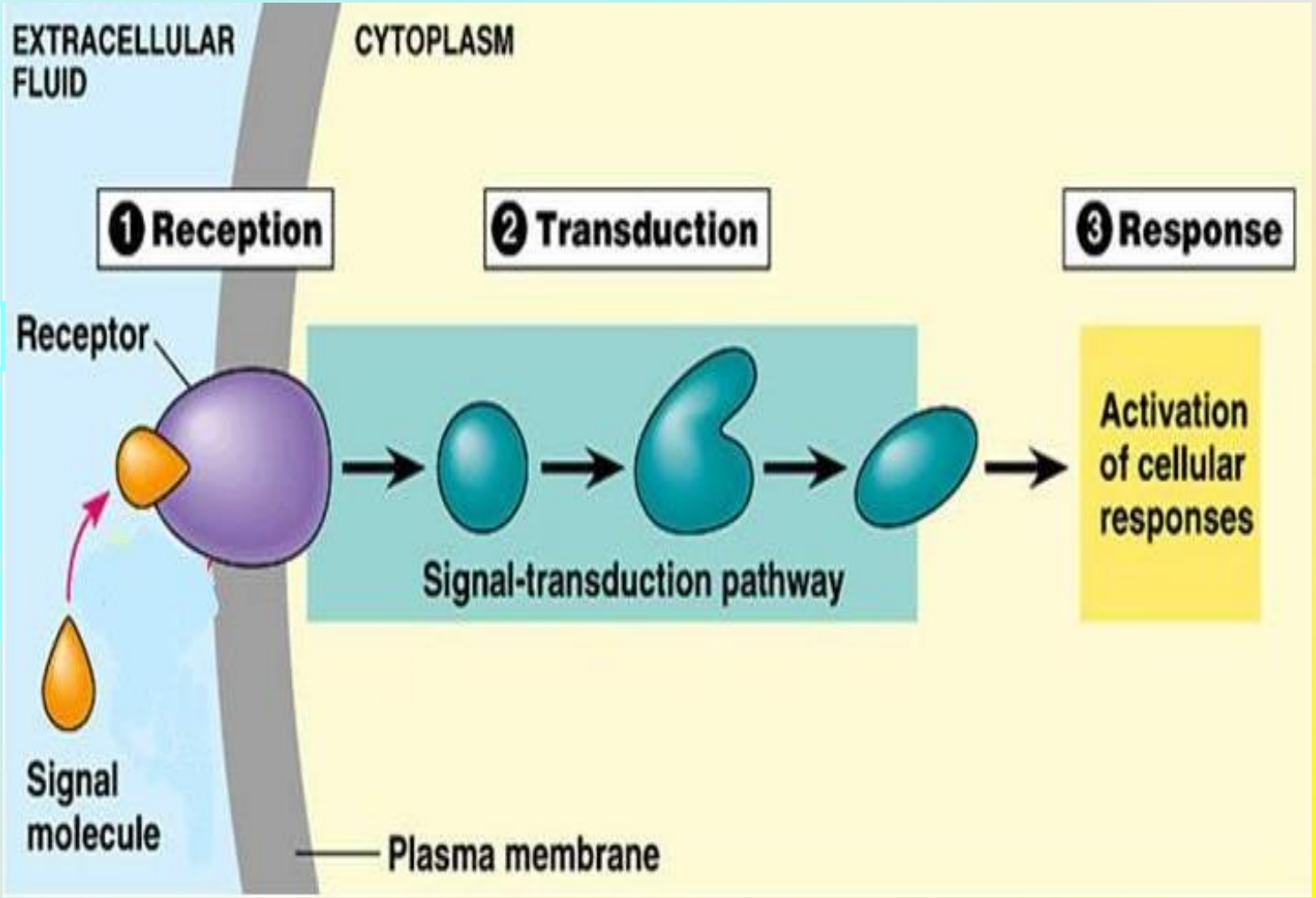
By the end of this lecture you will be able to :

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



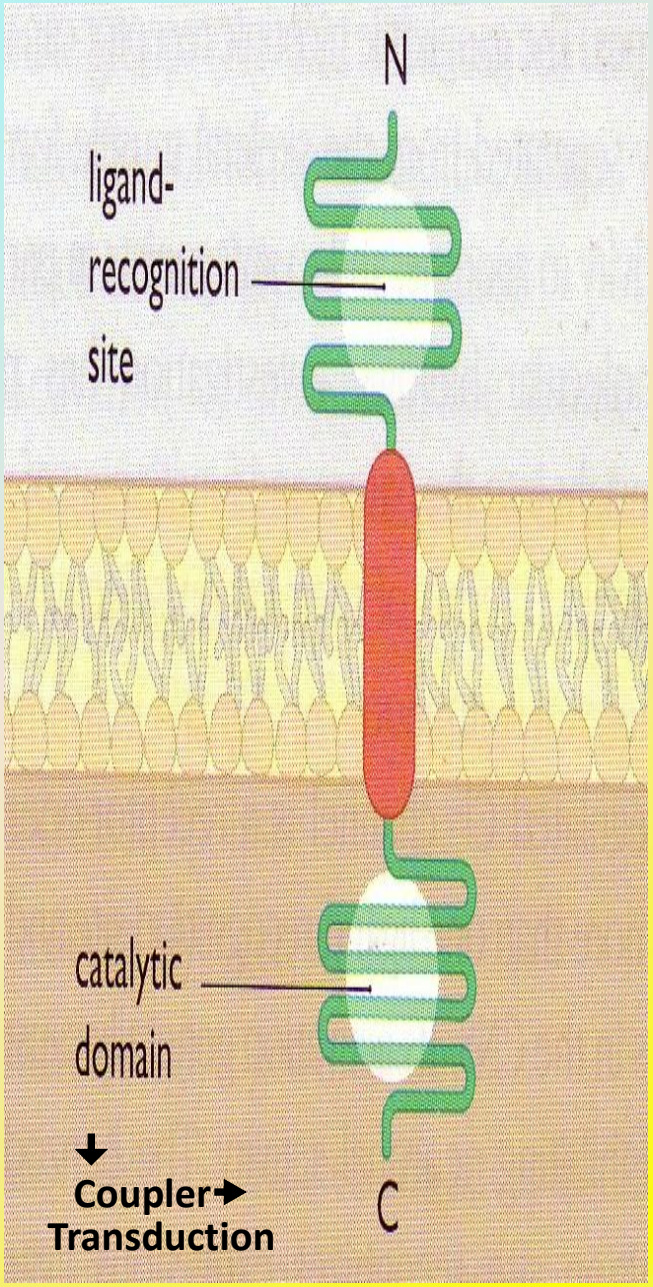
A RECEPTOR

- Recognition
- Reception
- Transduction
- Response



A RECEPTOR structure

- Ligand recognition site
- Inner catalytic domain



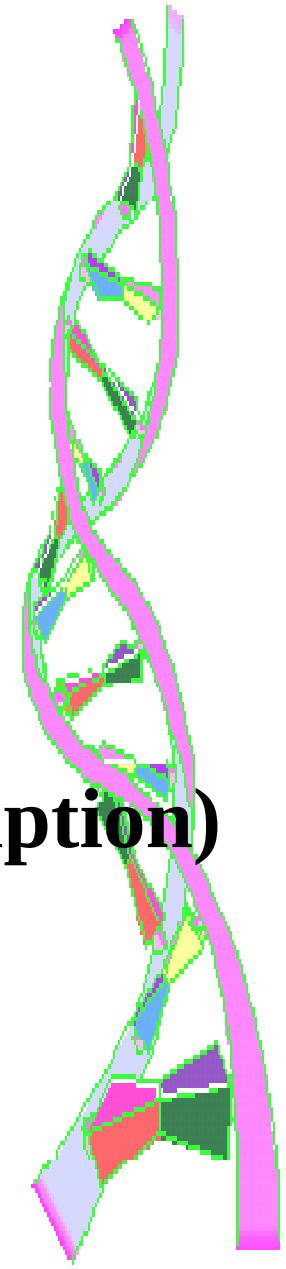
RECEPTOR FAMILIES

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

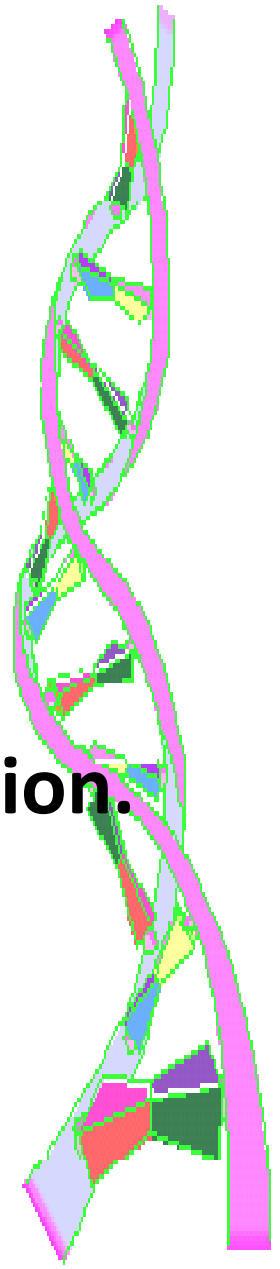
	Type I	Type II	Type III	Type III
Location	Membrane	Membrane	Membrane	Nucleus
Coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	Muscarinic receptors **Adrenergic receptors**	Insulin receptors	Estrogen Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	DNA

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.

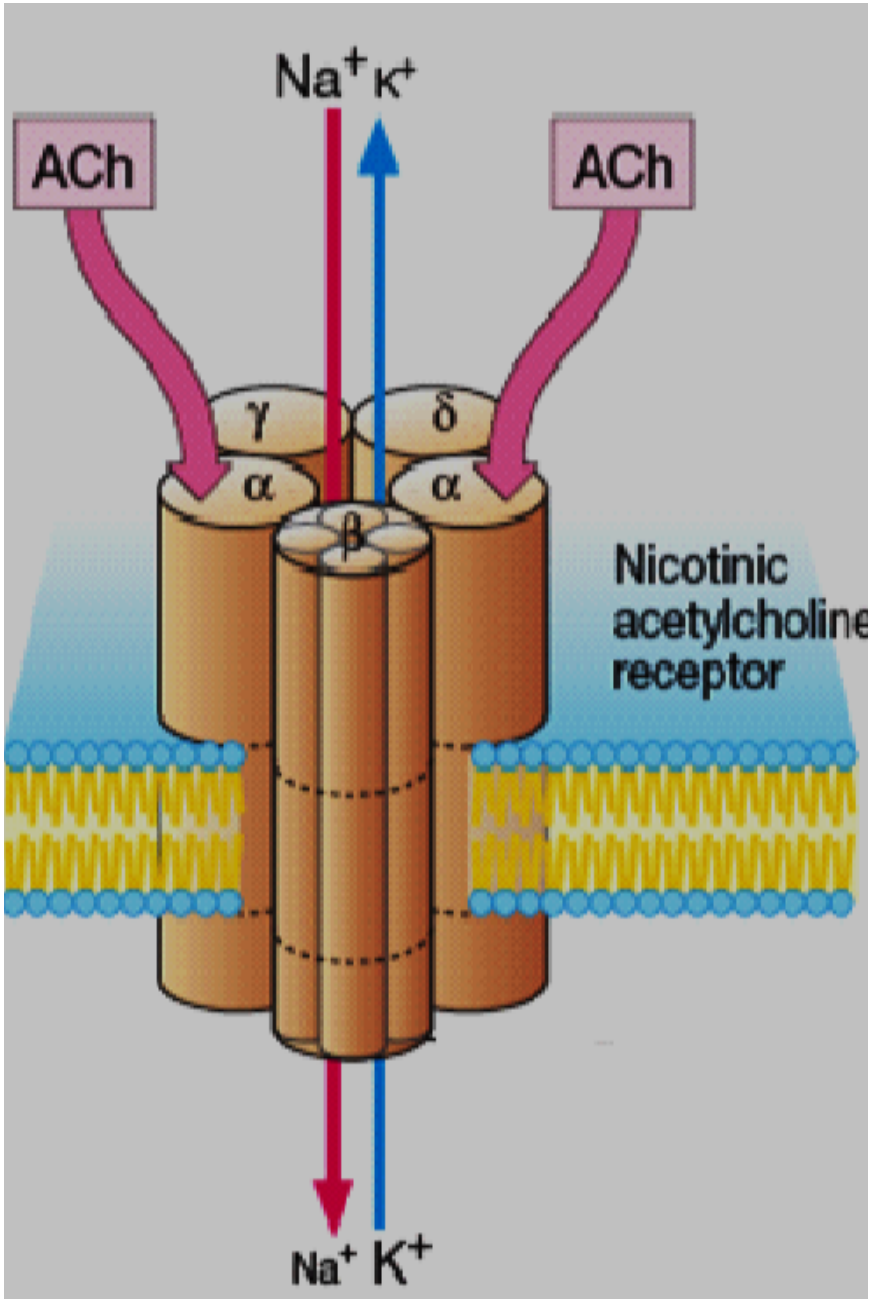


1 **Channel-Linked Receptor**

Ionotropic Receptor

Ligand-Gated-Ion Channel

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

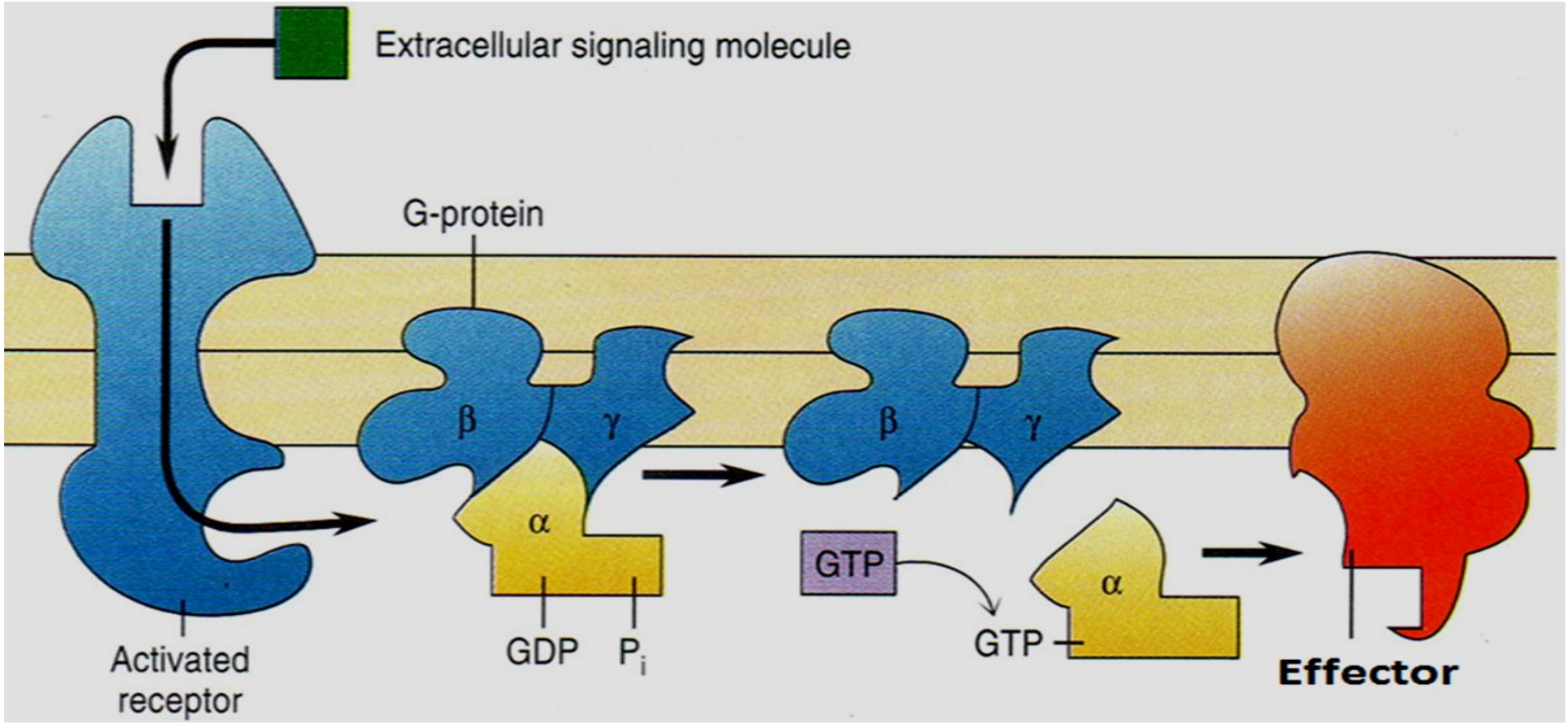


Type II: G-Protein coupled receptors
Metabotropic Receptor

- 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**
- **E.g. Adrenergic receptors of Noradrenaline**

G-protein (Guanine nucleotide-binding proteins)

- Regulatory proteins
- 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 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

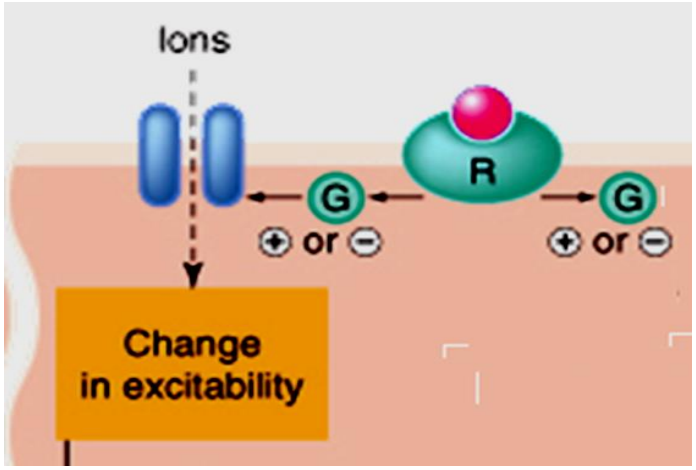
- When the G-protein **trimer** ($\alpha\beta\gamma$), binds to agonist-occupied receptor , **the α-subunit dissociates** & is then free to activate an effector.

- Activation of the effector is terminated when the bound GTP molecule is hydrolyzed to GDP which allow α-subunit to recombine with **($\beta\gamma$)** 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

- **Adenyl cyclase enzyme (AC)**
  Cyclic AMP system (cAMP)

- **Phospholipase C enzyme**
  Inositol phosphate system (IP3+DAG)

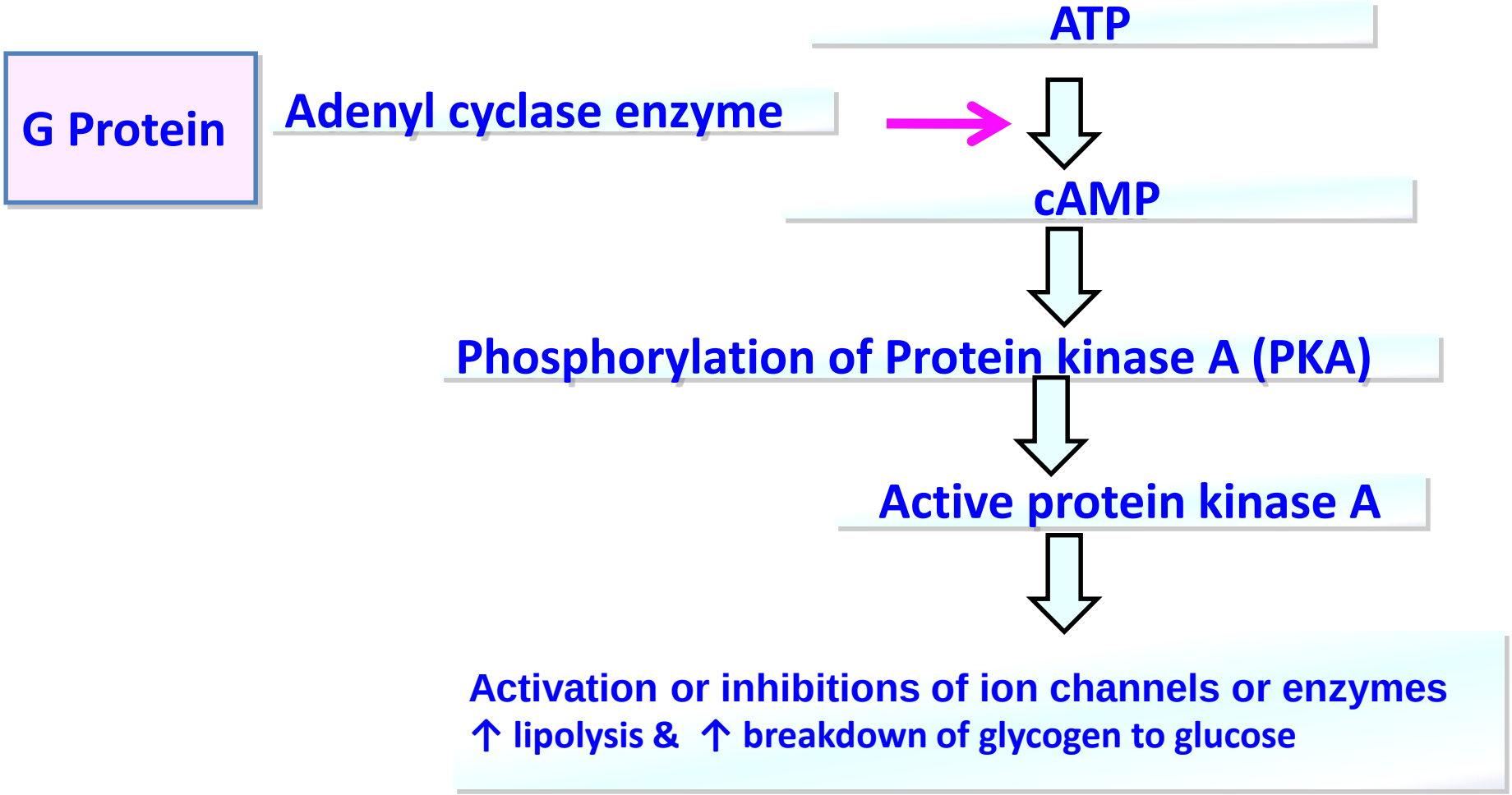
cAMP= cyclic adenosine monophosphate
IP3 = inositol triphosphate DAG= diacylglycerol

Type II receptors (G-Protein coupled receptors)

Targets for G-proteins

- Second messengers

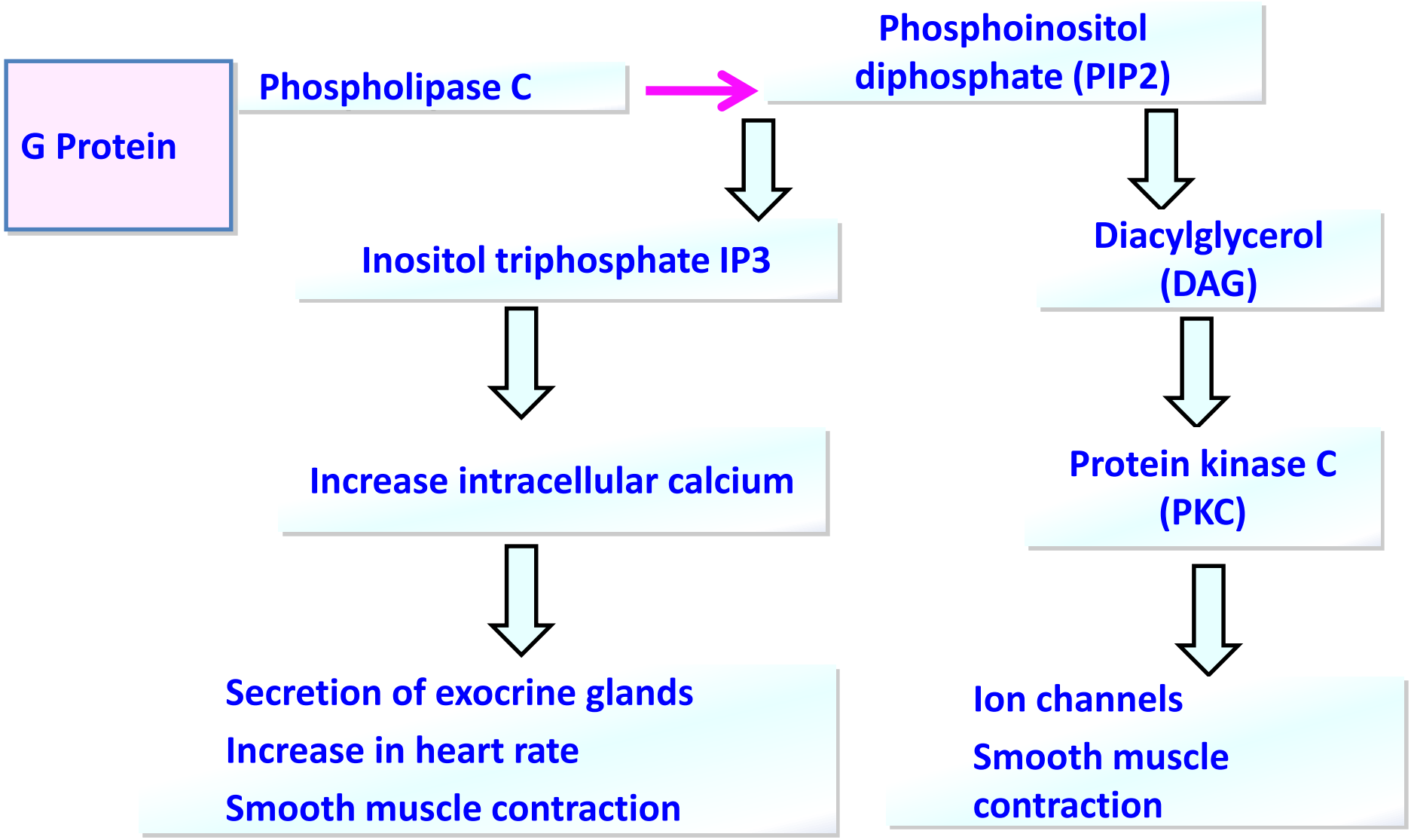
Cyclic AMP system (cAMP)



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) → α & β

Different Receptors Subtypes

m Ach; m_1, m_2, m_3, m_4

β Adrenergic receptors; β_1, β_2 , β_3

Difference in their related G-Protein Classes

G-protein

(Guanine nucleotide-binding proteins)

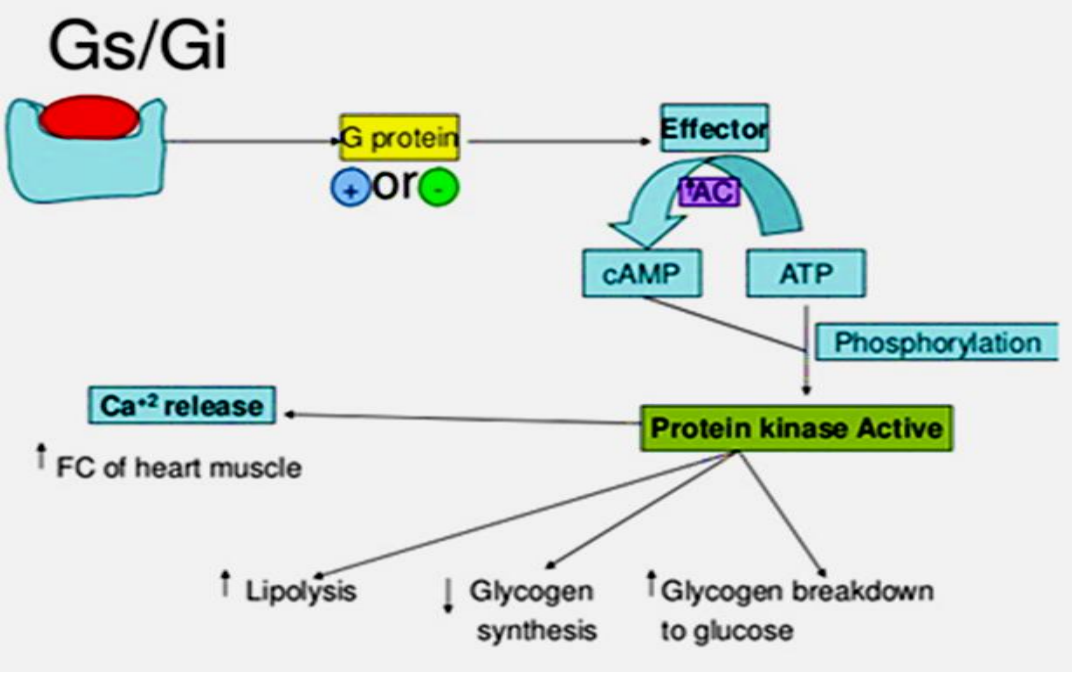
are divided according to their α-subunits into:

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

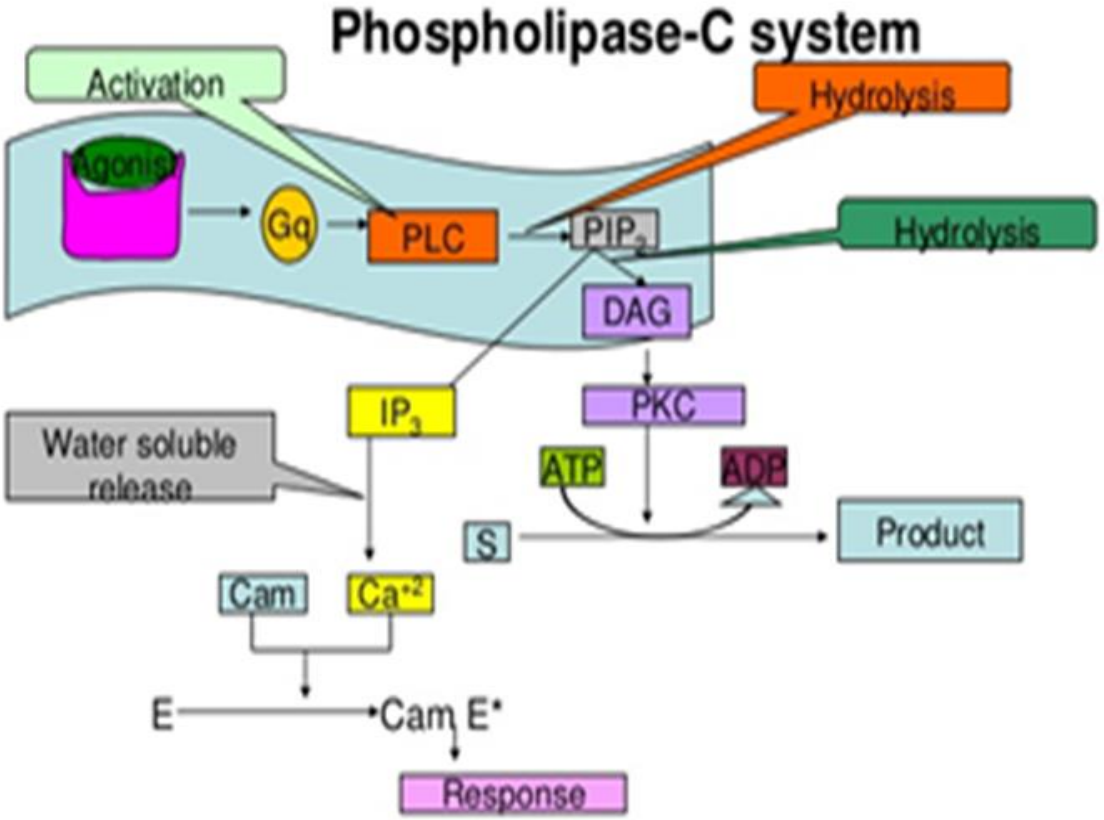
Gi: Inhibition of the effector
Linked to the **cAMP-dependent pathway**

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

- **Type II receptors** (G-Protein coupled receptors)
  - Targets for G-proteins
  - Second messengers
  - Cyclic AMP system (cAMP)
    - M_2 & M_4 Ach receptors couple to Gi to inhibit AC
    - α_2 Adrenoceptors couple to Gi to inhibit AC.
    - $\beta_{1\&2}$ Adrenoceptors couple to Gs to stimulate AC



- **Type II receptors** (G-Protein coupled receptors)
- Targets for G-proteins
- Second messengers
  - Inositol phosphate system (IP3+DAG)
  - M_1 & M_3 Ach receptors couple to Gq to stimulate PLC
  - α_1 Adrenoceptors couple to Gq to stimulate PLC.



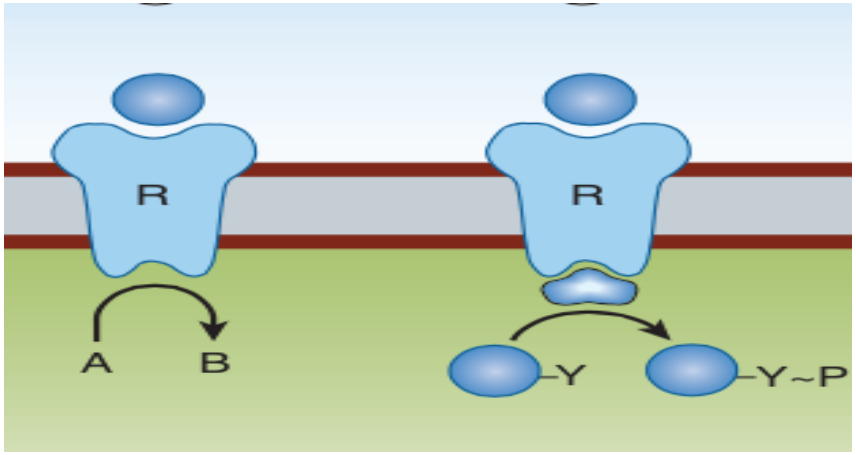
Ach receptors	Couple to		
M_1 stimulatory	Gq	stimulate PLC	stimulation
M_2 inhibitory	Gi	Inhibit AC (⬇ cAMP) Opening of K-channels	Heart (Bradycardia)
M_3 stimulatory	Gq	stimulate PLC	Contraction of Smooth muscles (brocnchoconstriction)
M_4 inhibitory	Gi	Inhibit AC (⬇ cAMP)	Inhibition

Adrenoceptors	Couple to		
β_1 stimulatory	Gs	stimulate AC	Stimulation (tachycardia)
α_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.

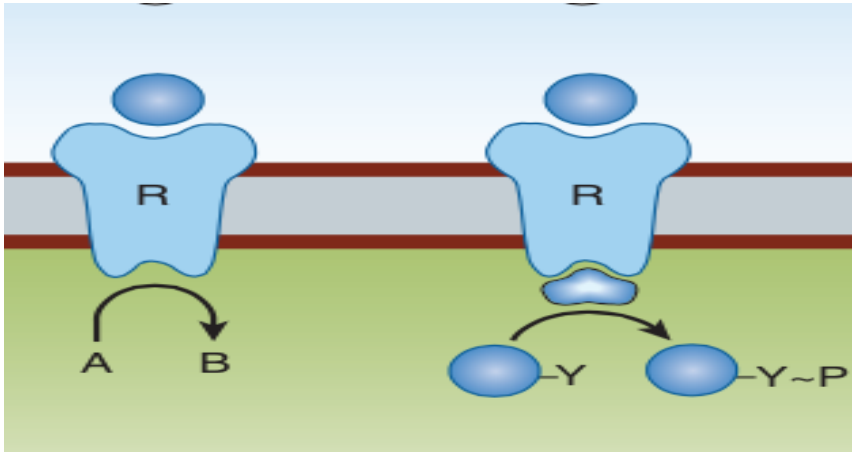


Type III (Enzyme-Linked receptors)

(Tyrosine Kinase-linked receptor)

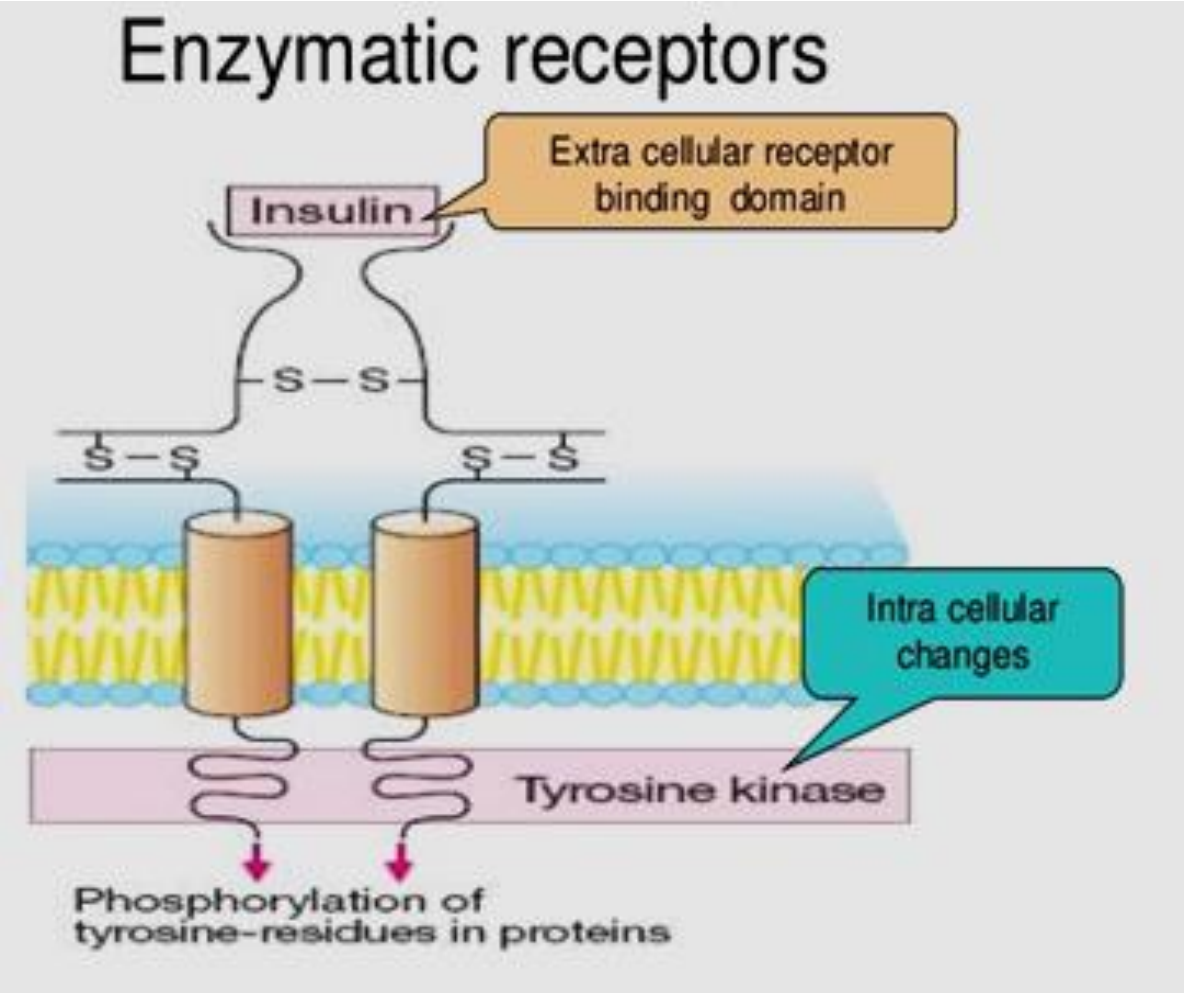
- **Activation of Type III receptors results in**
  - Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

E.g. Insulin receptors



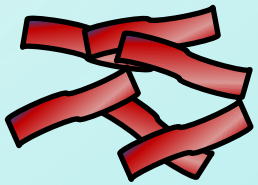
Type III (tyrosine kinase-Linked receptors)

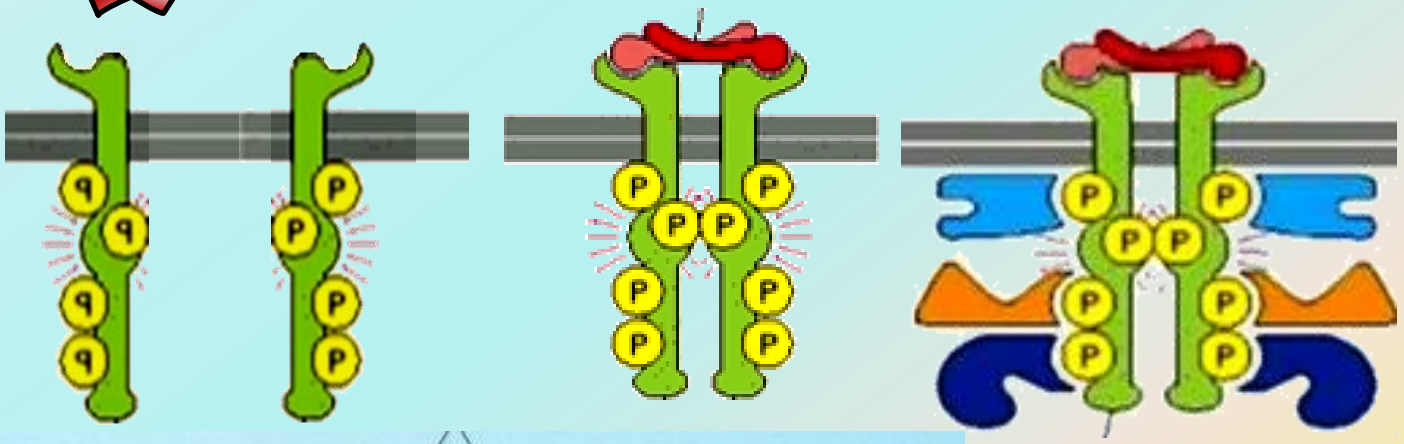
Insulin receptors

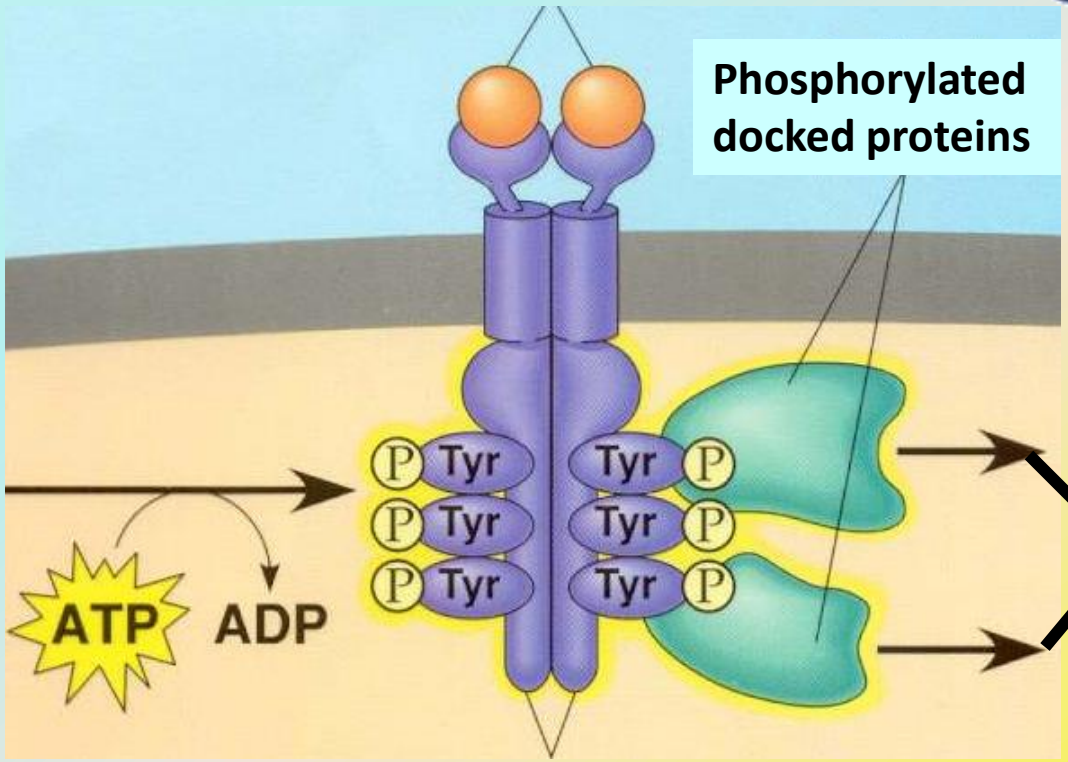


3 Enzyme-Linked Receptors

Tyrosine Kinase-Linked Receptors







Phosphorylate other proteins that it docks

Example

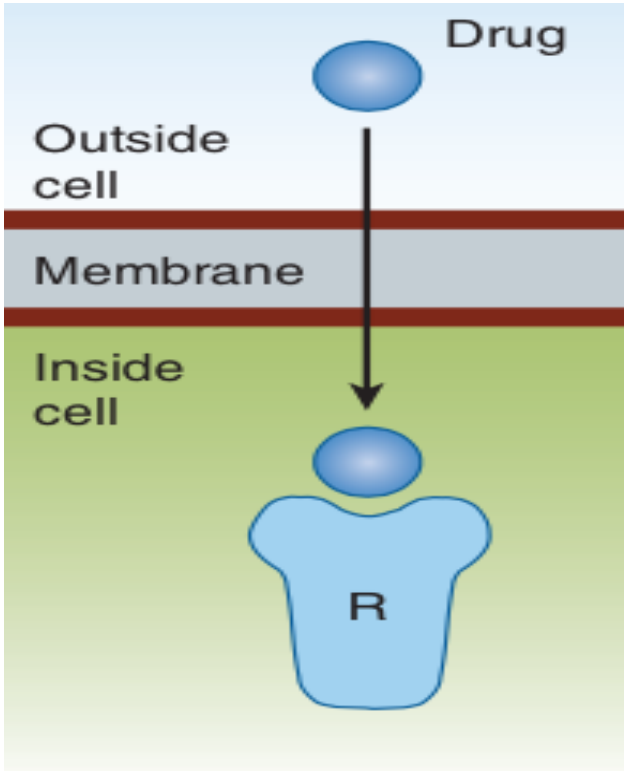
Insulin Receptor

RESPONSE

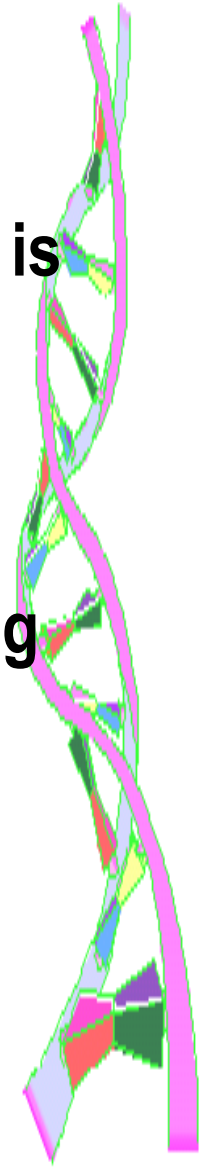
Type IV: Nuclear receptors

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.



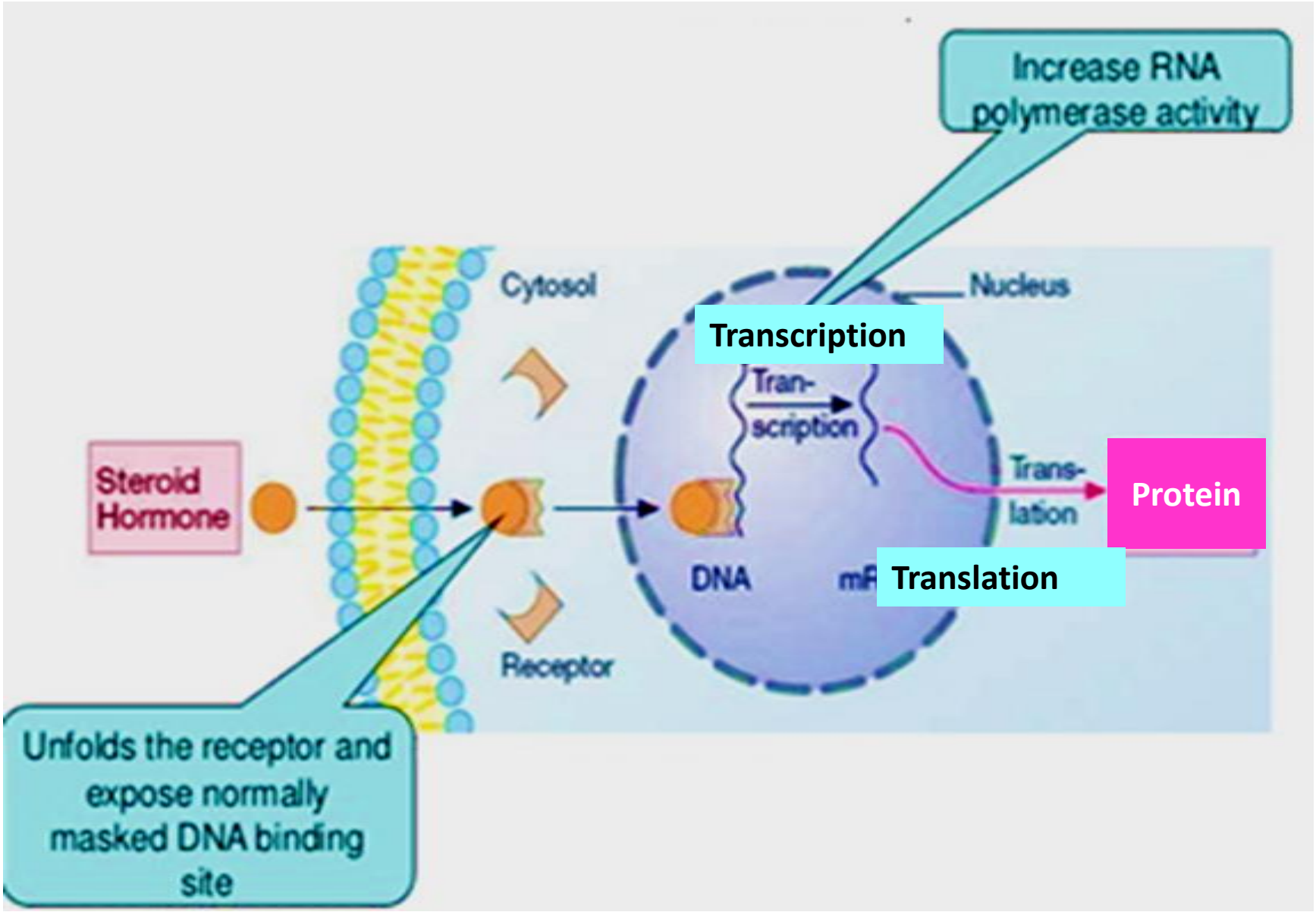
Type IV: Gene transcription receptors



▶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



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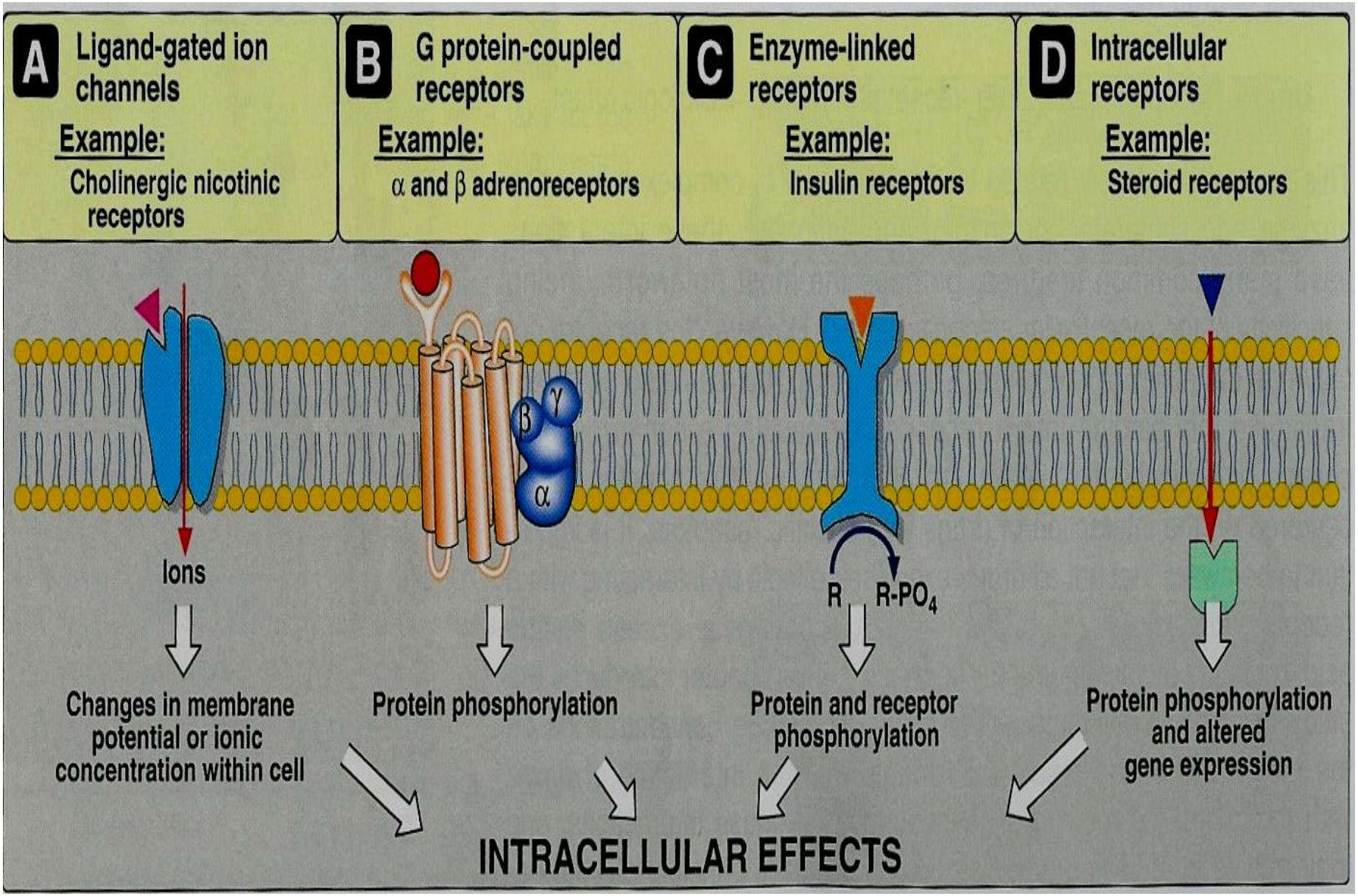
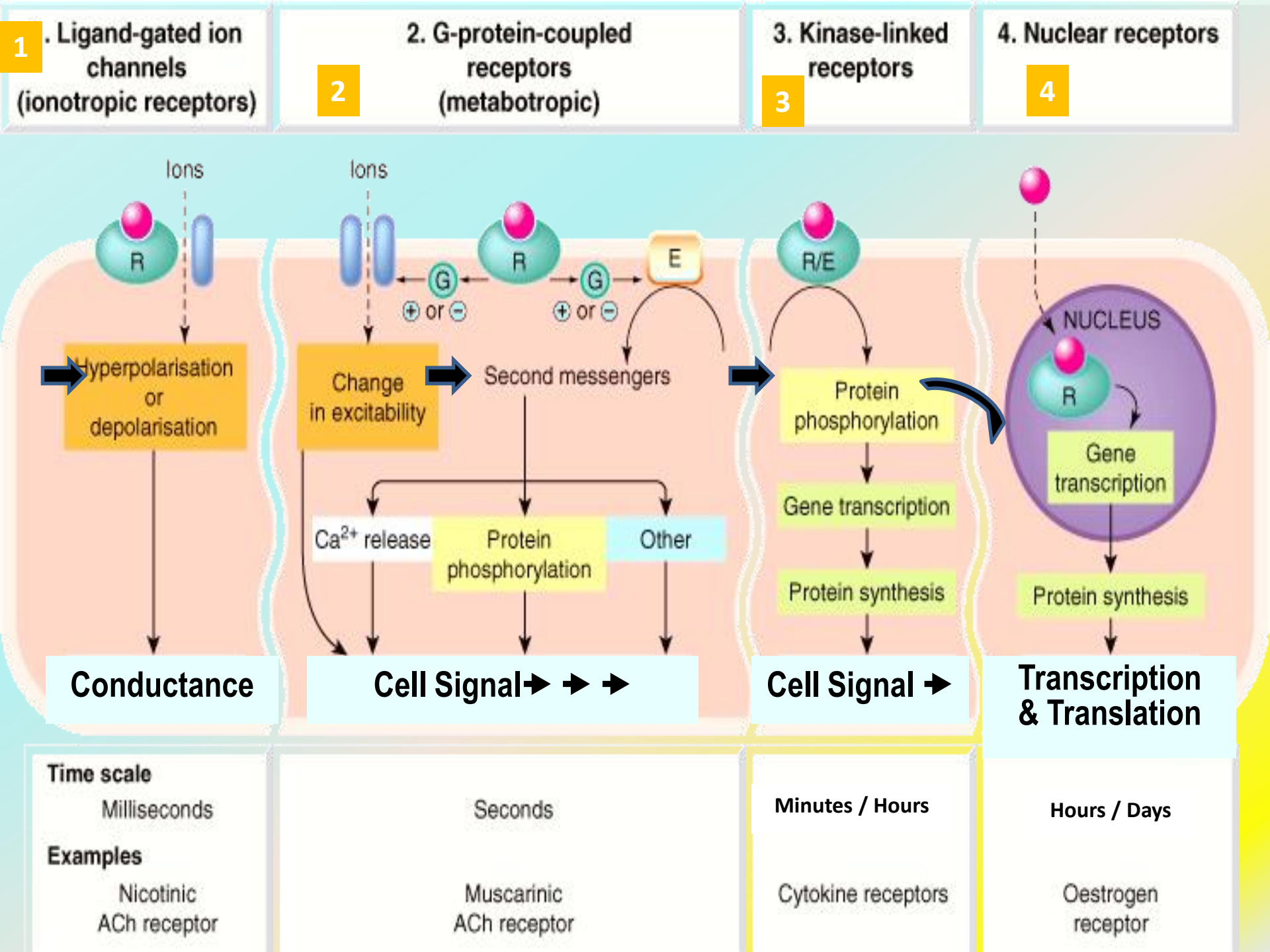
SIGNALING MECHANISMS




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