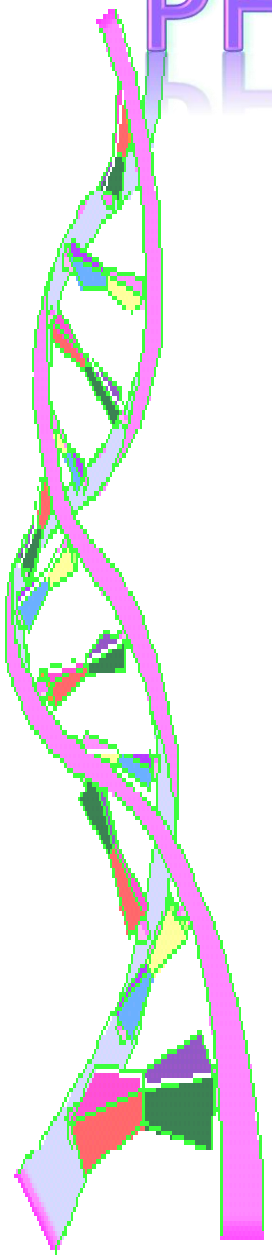
PHARMACODYNAMICS III



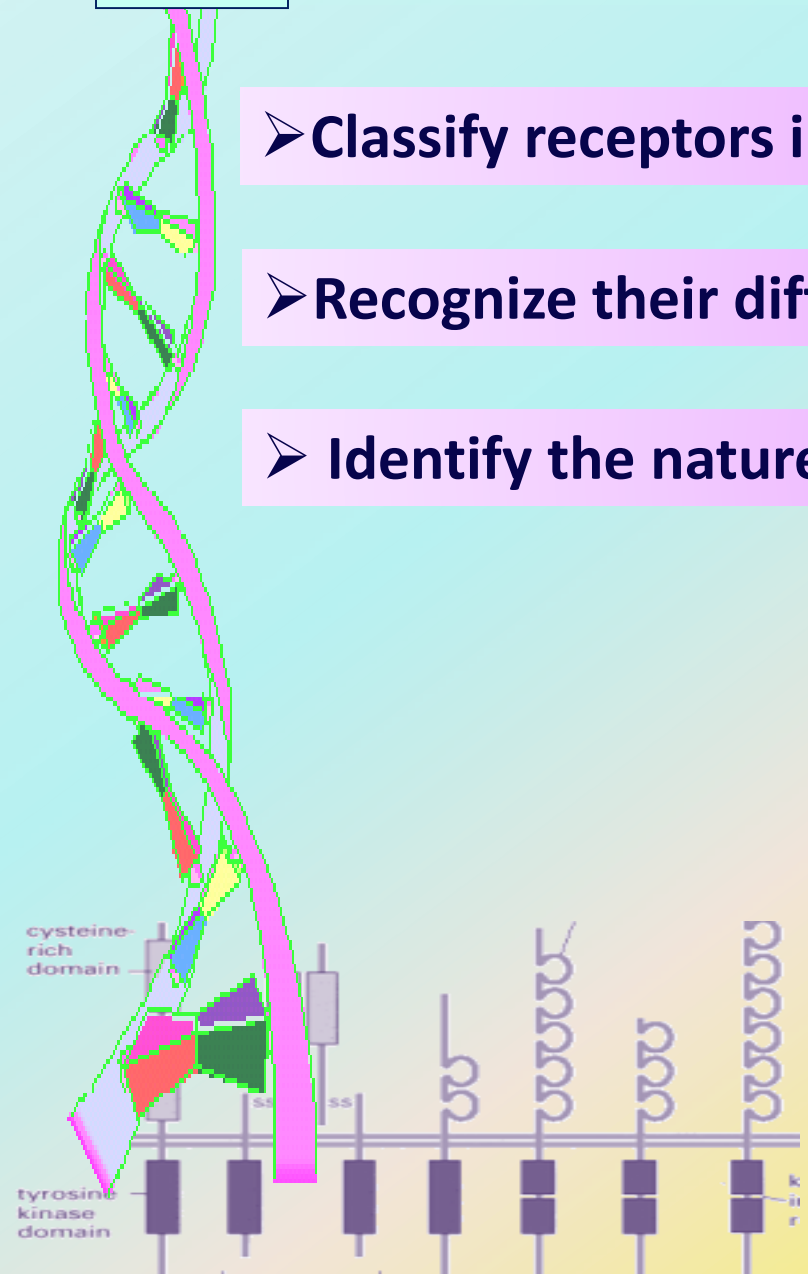
RECEPTOR FAMILIES

Prof. Hanan Hagar

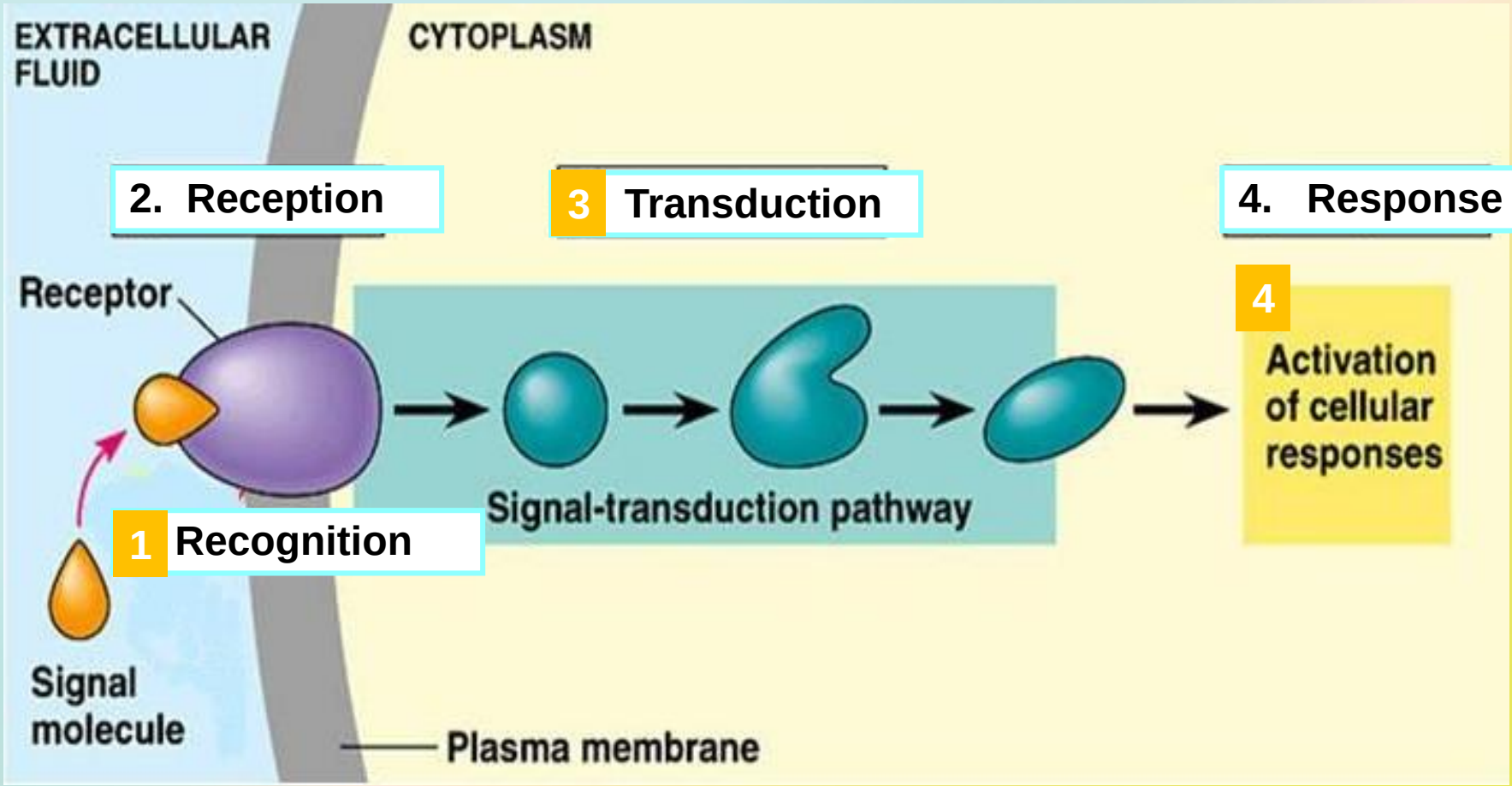
ILOs

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

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

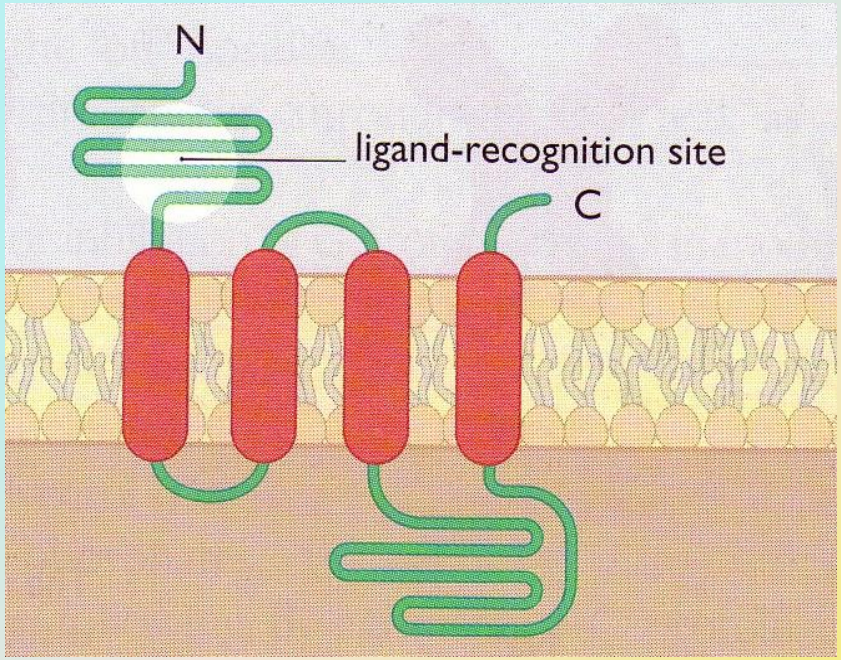


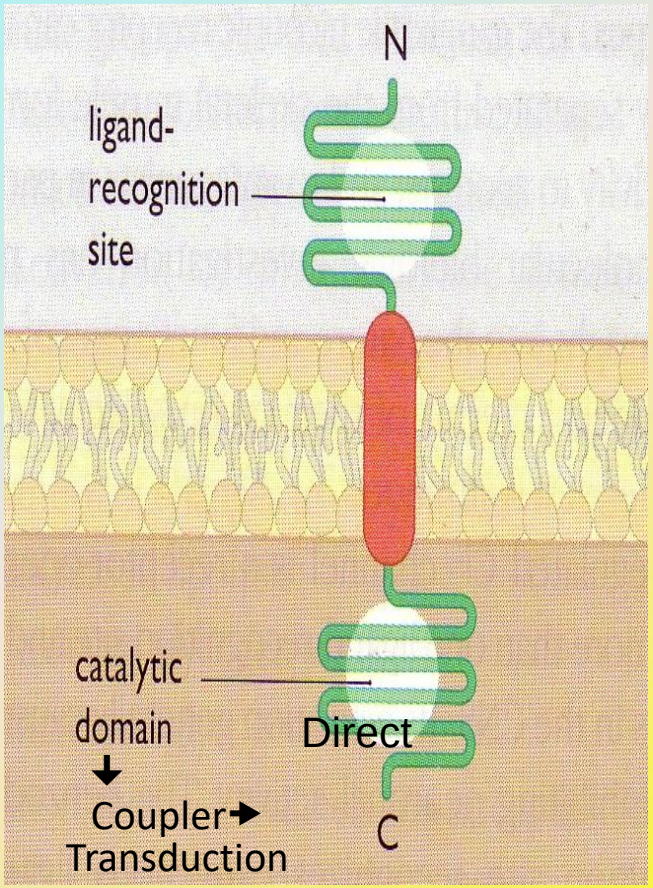
A RECEPTOR


EXTRACELLULAR FLUID
CYTOPLASM
2. Reception
3 Transduction
4. Response
Receptor
4
Activation of cellular responses
Signal-transduction pathway
1 Recognition
Signal molecule
Plasma membrane

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 channels
Ionotropic receptors

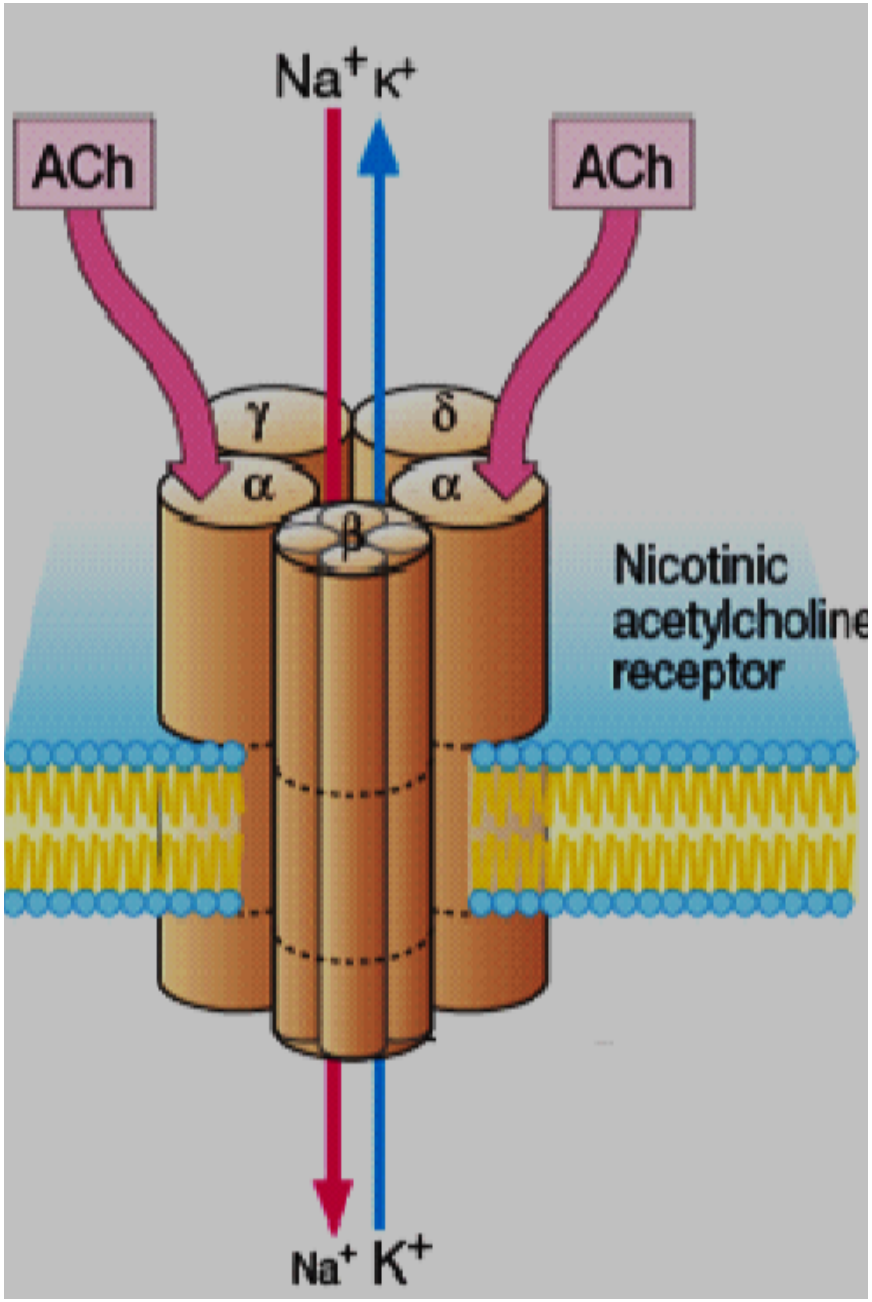
- Located at cell membrane
- Directly activated by ligand binding
- Directly related to ion channels.
- Involved in very fast synaptic transmission.
- Response occurs in milliseconds.
- E.g. Nicotinic receptors activated by acetylcholine

1 **Channel-Linked Receptor**

Ionotropic Receptor

Ligand-Gated-Ion Channel

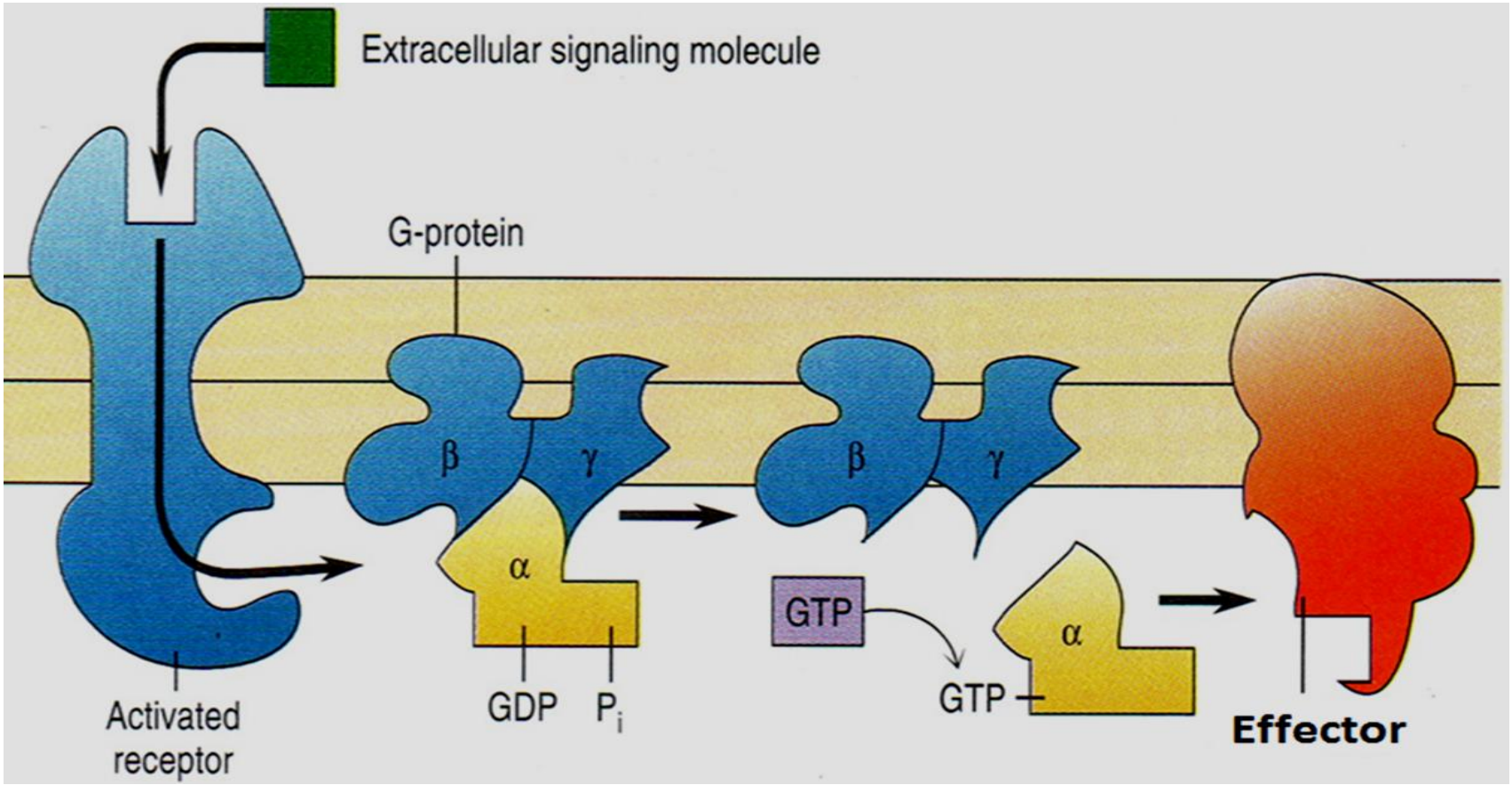
e.g. nicotinic acetycholine receptor that is activated by occupancy of a ligand as acetycholine.



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 (muscarinic receptors)
- E.g. **Adrenergic receptors** of Noradrenaline (α and β)

Type II: G-Protein coupled receptors



Type II: G-Protein coupled receptors

G-Protein

- Comprise of three subunits (αβγ), α subunits possess GTPase activity
- Regulates guanine nucleotides GDP, GTP.
- 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 allow α-subunit to recombine with **(βγ)** and returns to its **inactive state**.

Targets for G-proteins

1) Ion channels

– Muscarinic receptors in heart (K-channel), decrease heart rate

Second messengers

2) Adenyl cyclase enzyme (AC)

Cyclic AMP system **(cAMP)**

3) Phospholipase C enzyme

Inositol phosphate system **(IP3+DAG)**

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

Targets for G-proteins

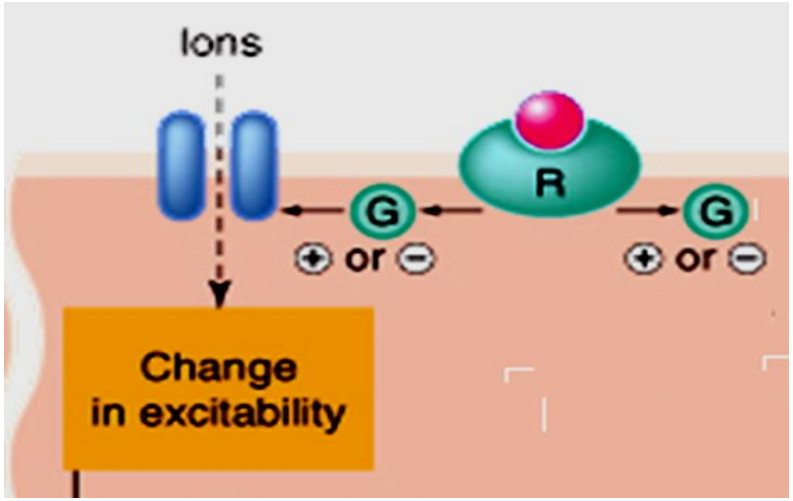
Can open or close ion channels causing change in the excitability

Ion channels

e.g. muscarinic receptors in heart
Ach acts upon muscarinic receptors to produce decrease in heart rate

How ?

opening of K-channel and increase K efflux (hyper-polarization).



Targets for G-proteins

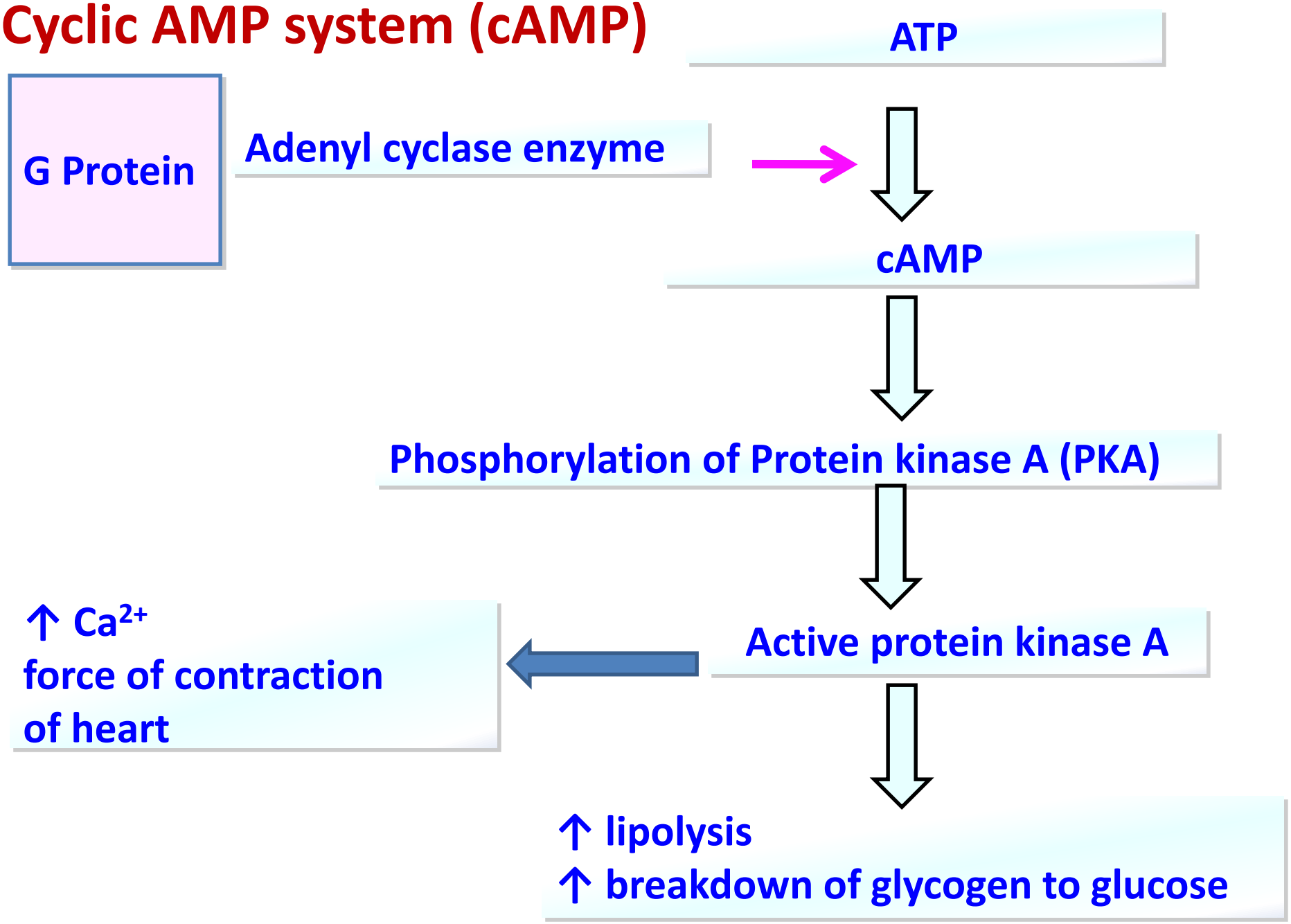
Enzymes

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

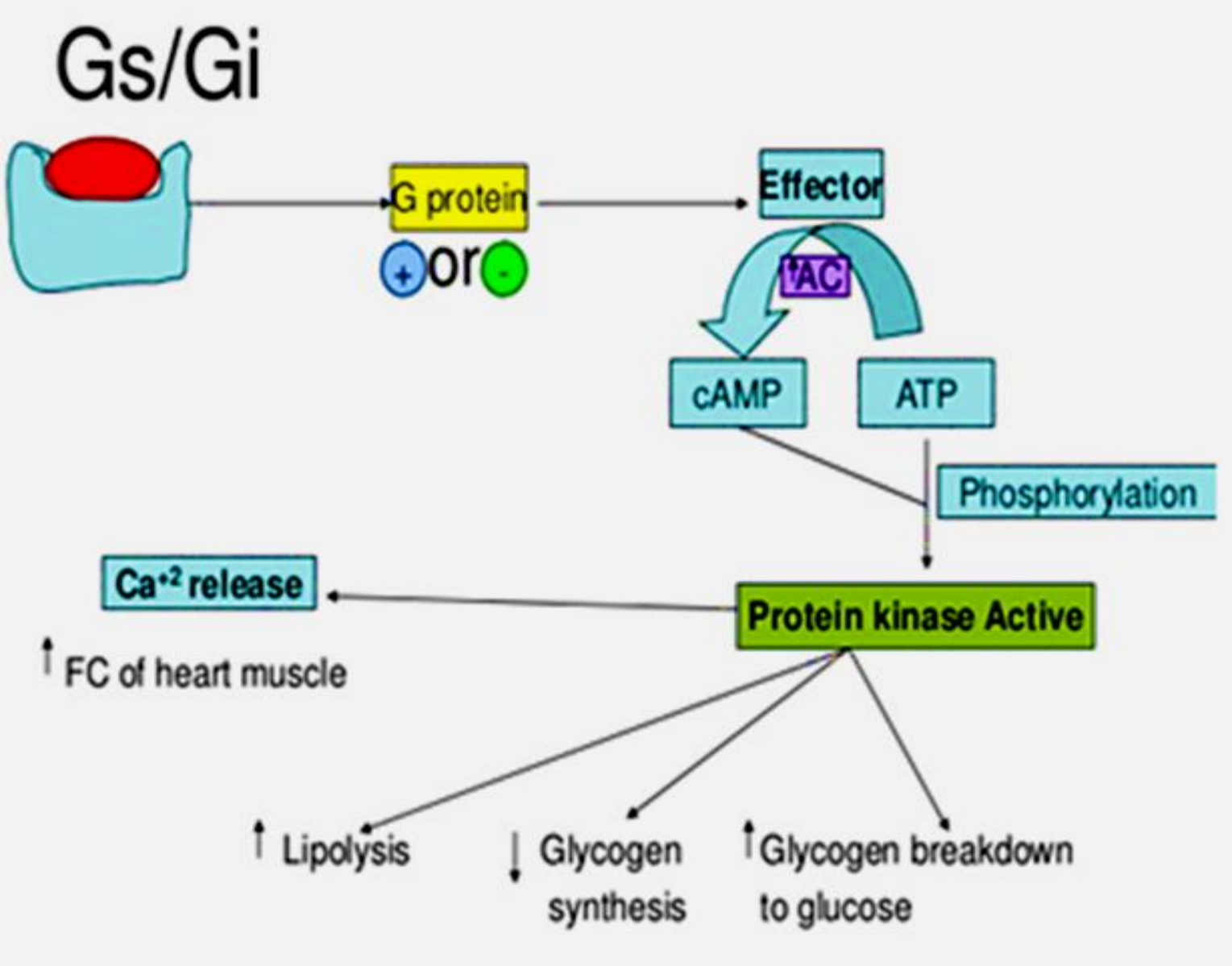
- Phospholipase C enzyme
  Inositol phosphate system (IP3+DAG)

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

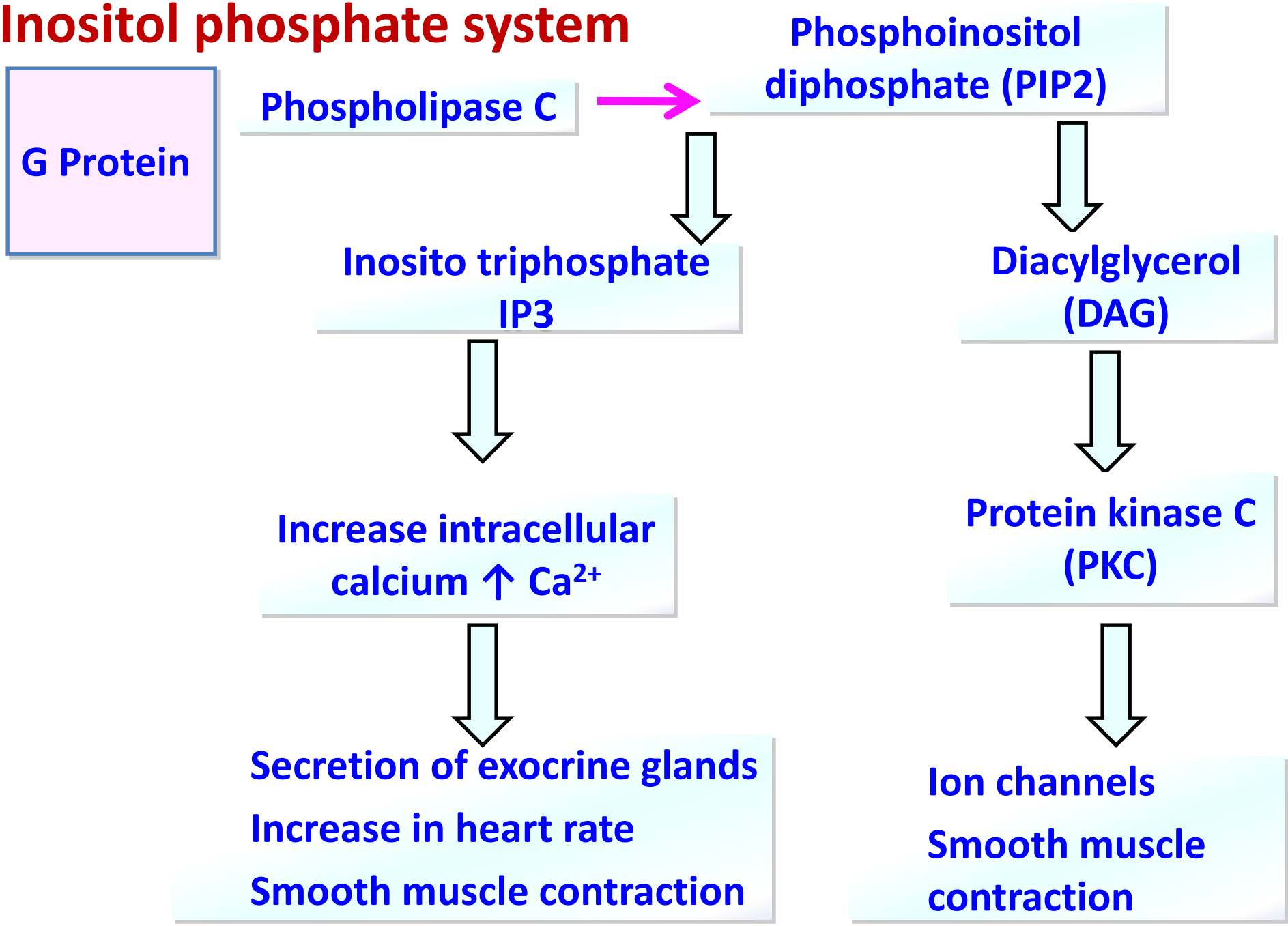
Cyclic AMP system (cAMP)



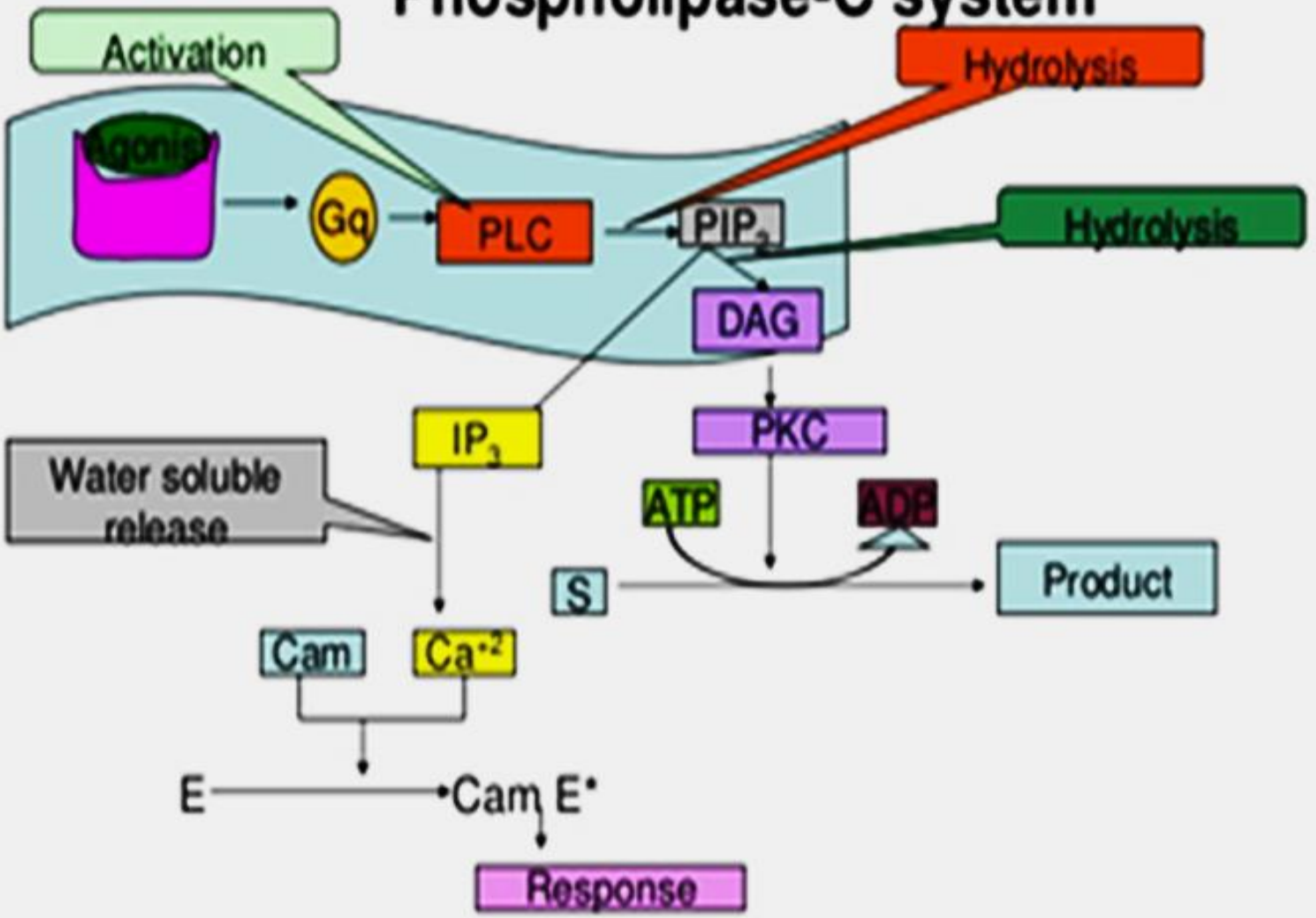
Adenyl cyclase system (AC)



Inositol phosphate system



Phospholipase-C system



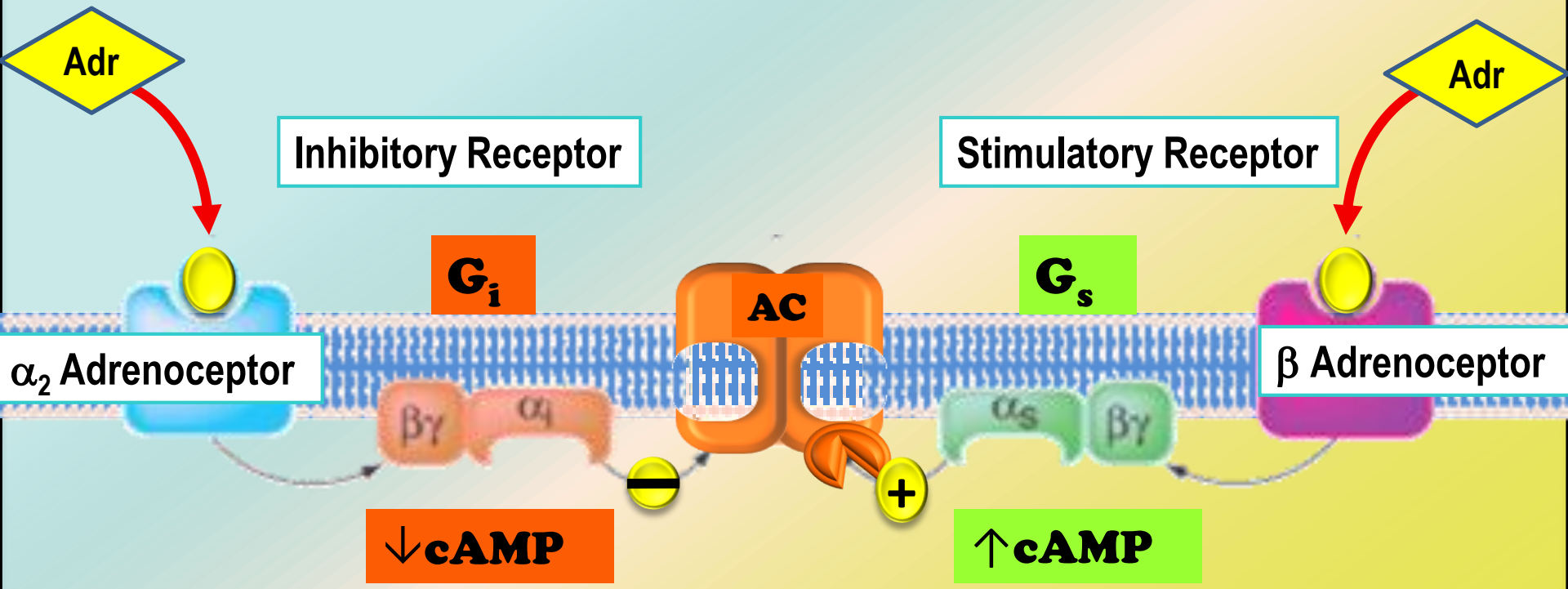
PLC= Phospholipase-C
PIP2 =Phosphotiydl inositol 4,5 di phosphate
IP3 =Inositol tri phosphate
DAG = Diacylglycerol
E= Ezyme
PKC = Phosphokinase -C

Type II: G-Protein coupled receptors

- There are different classes of G-Protein according to their α-subunits into **G_s, G_i and G_q**:
  - **Gs : stimulation** of adenyl cyclase
  - **Gi** : **Inhibition** of adenyl cyclase
  - **Gq**: is linked to activation of Phospholipase C

ADRENOCEPTORS

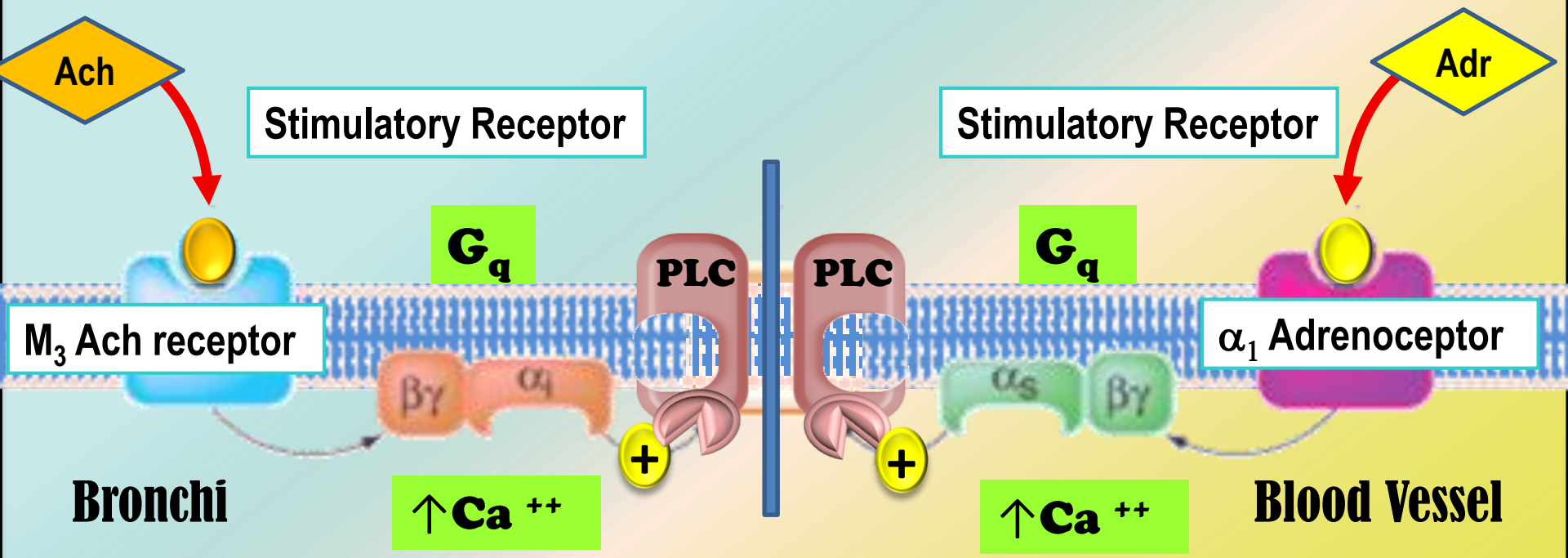
a_1 Adrenoceptors couple to G_q to stimulate PLC.
α_2 Adrenoceptors couple to G_i to inhibit AC.
$\beta_{1\&2}$ Adrenoceptors couple to G_s to stimulate AC



CHOLINERGIC RECEPTORS

M_1 & M_3 Ach receptors couple to G_q to stimulate PLC

M_2 & M_4 Ach receptors couple to G_i to inhibit AC



Type III (Enzyme-Linked receptors)

(Tyrosine Kinase-linked receptor)

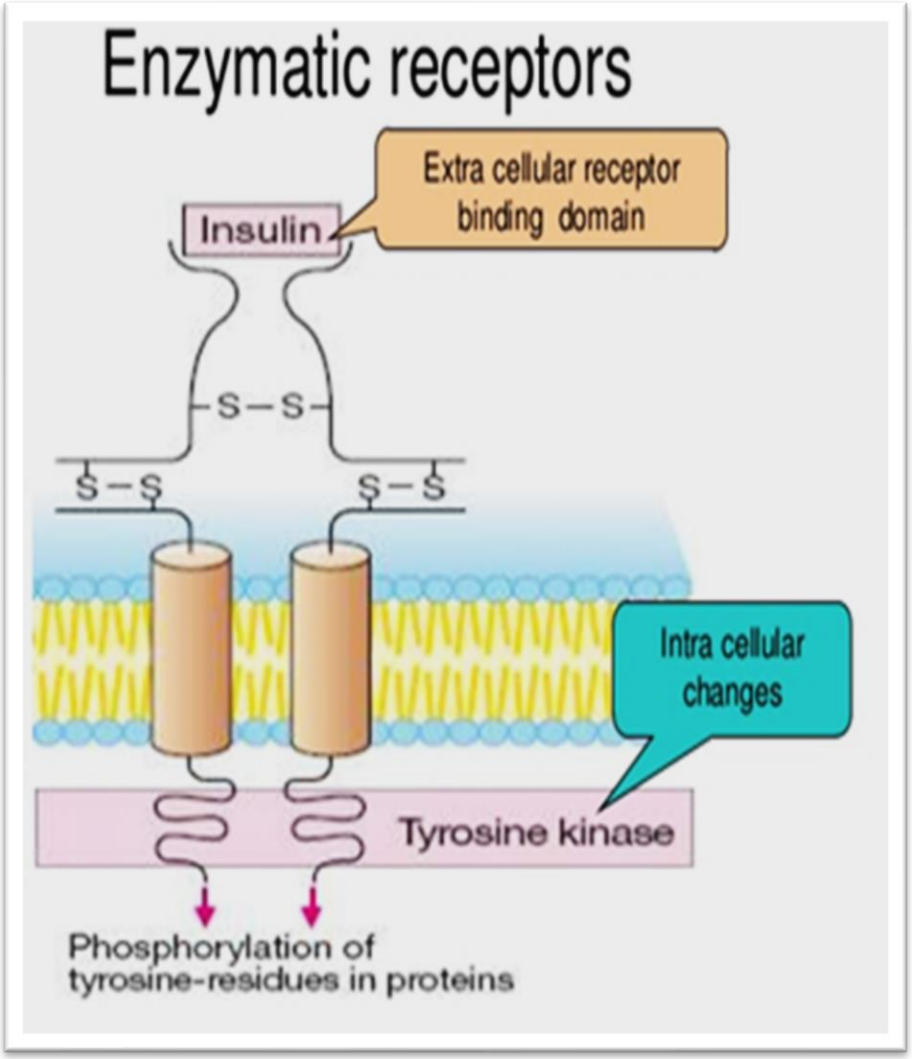
- Located at cell membrane
- Linked to enzyme (with intrinsic enzymatic activity)
- Response occurs in minutes to hours.
- Involved in response to hormones, growth factors.
- They control many cellular functions as metabolism and growth.

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

Activation of Type III receptors results in

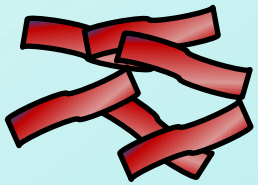
Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

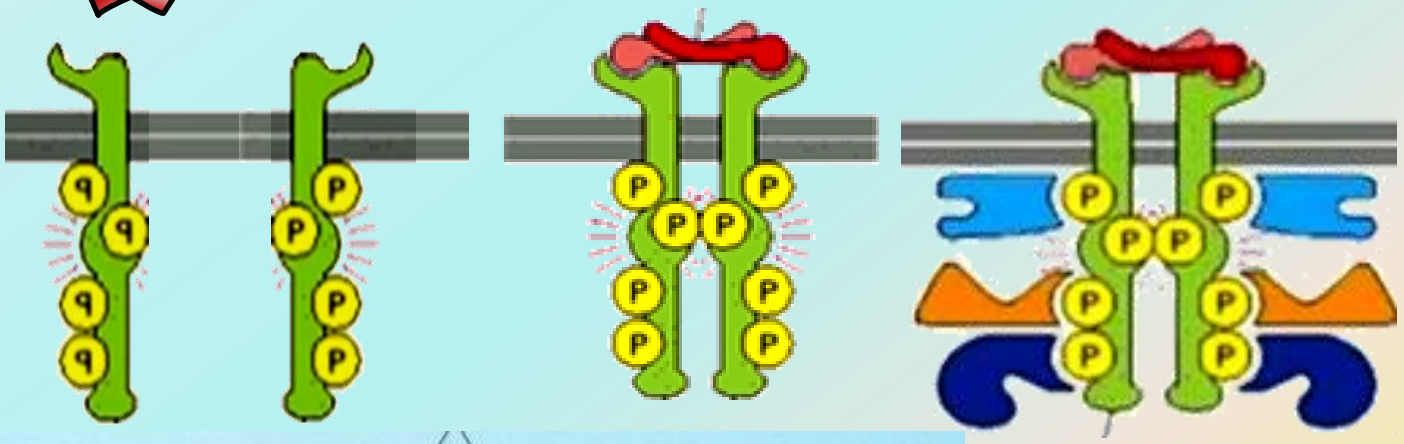
E.g. Insulin receptors

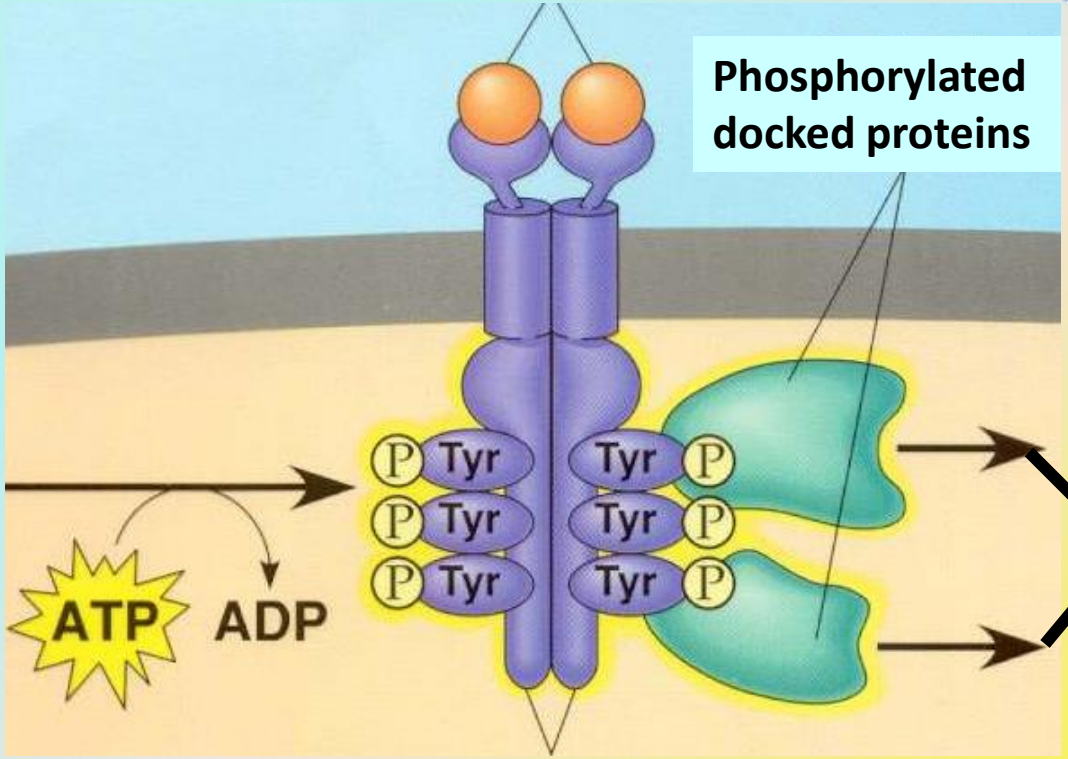


3 Enzyme-Linked Receptors

Tyrosine Kinase-Linked Receptors







Phosphorylate other proteins that it docks

Example

Insulin Receptor

RESPONSE

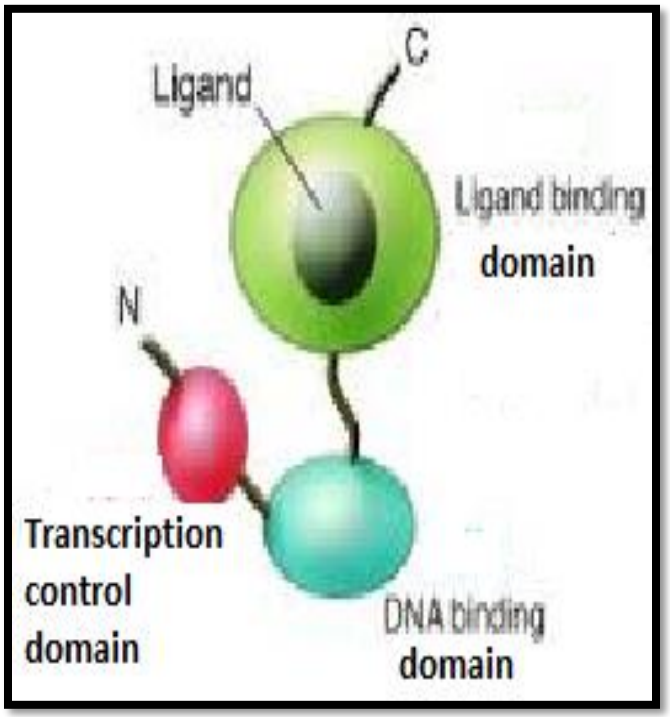
Type IV: Gene transcription receptors
Nuclear receptors

- 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.

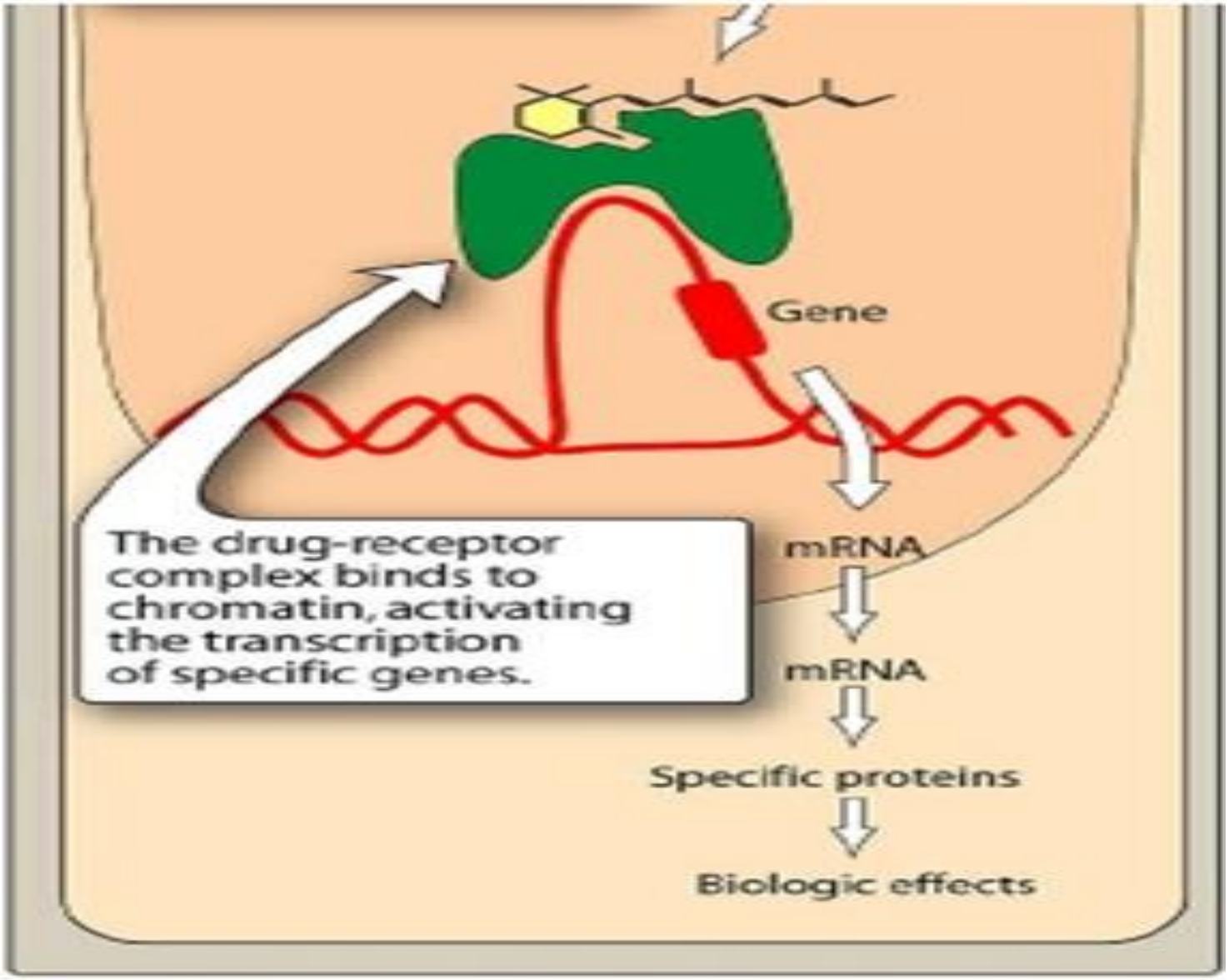
Type IV: Gene transcription receptors

▶They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE] .

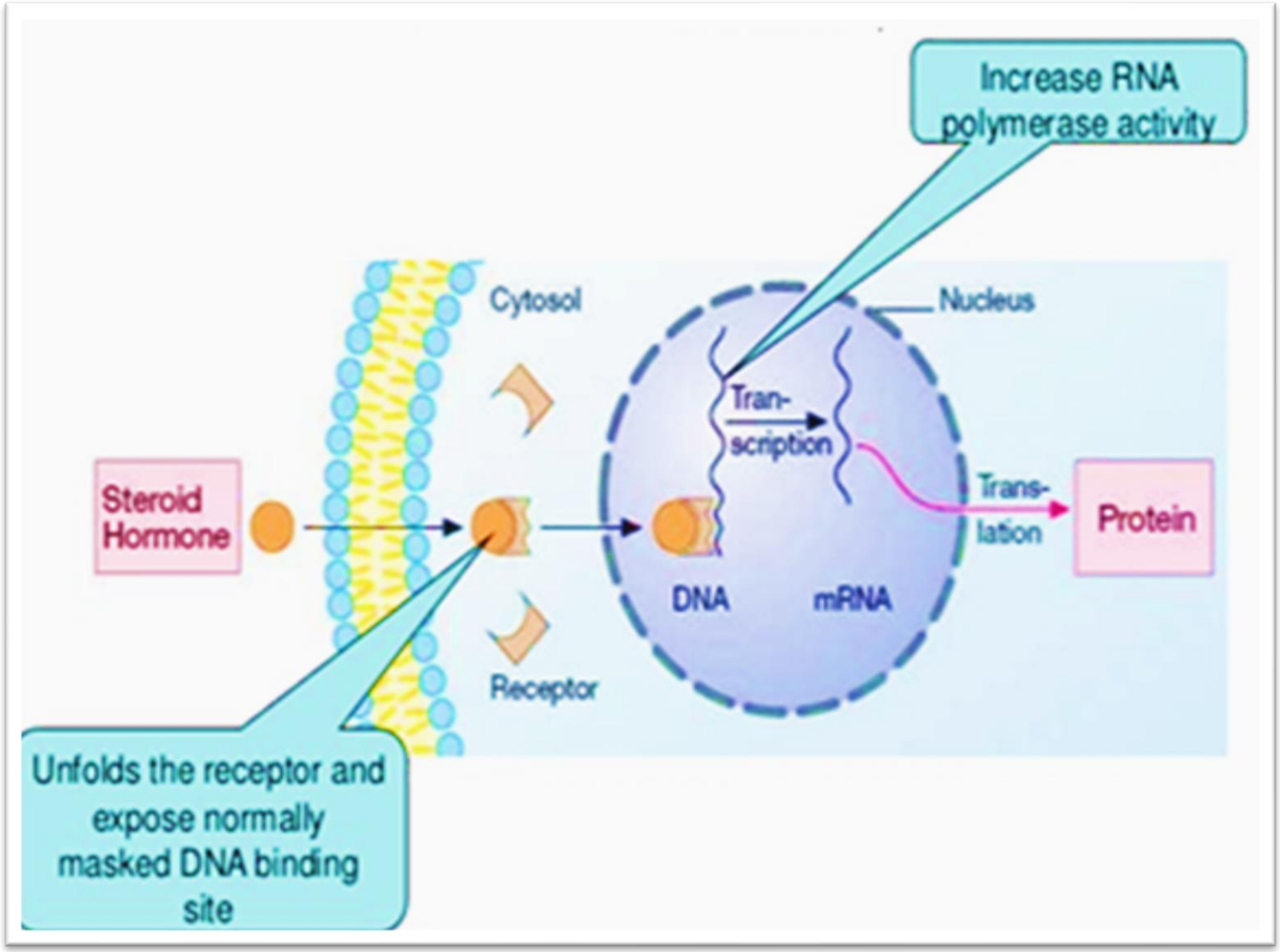
▶This means that the activated receptors are acting as **Transcription Factors** → expressing or repressing target genes.



Type IV: Gene transcription receptors



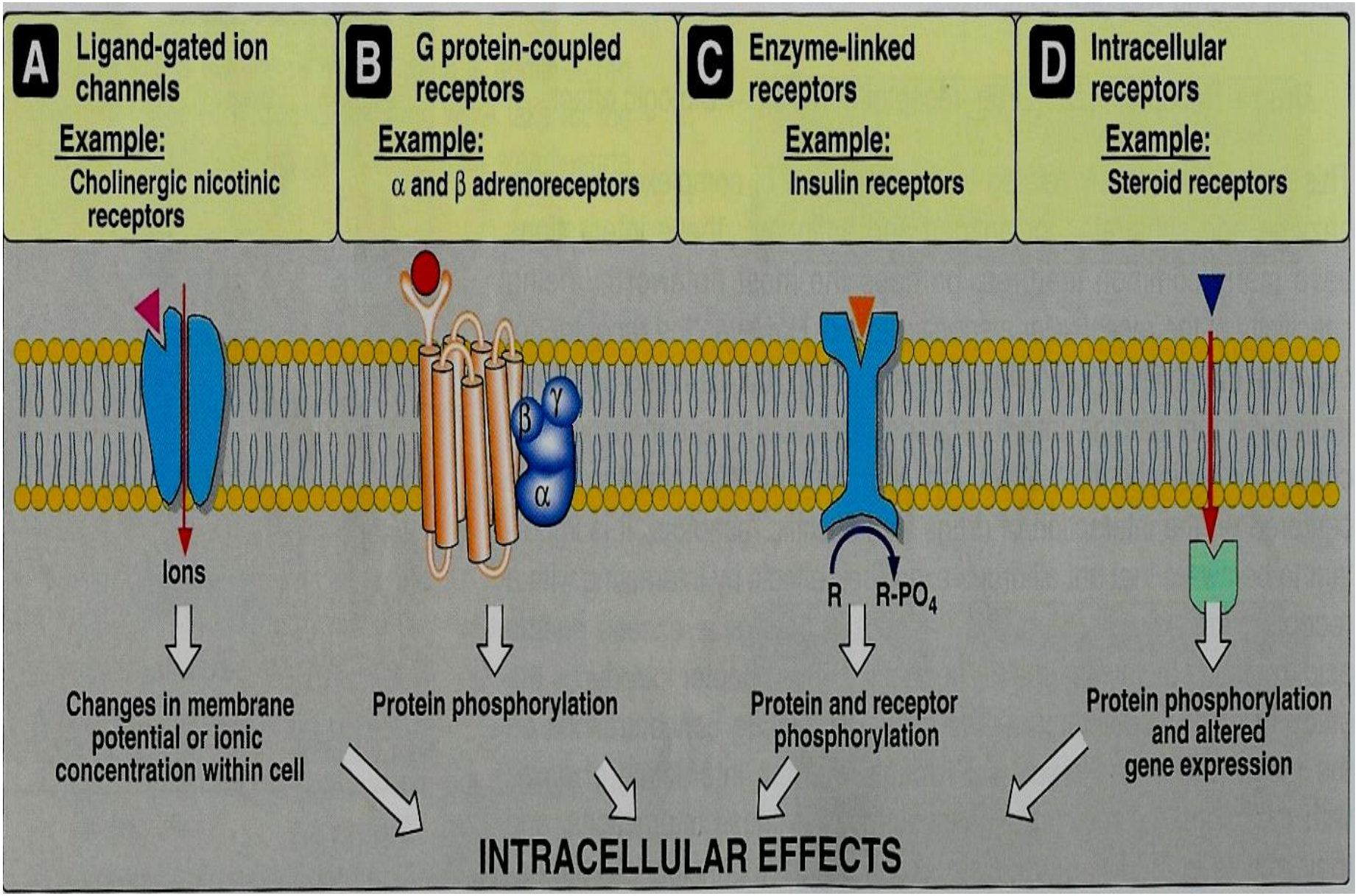
Type IV: Gene transcription receptors

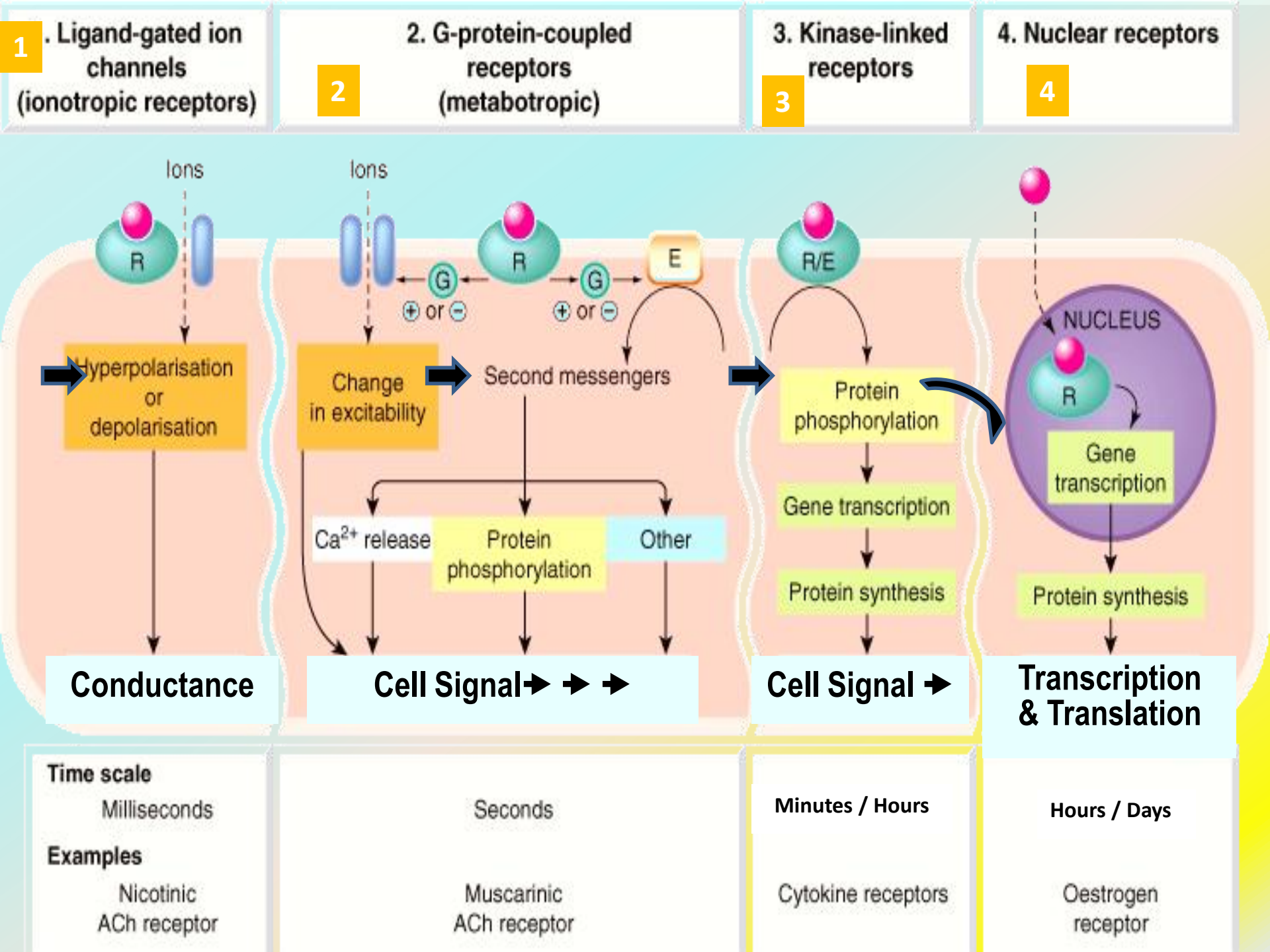


RECEPTOR FAMILIES

	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
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
Ca^{2+} 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