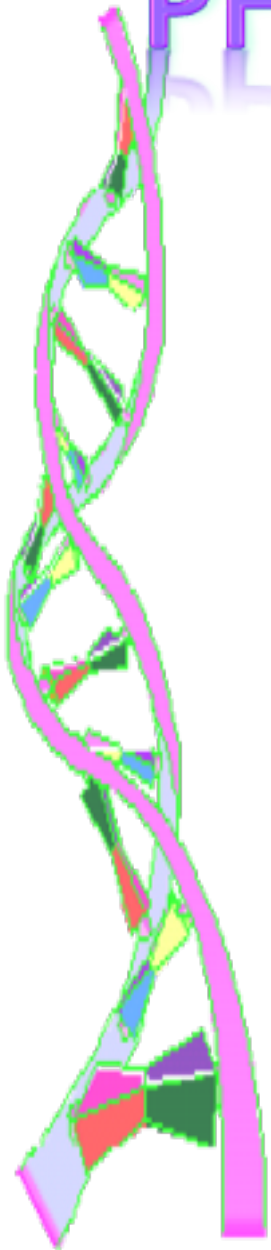


PHARMACODYNAMICS III

RECEPTOR FAMILIES

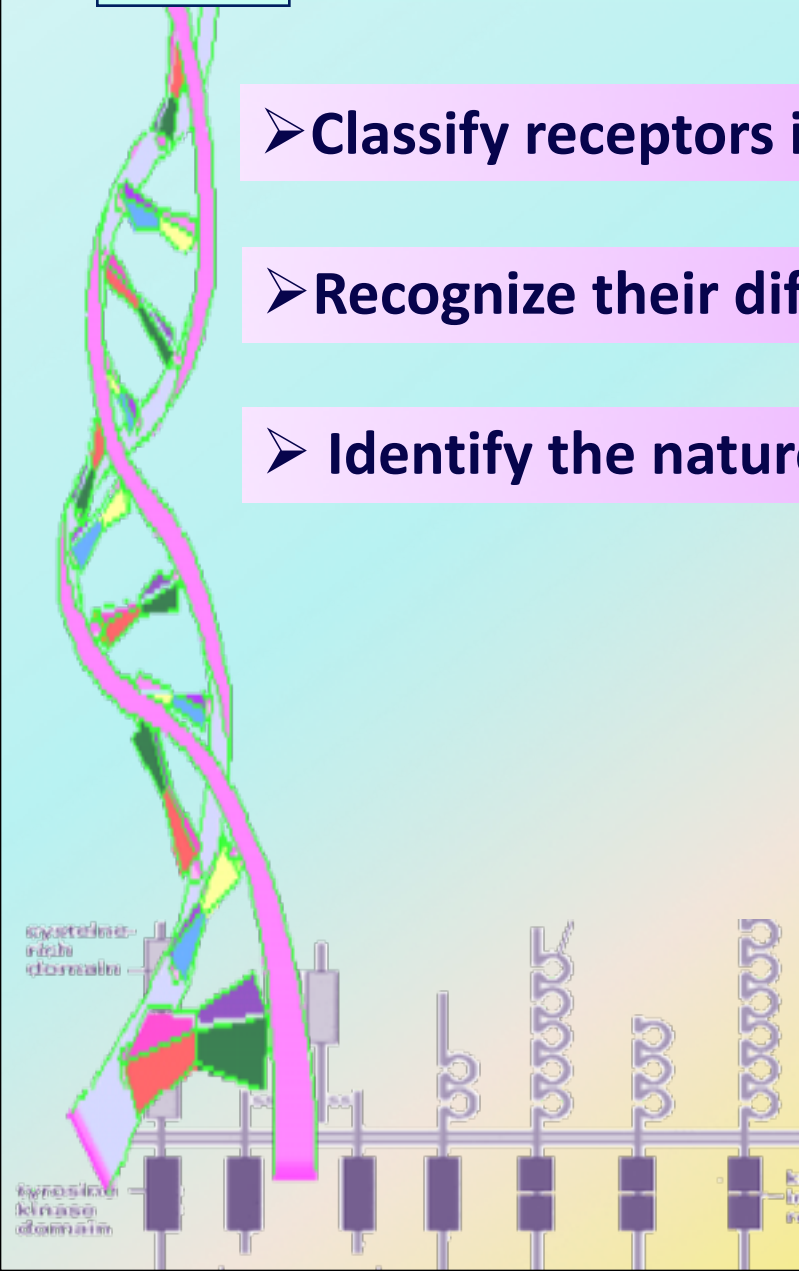
Prof. Hanan Hagar



I/Os

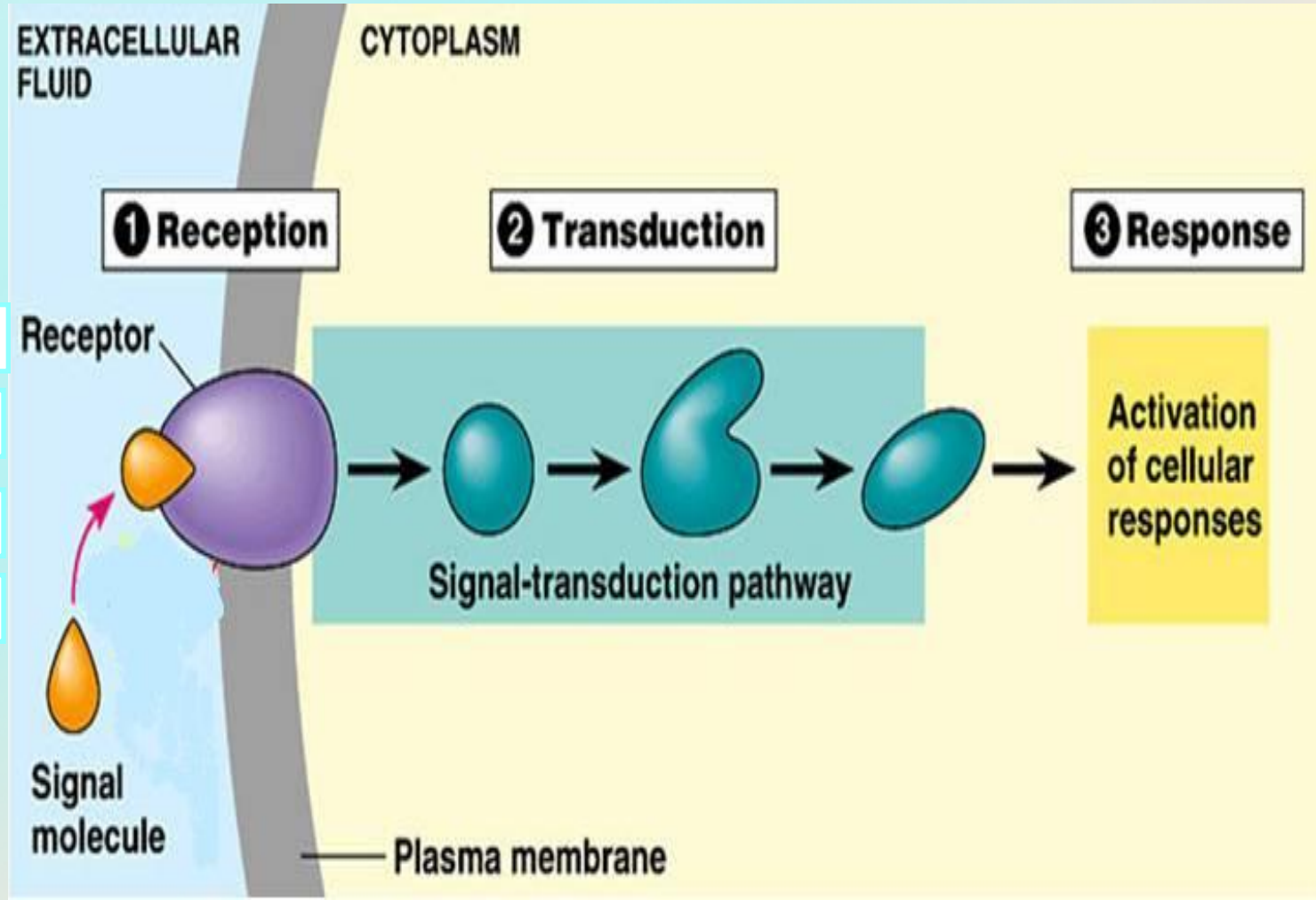
By the end of this lecture you will be able to :

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



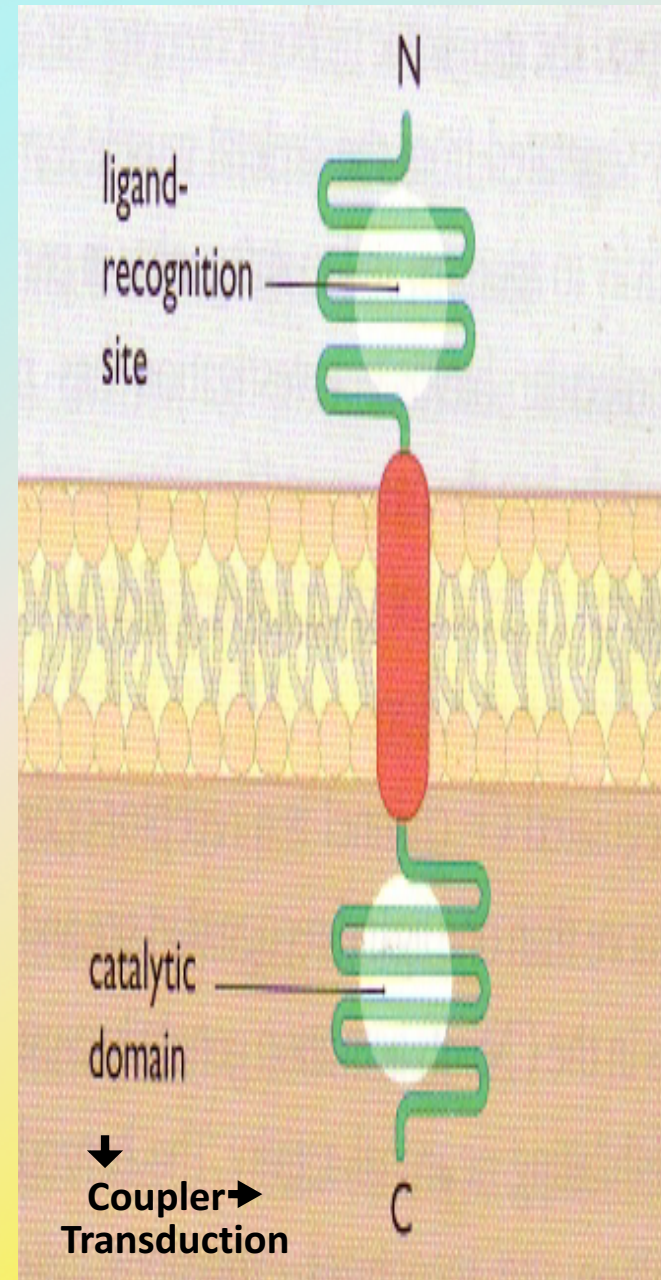
A RECEPTOR

- Recognition
- Reception
- Transduction
- Response



A RECEPTOR structure

- **Ligand recognition site**
- **Inner catalytic domain**



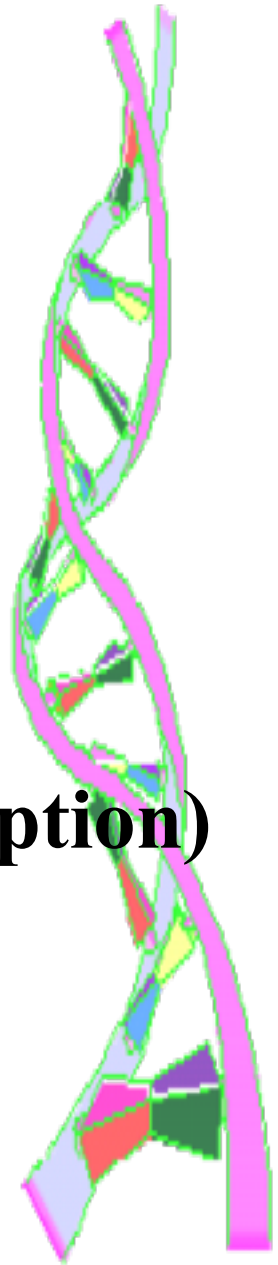
RECEPTOR FAMILIES

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

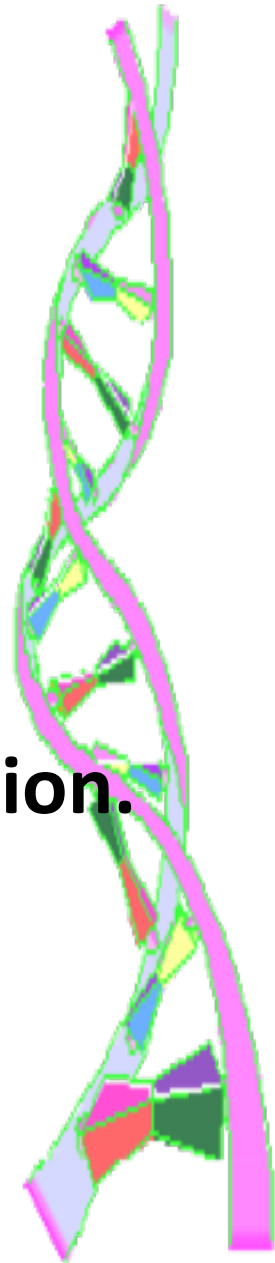
	Type I	Type II	Type III	Type III
Location	Membrane	Membrane	Membrane	Nucleus
Coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	Muscarinic receptors Adrenergic receptors	Insulin 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.**

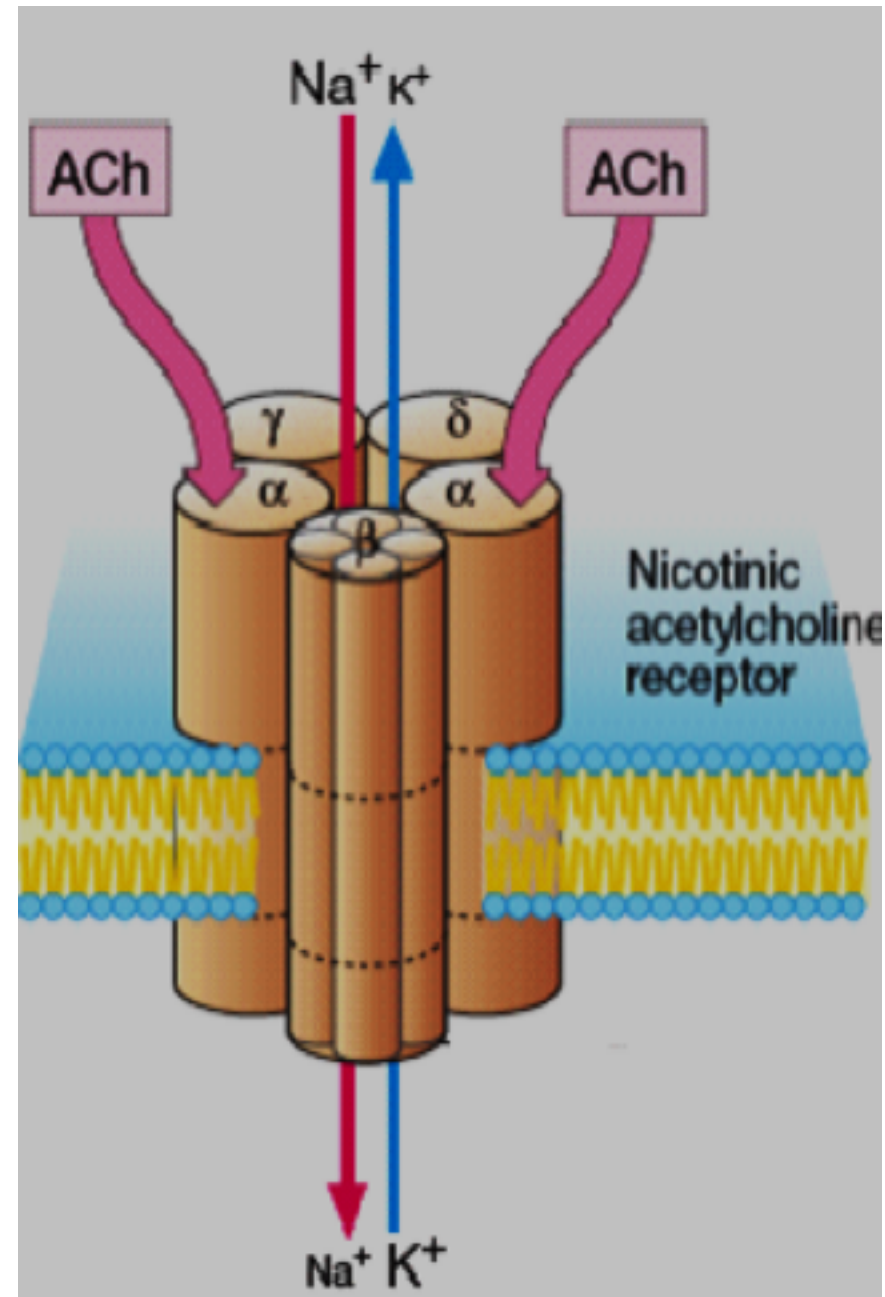


1 Channel-Linked Receptor

Ionotropic Receptor

Ligand-Gated-Ion Channel

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



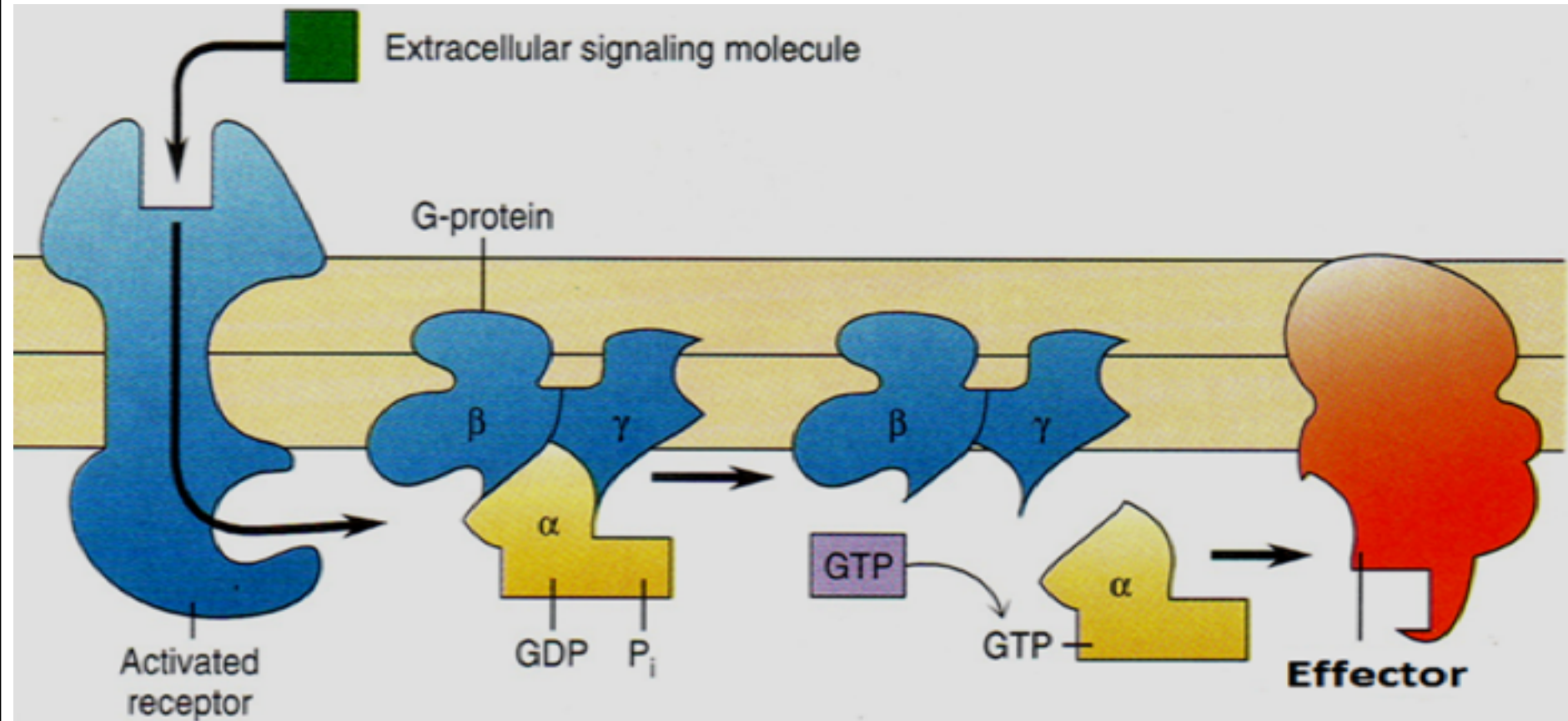
Type II: G-Protein coupled receptors Metabotropic Receptor

- 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 ($\alpha\beta\gamma$), 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

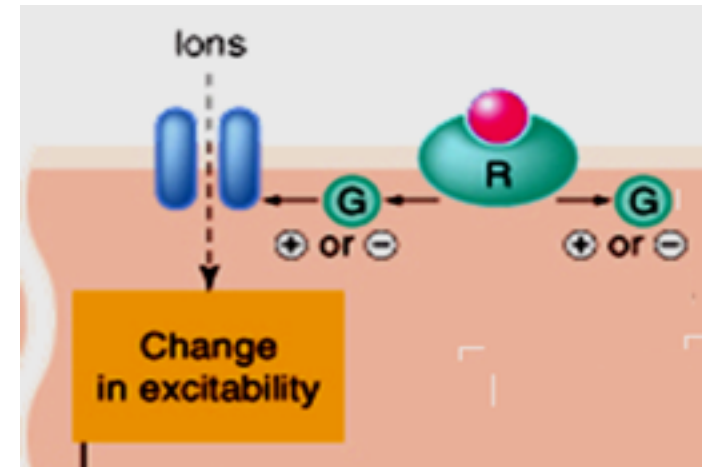
To give Second messengers

- 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

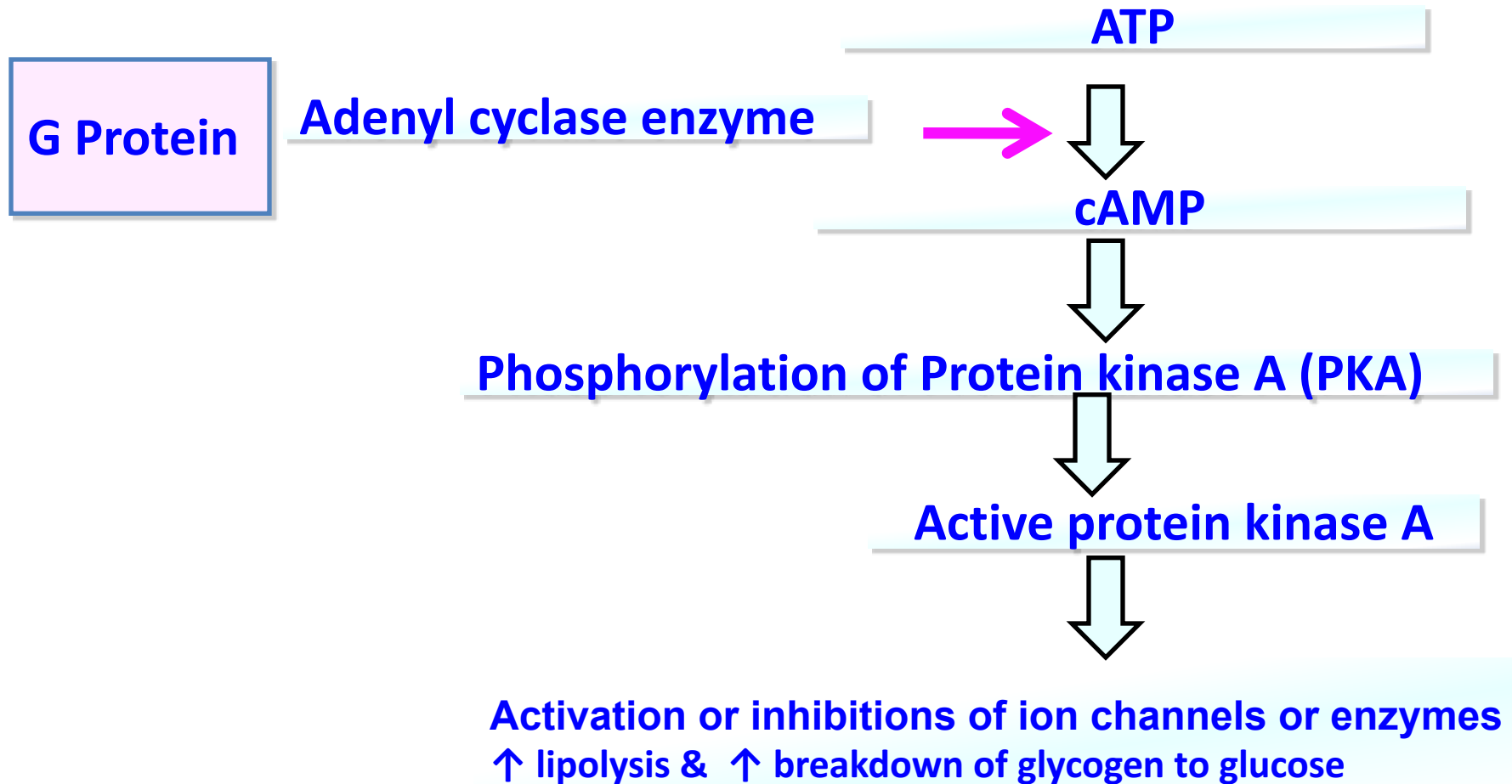


Type II receptors (G-Protein coupled receptors)

Targets for G-proteins

- Second messengers

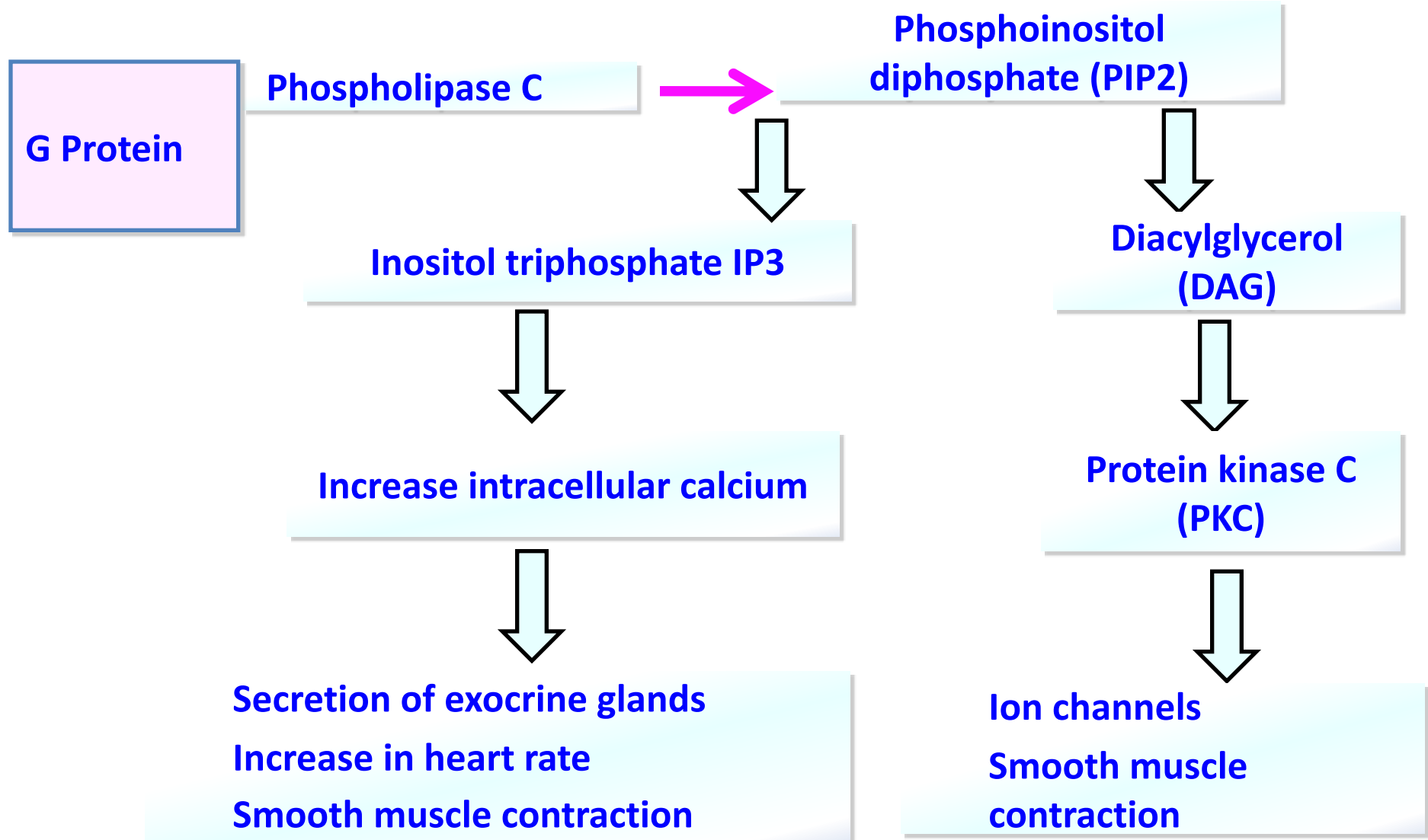
Cyclic AMP system (cAMP)



Type II receptors

Targets for G-proteins

Inositol phosphate system



Type II receptors (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

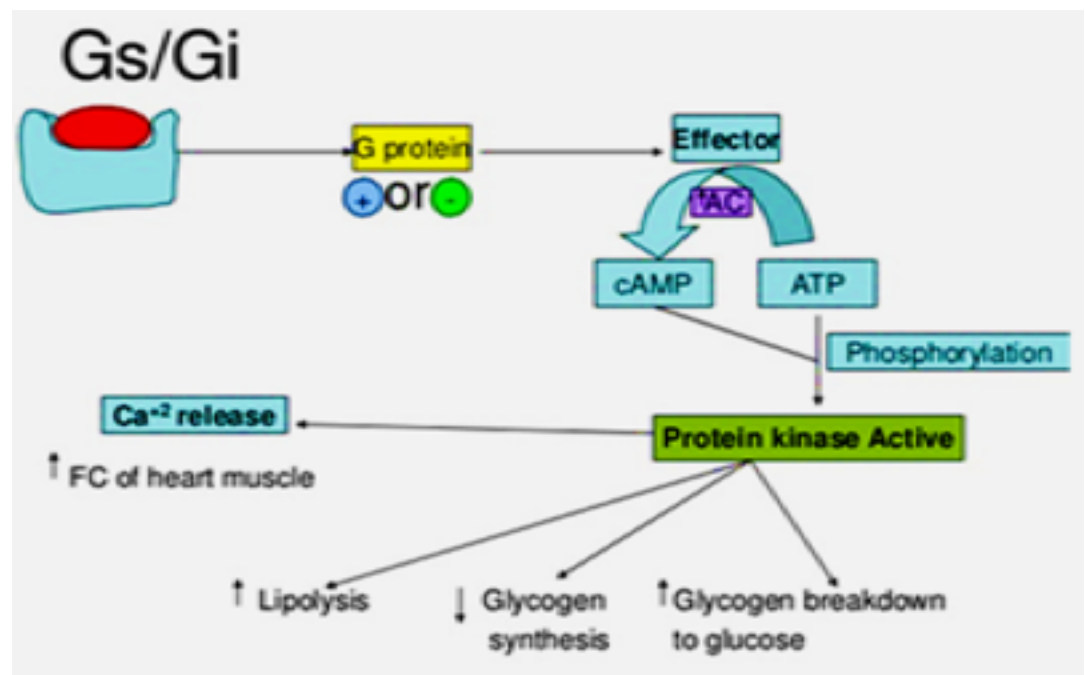
Linked to the **cAMP-dependent pathway**

Gi: Inhibition of the effector

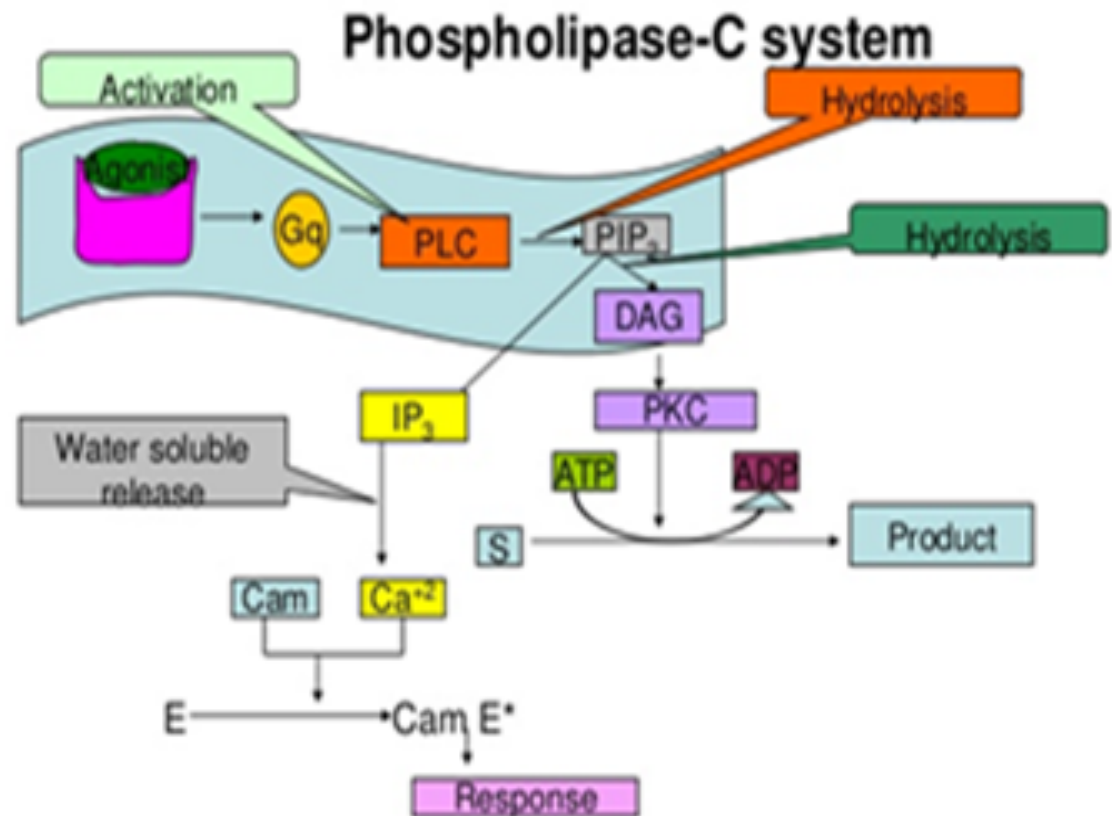
Linked to the **cAMP-dependent pathway**

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 G_i to inhibit AC
 - α_2 Adrenoceptors couple to G_i to inhibit AC.
 - $\beta_{1\&2}$ Adrenoceptors couple to G_s to stimulate 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 G_q to stimulate PLC
 - ▣ α₁ Adrenoceptors couple to G_q to stimulate PLC.



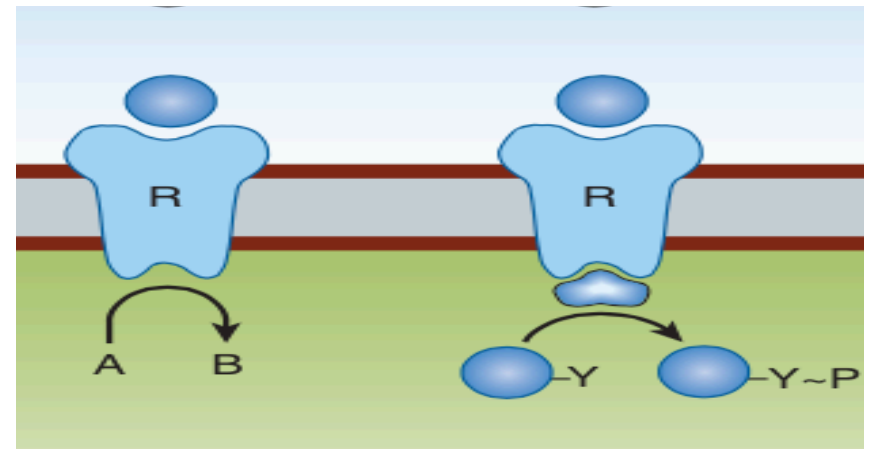
Ach receptors	Couple to		
M ₁ stimulatory	Gq	stimulate PLC	stimulation
M ₂ inhibitory	Gi	Inhibit AC (↓ cAMP) Opening of K-channels	Heart (Bradycardia)
M ₃ stimulatory	Gq	stimulate PLC	Contraction of Smooth muscles (brocnchoconstriction)
M ₄ inhibitory	Gi	Inhibit AC (↓ cAMP)	Inhibition

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)

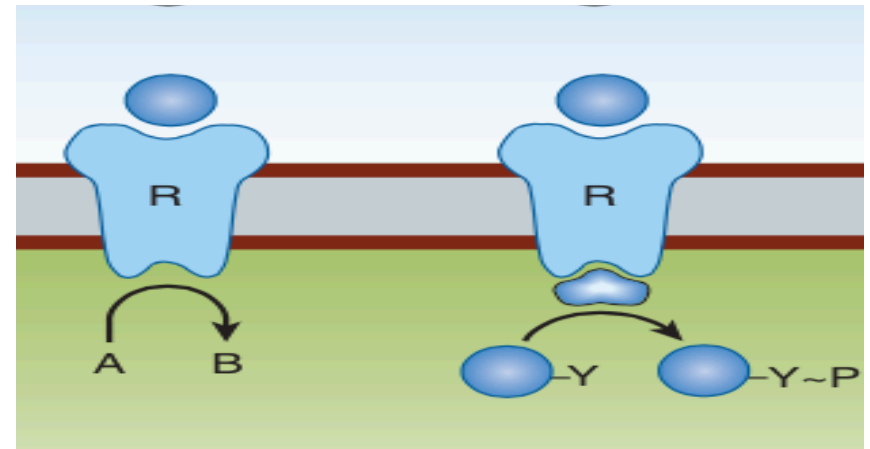
- Located at cell membrane
- Linked to enzyme (with intrinsic enzymatic activity)
- Response occurs in minutes to hours.
- Involved in response to hormones, growth factors.
- They control many cellular functions as metabolism and growth.



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

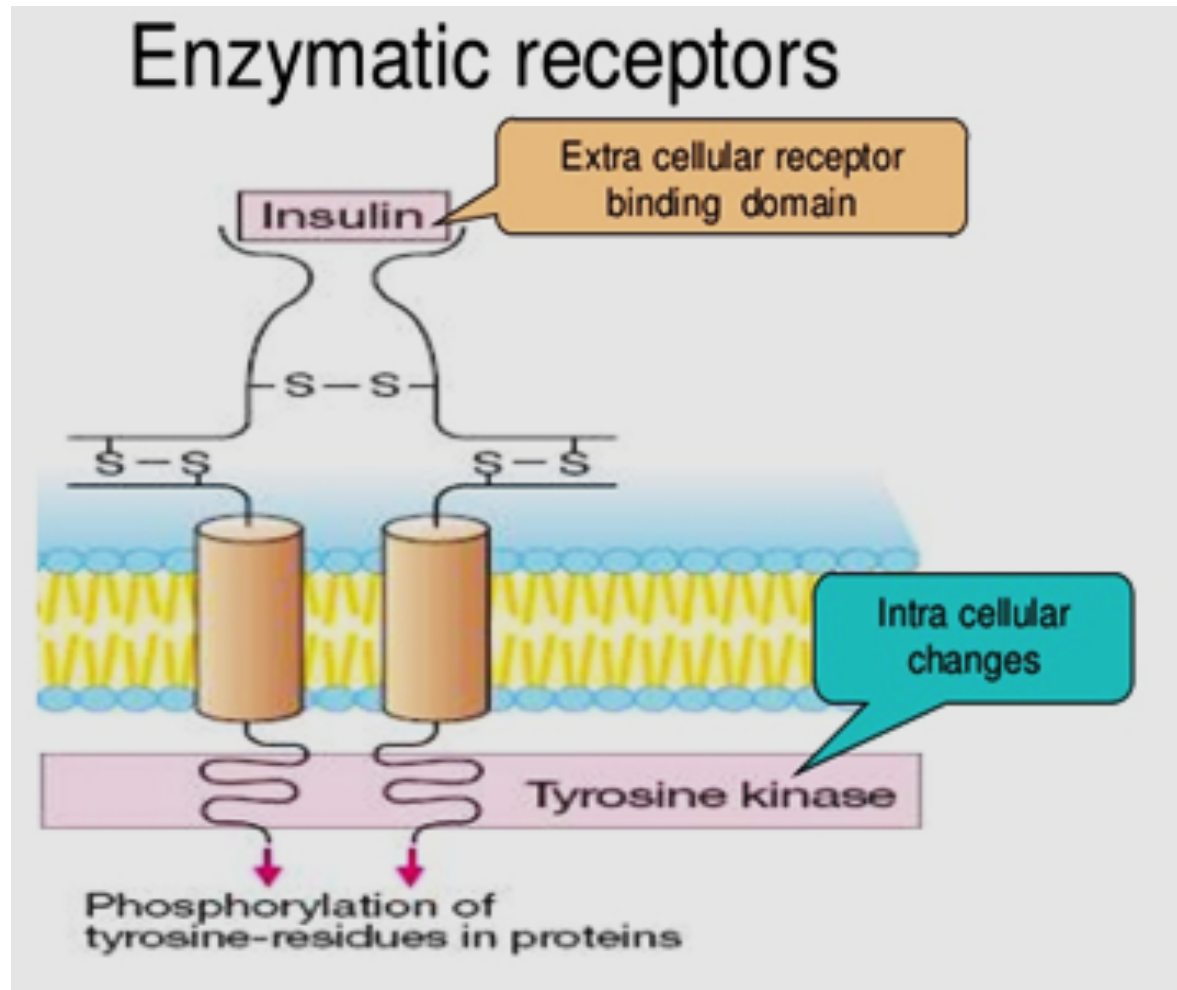
- **Activation of Type III receptors results in**
 - Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

E.g. Insulin receptors



Type III (tyrosine kinase-Linked receptors)

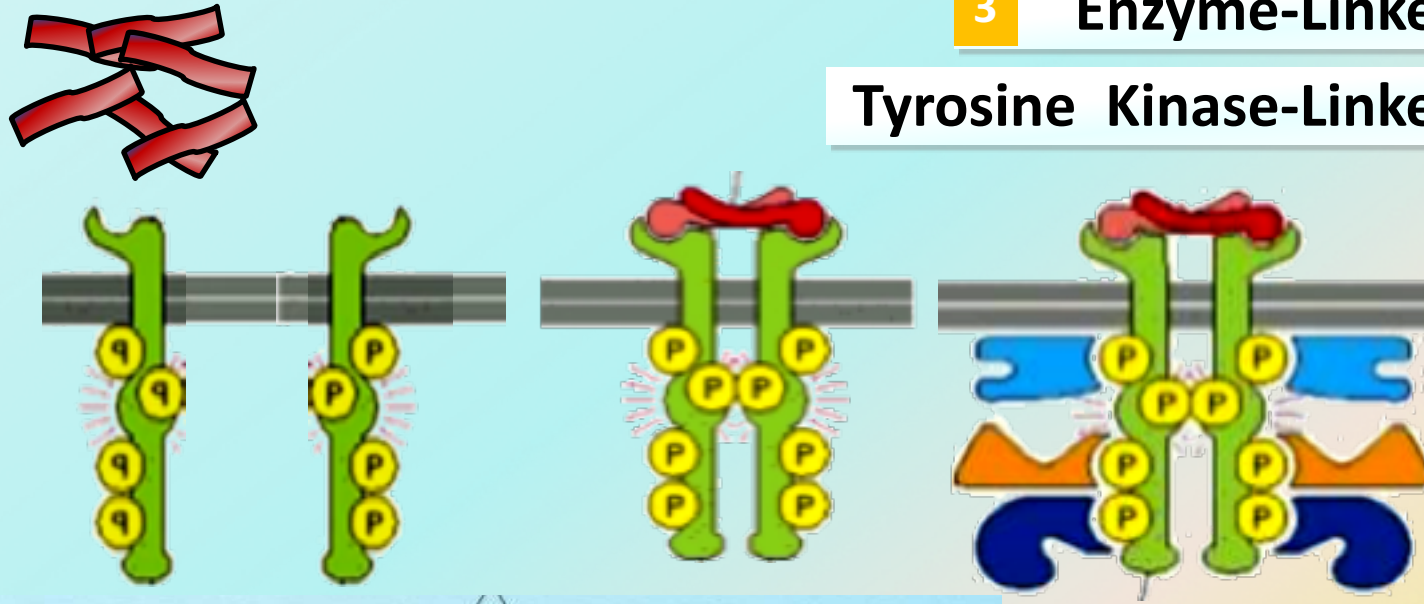
Insulin receptors



3

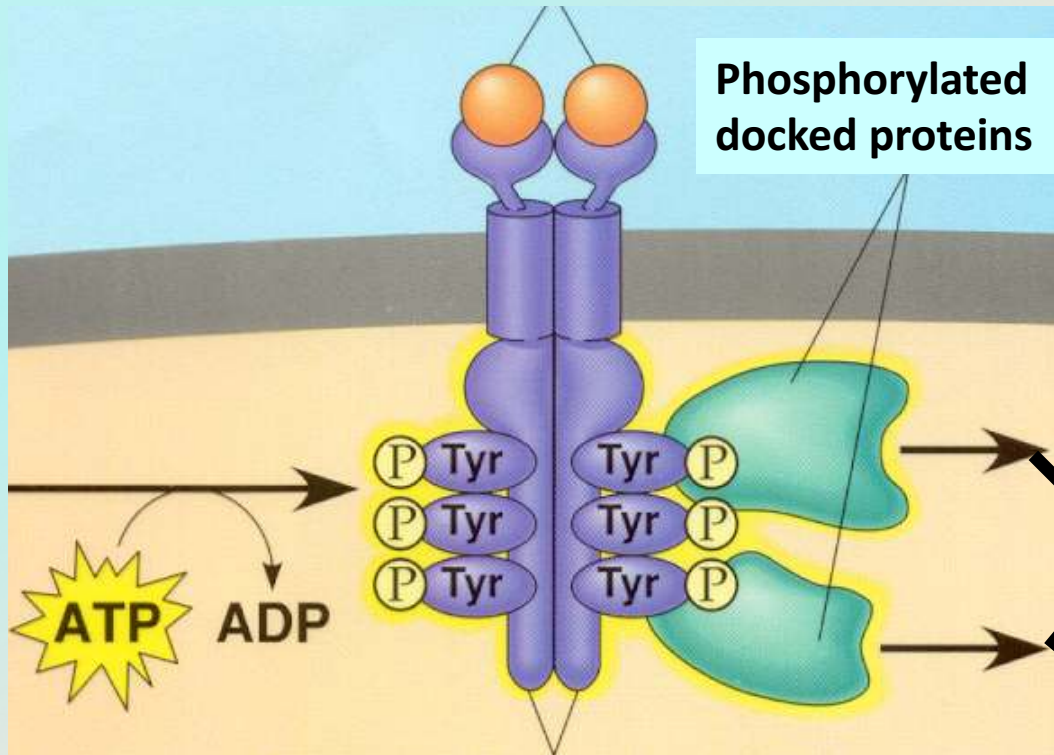
Enzyme-Linked Receptors

Tyrosine Kinase-Linked Receptors



Phosphorylated docked proteins

Phosphorylate other proteins that it docks



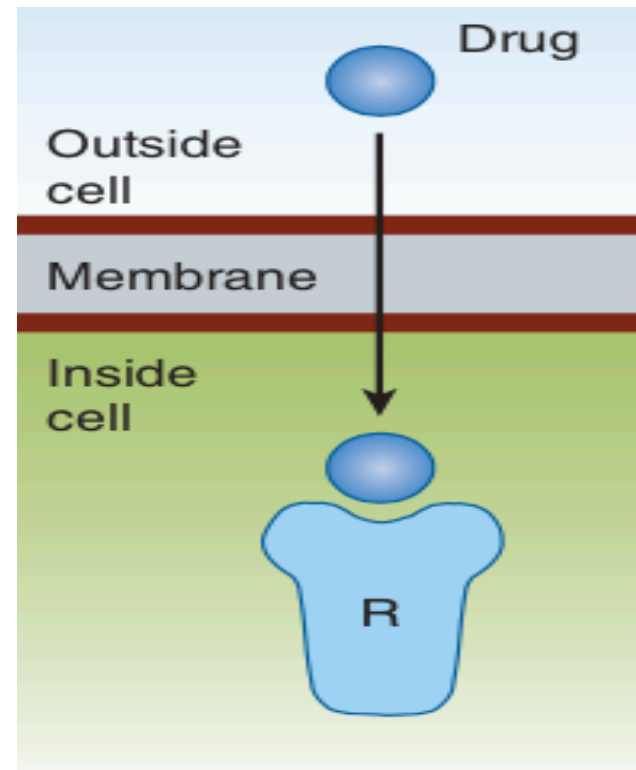
Example
Insulin Receptor

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.



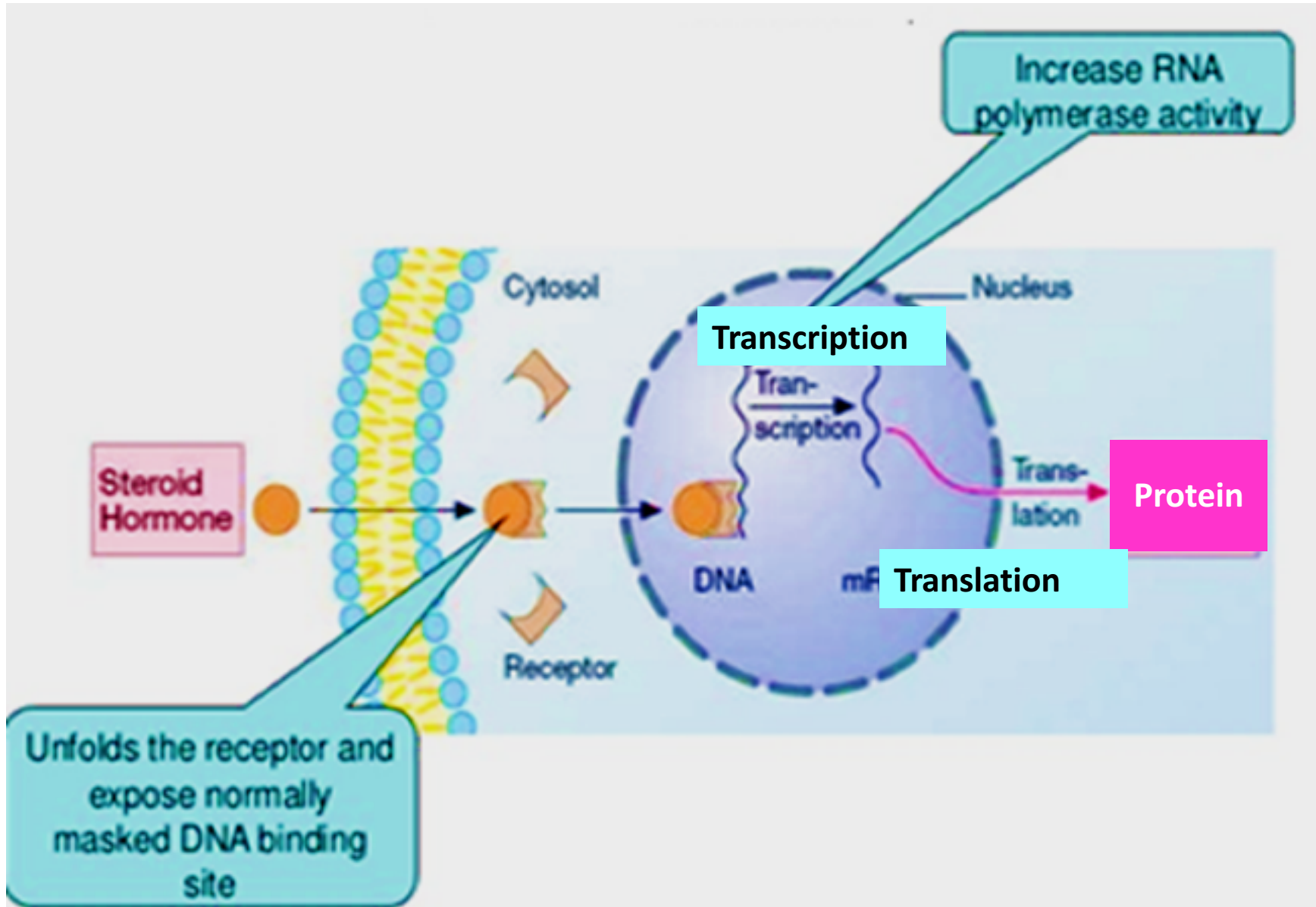
Type IV: Gene transcription receptors

▶ 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 III
Location	Membrane	Membrane	Membrane	Nucleus
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Examples	Nicotinic receptors	Muscarinic receptors Adrenergic receptors	Insulin receptors	Estrogen Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	DNA

SIGNALING MECHANISMS

A Ligand-gated ion channels

Example:

Cholinergic nicotinic receptors

B G protein-coupled receptors

Example:

α and β adrenoreceptors

C Enzyme-linked receptors

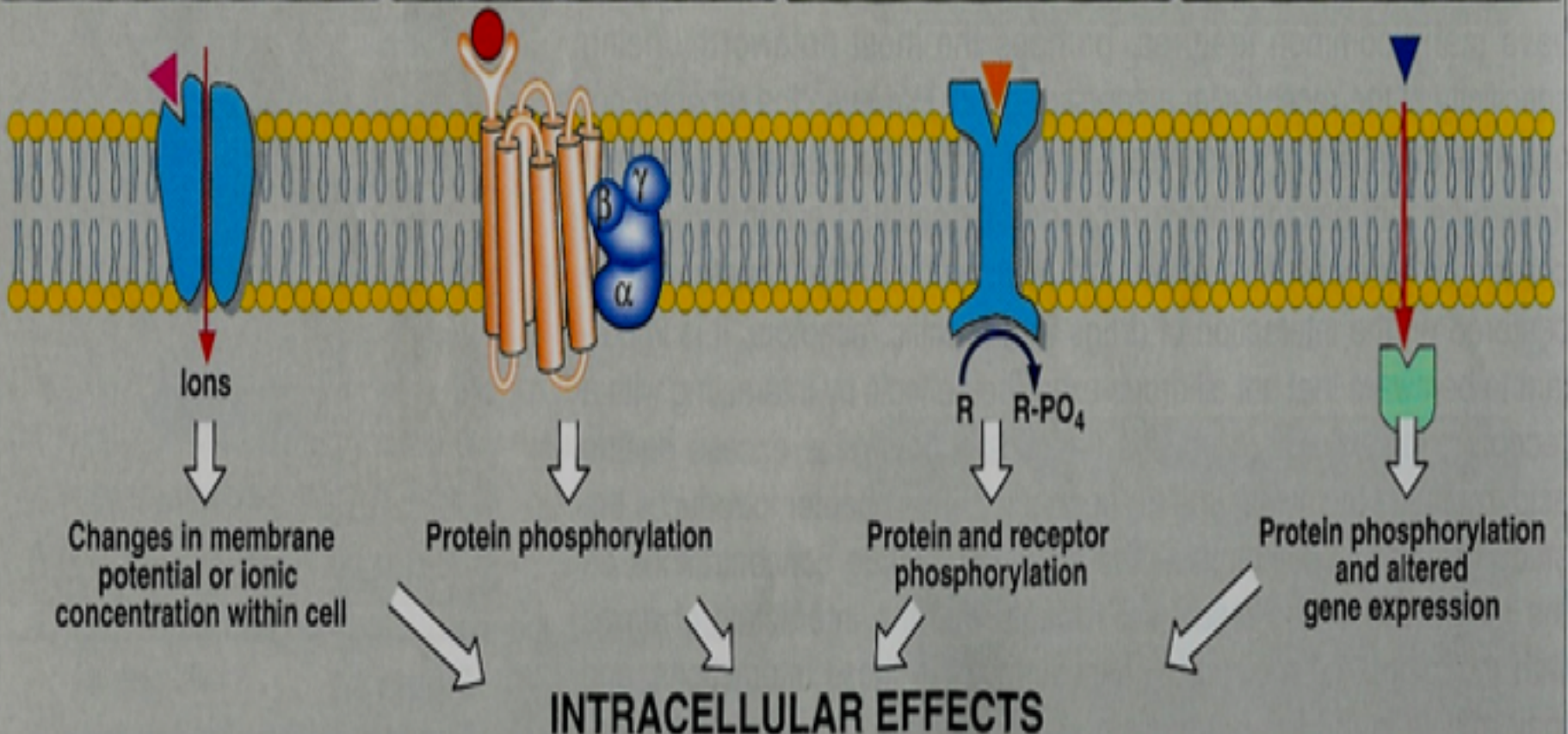
Example:

Insulin receptors

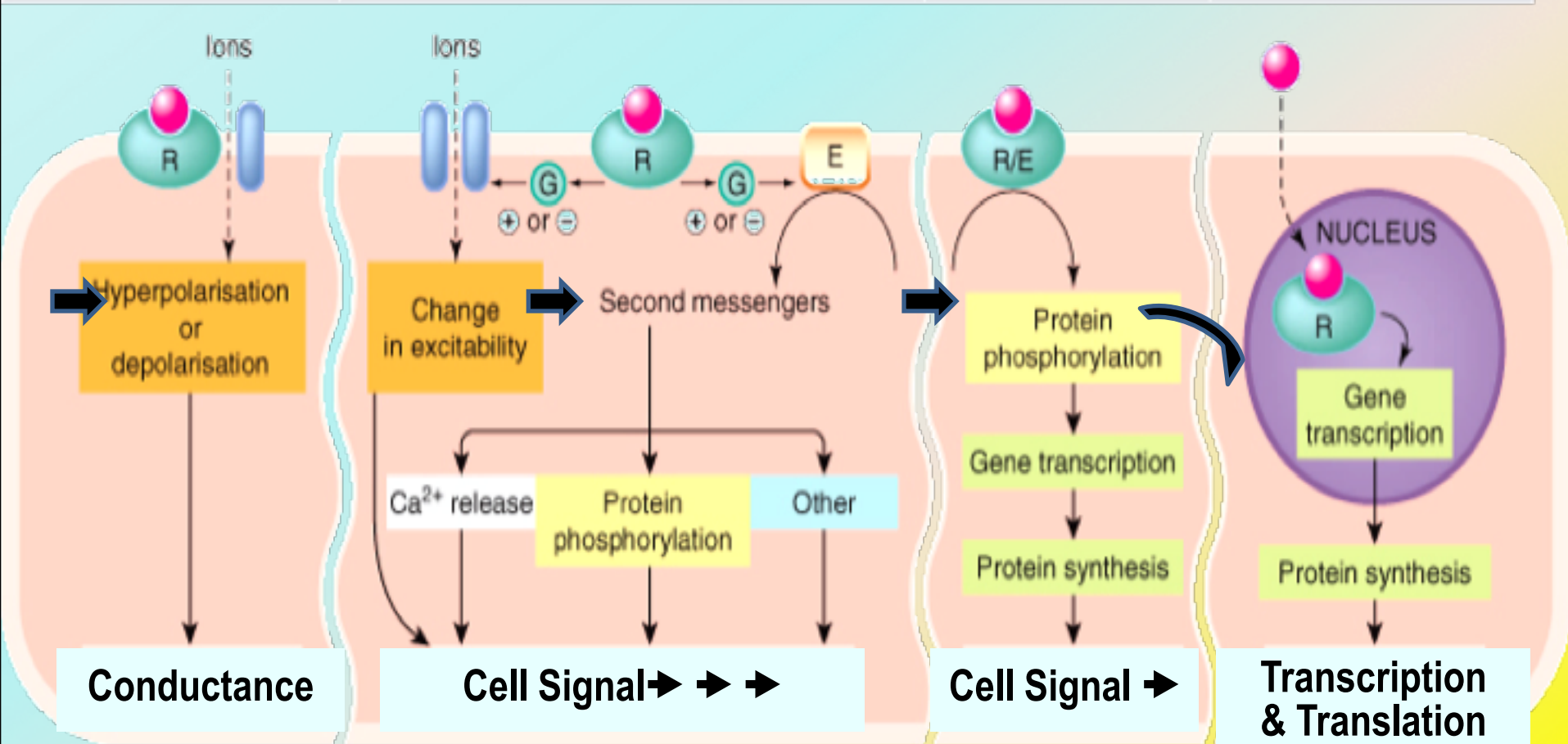
D Intracellular receptors

Example:

Steroid receptors



1 . Ligand-gated ion channels (ionotropic receptors)	2 2. G-protein-coupled receptors (metabotropic)	3 3. Kinase-linked receptors	4 4. Nuclear receptors
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Time scale Milliseconds Examples Nicotinic ACh receptor	Time scale Seconds Examples Muscarinic ACh receptor	Time scale Minutes / Hours Examples Cytokine receptors	Time scale Hours / Days Examples Oestrogen receptor
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