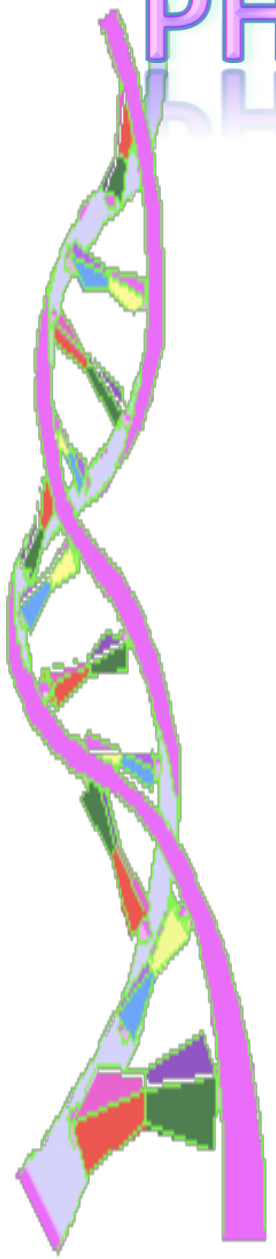
PHARMACODYNAMICS III



RECEPTOR FAMILIES

Prof. Hanan Hagar

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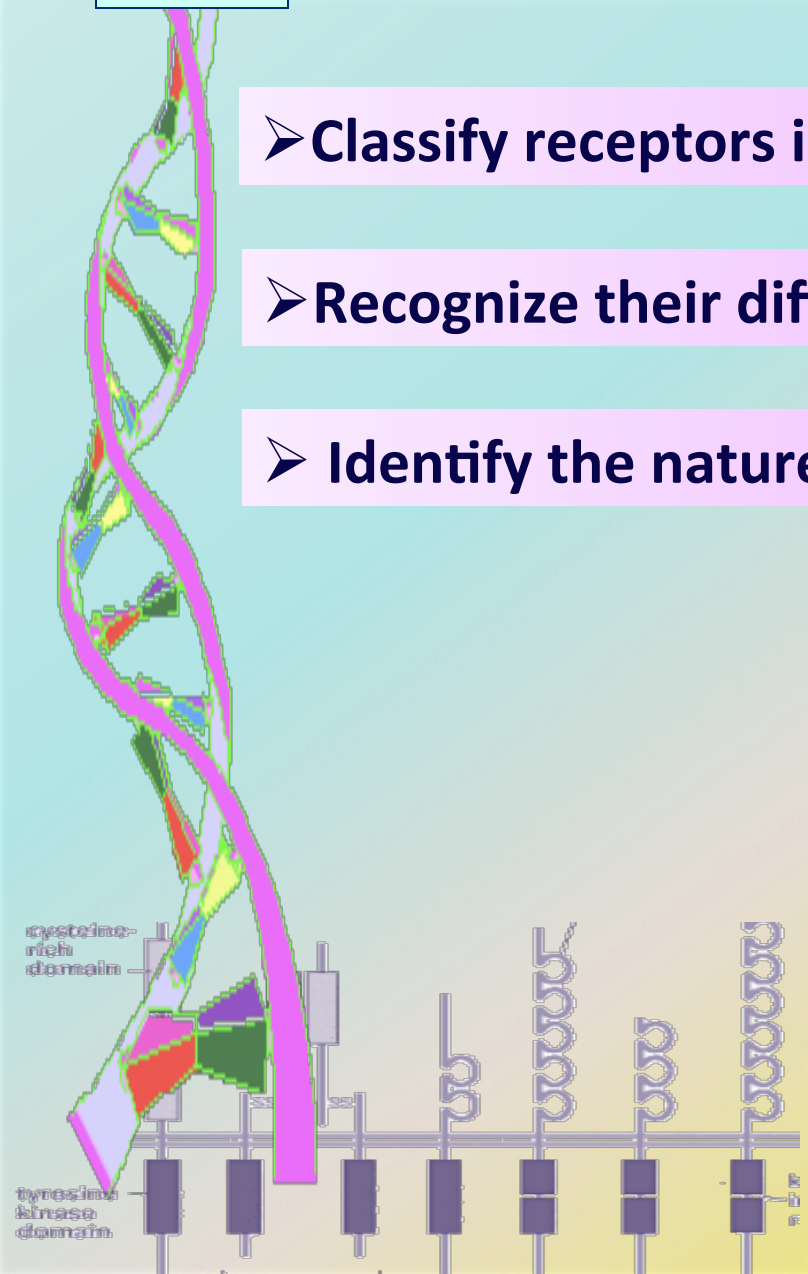
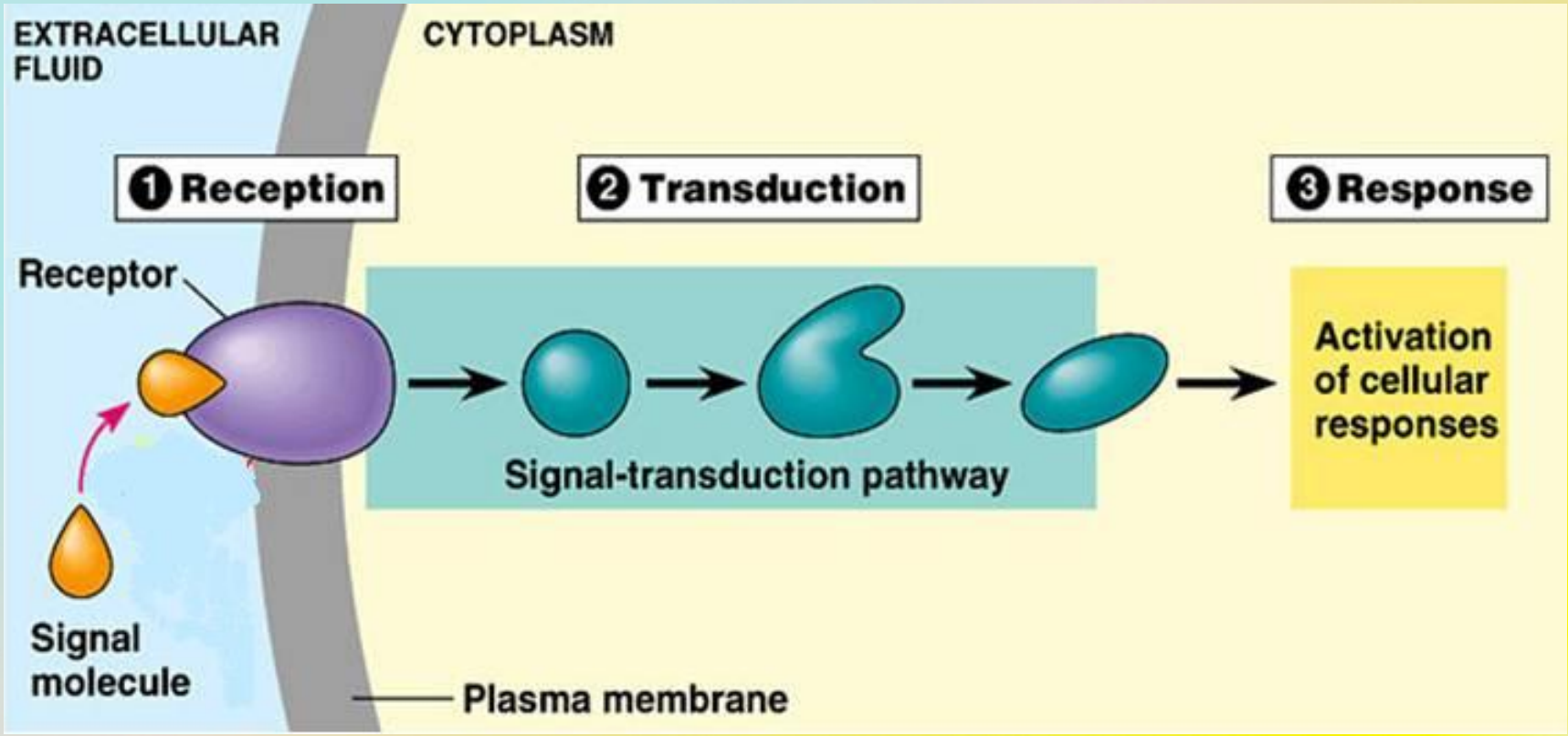
By the end of this lecture you will be able to :

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



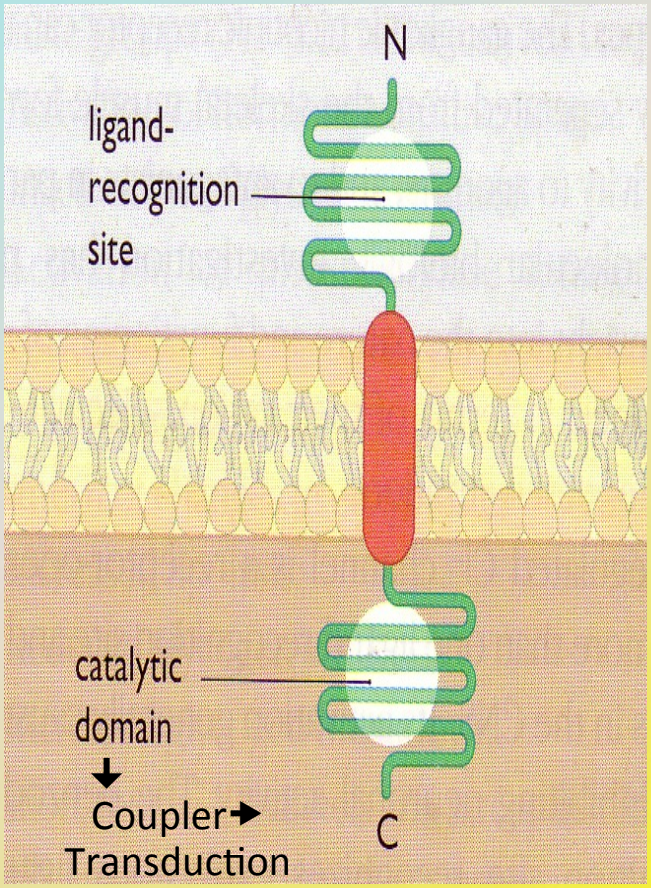
A RECEPTOR

1. Recognition
2. Reception
3. Transduction
4. Response



A RECEPTOR structure

- Ligand recognition site
- Inner catalytic domain



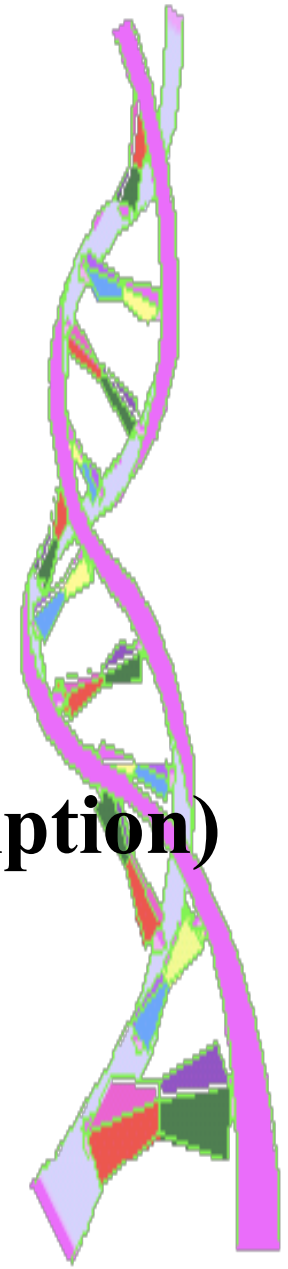
RECEPTOR FAMILIES

Type I (Ion Channel-Linked receptors)

Type II (G-Protein coupled receptors)

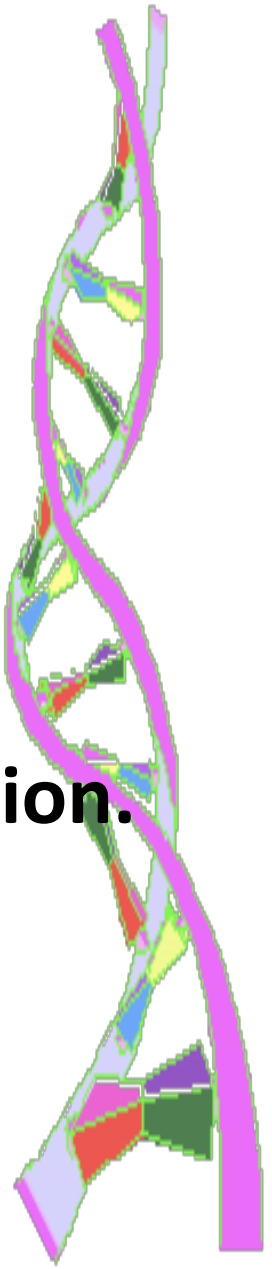
Type III (Enzyme-Linked receptors)

Type IV (Receptors linked to gene transcription)



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

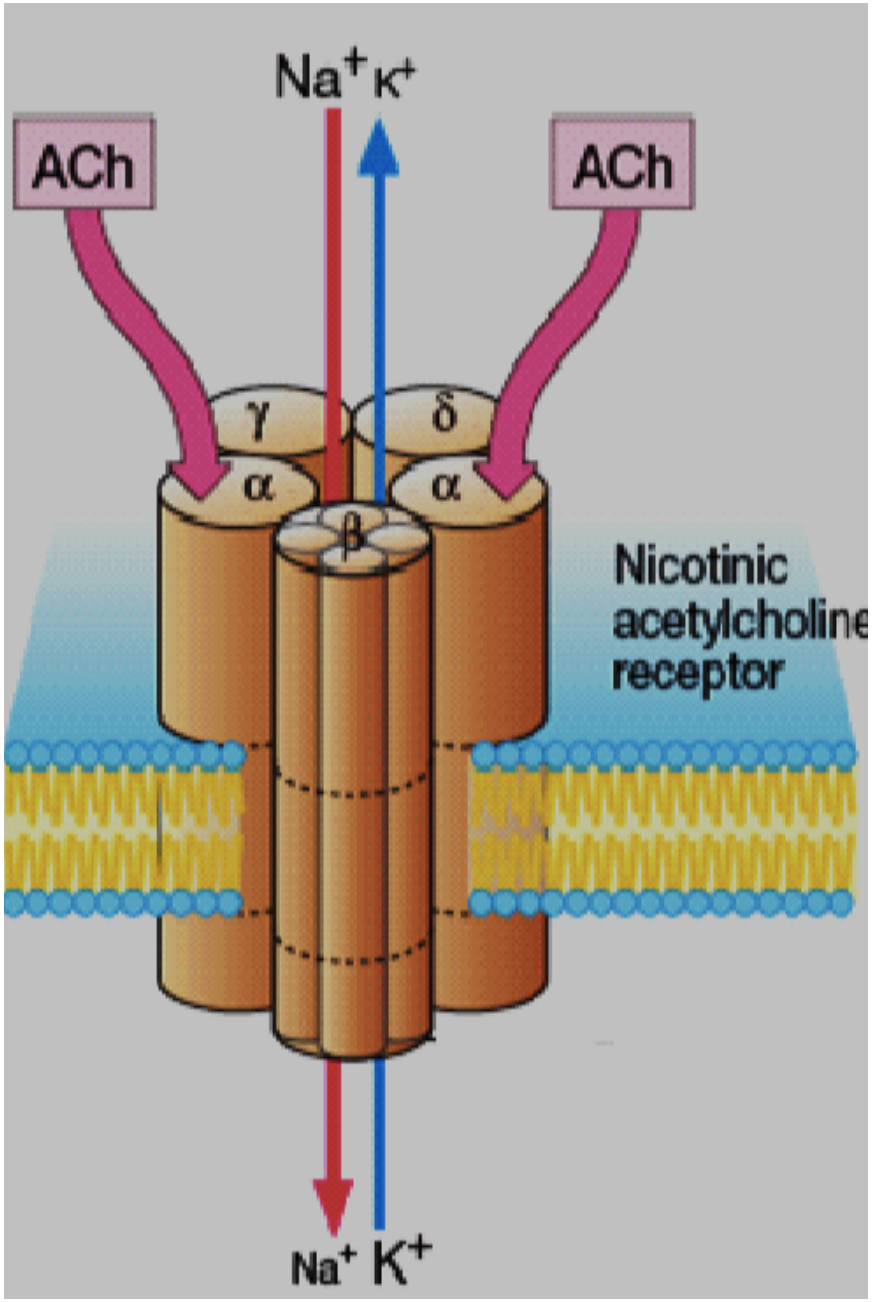


1 **Channel-Linked Receptor**

Ionotropic Receptor

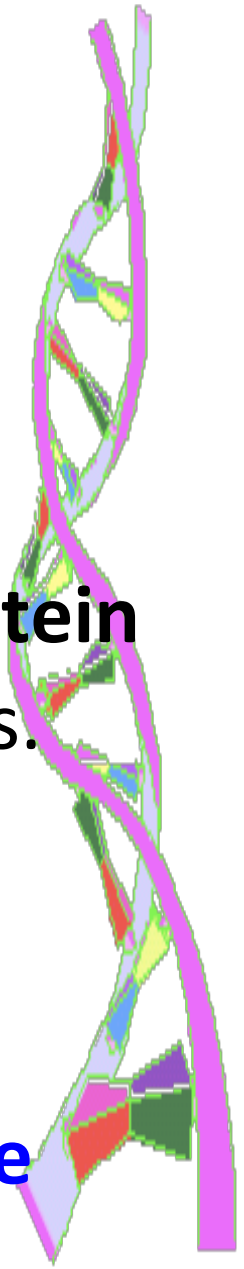
Ligand-Gated-Ion Channel

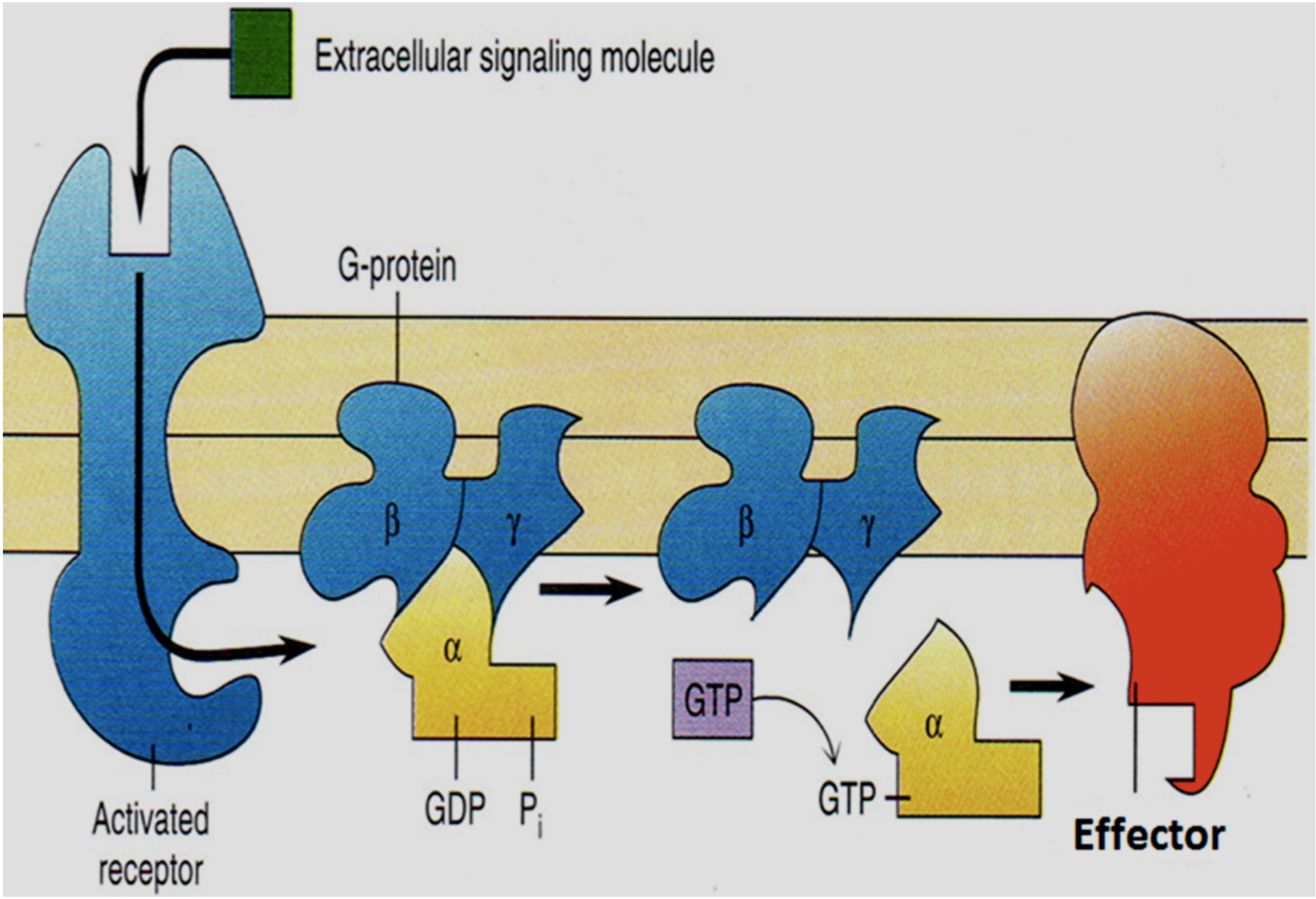
e.g. nicotinic acetycholine receptor that is activated by occupancy of a ligand as acetycholine.



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




Extracellular signaling molecule
G-protein
β
γ
α
GDP
P_i
Activated receptor
GTP
GTP
α
β
γ
Effector

G-protein

- Regulatory proteins
- Regulate guanine nucleotides GDP, GTP.
- Comprise of three subunits (αβγ), α subunits possess GTPase activity
- When the **trimer** 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 the bound GTP to GDP which allow α-subunit to recombine with **(βγ)** and returns to its inactive state.

Targets for G-proteins

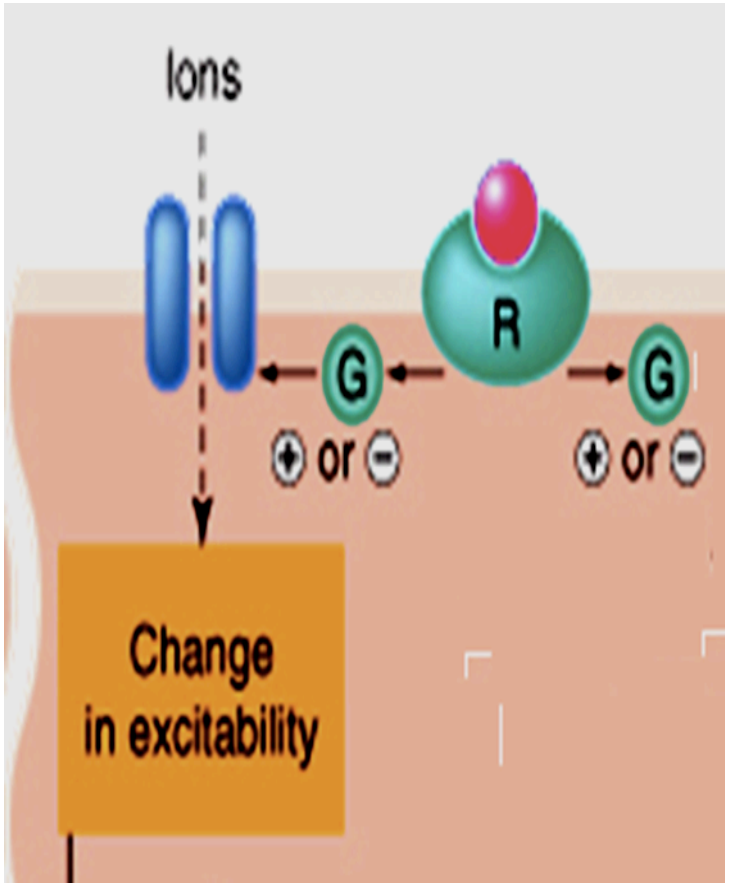
Ion channels

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

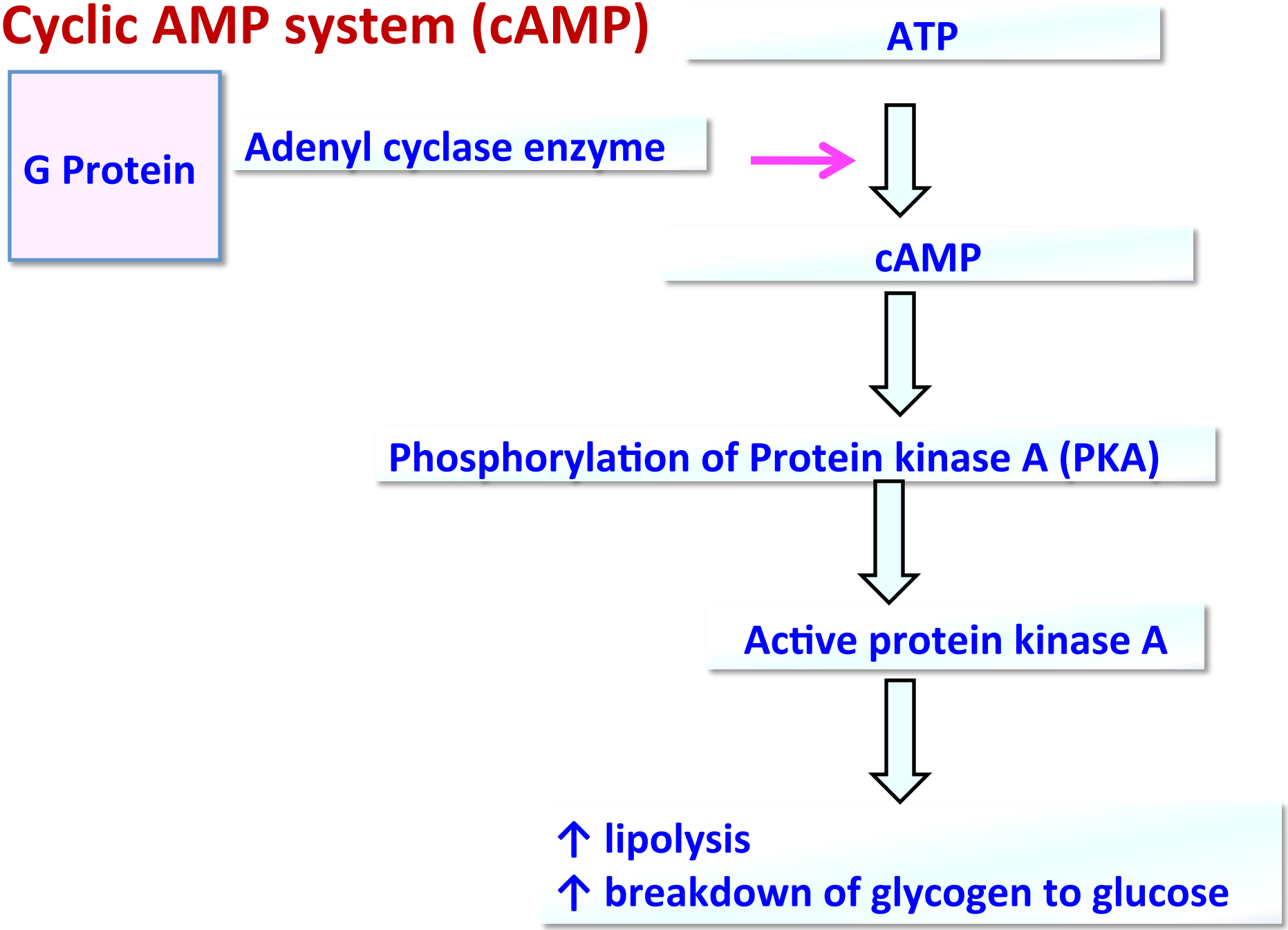
Enzymes

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

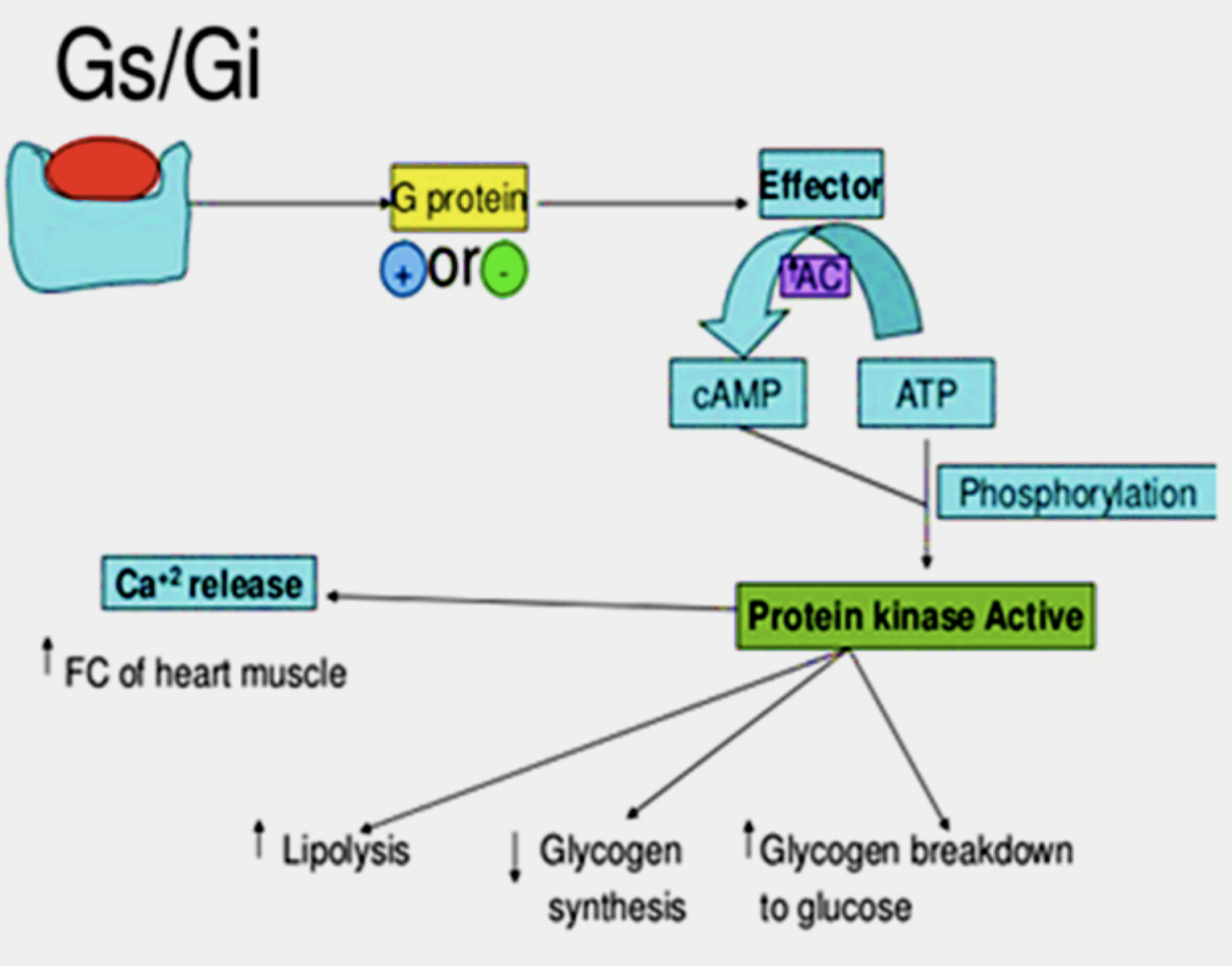
- Phospholipase C enzyme
  Inositol phosphate system (IP3+DAG)

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

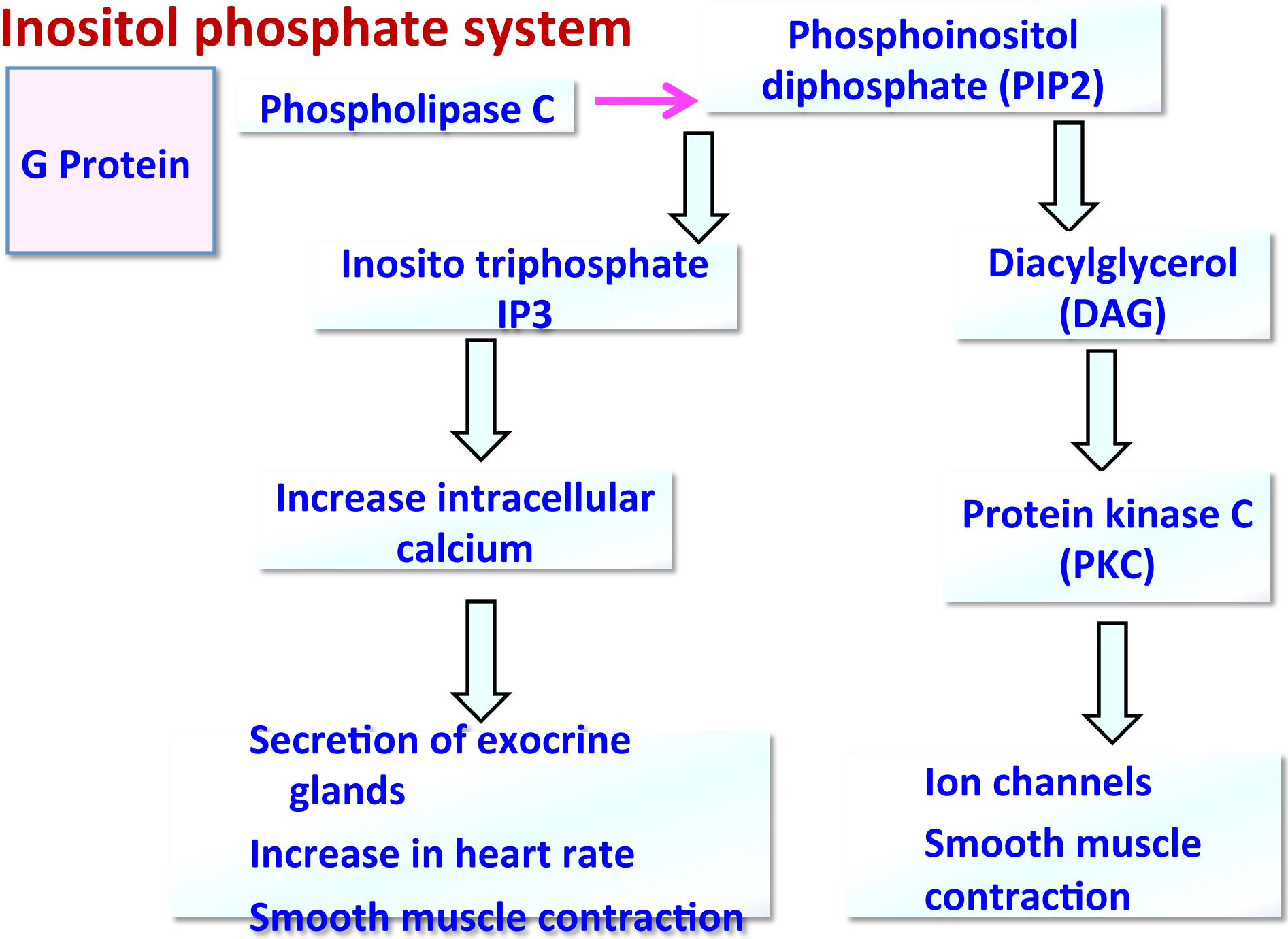
Cyclic AMP system (cAMP)



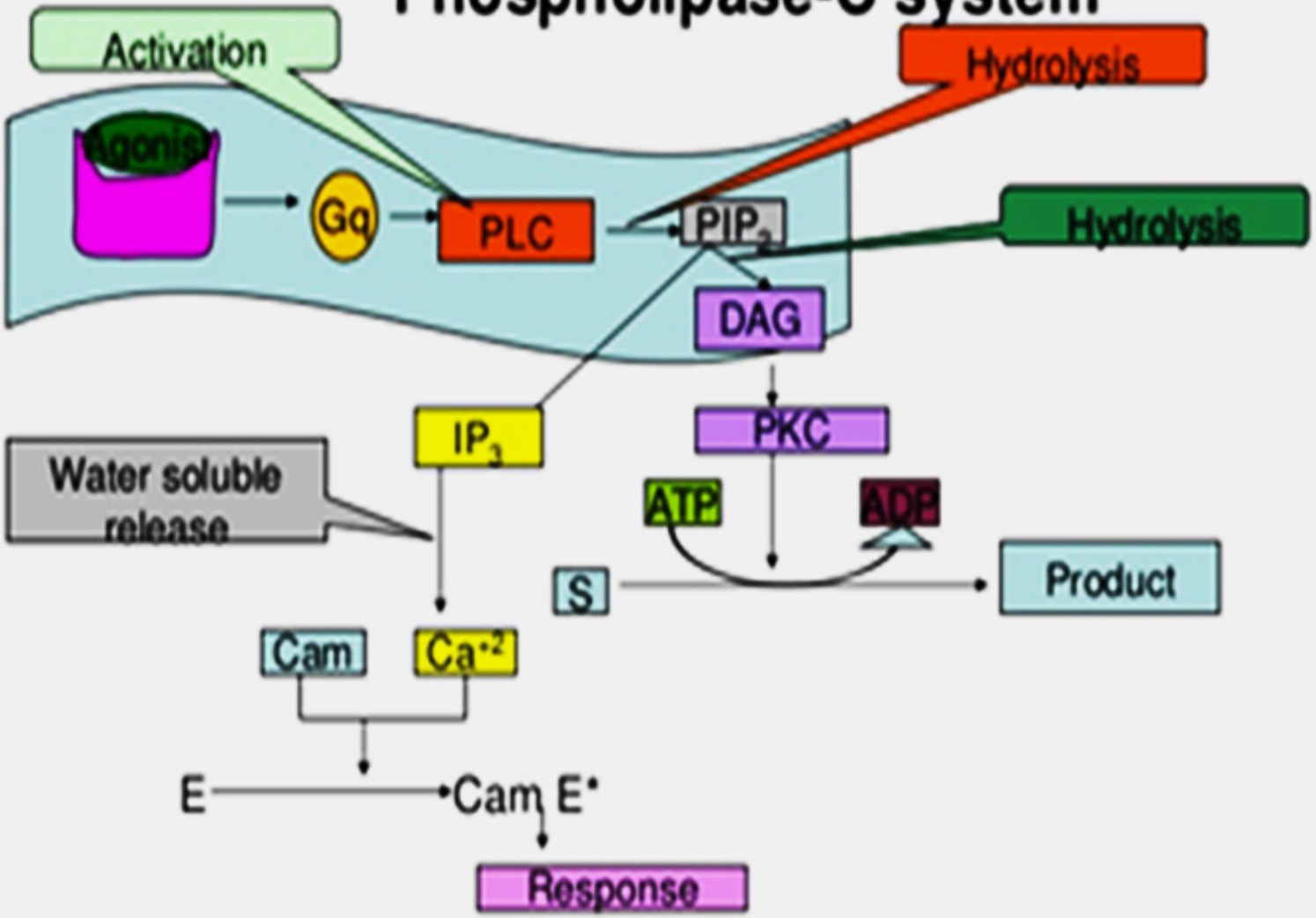
Adenyl cyclase system (AC)



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

G-Protein-Coupled Receptor

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

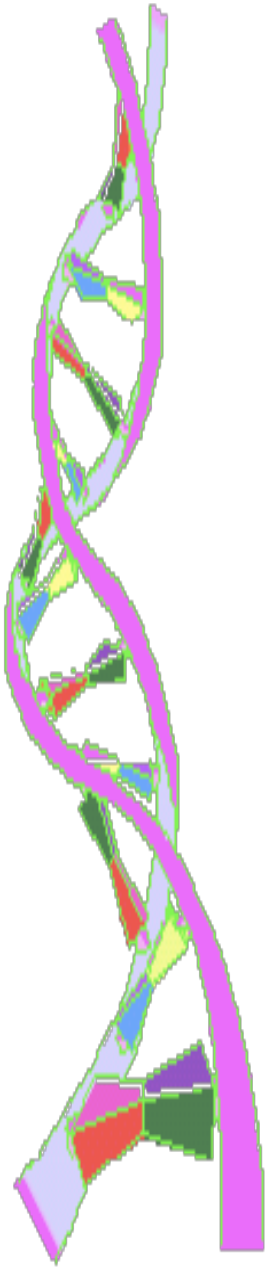
Classes of G protein

Divided according to their α-subunits into **G_s, G_i and G_q**

G_s and G_i produce, respective, stimulation and inhibition of AC

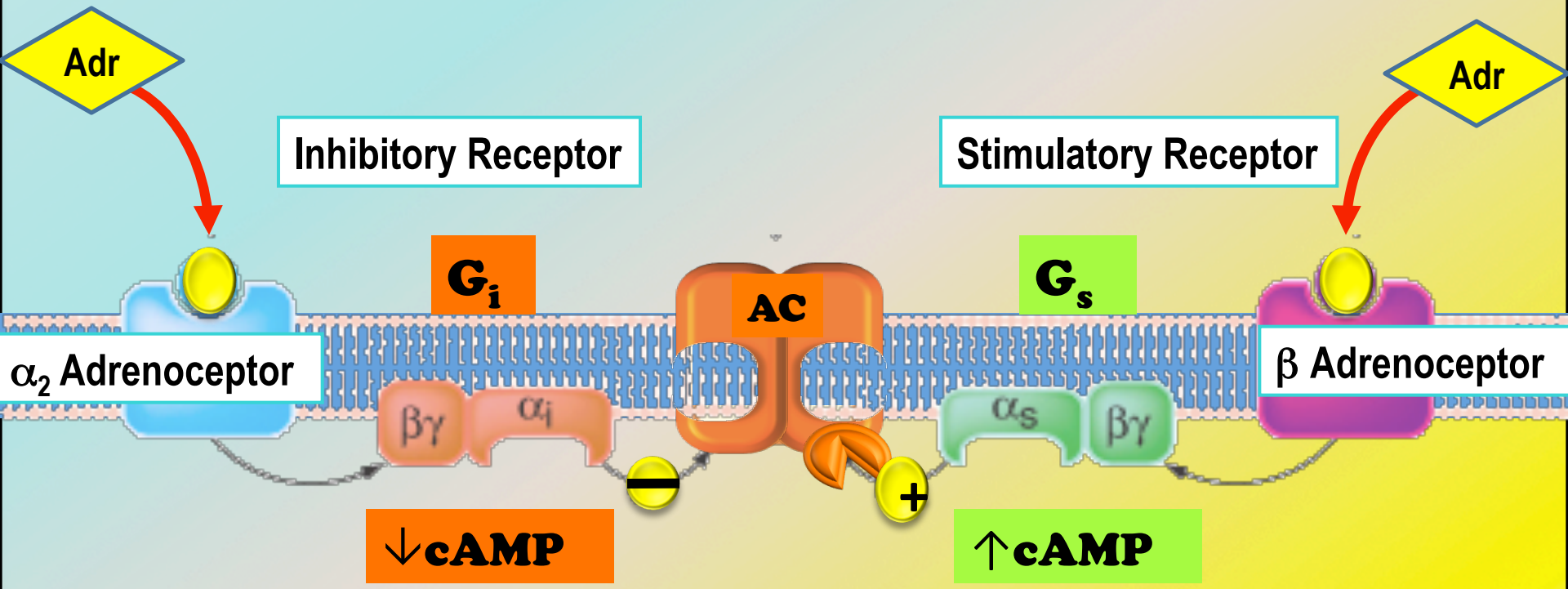
G_q is linked to activation of Phospholipase C system

Receptors are selective to α subunit & effector with which they couple



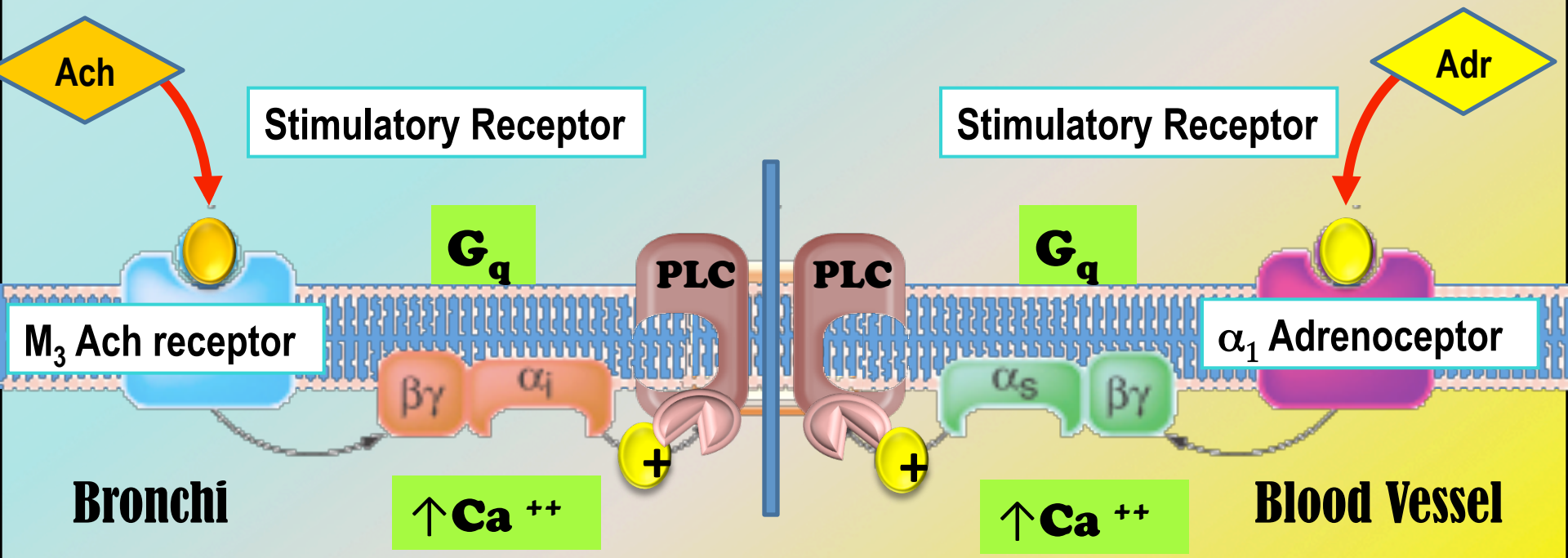
ADRENOCEPTORS

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)

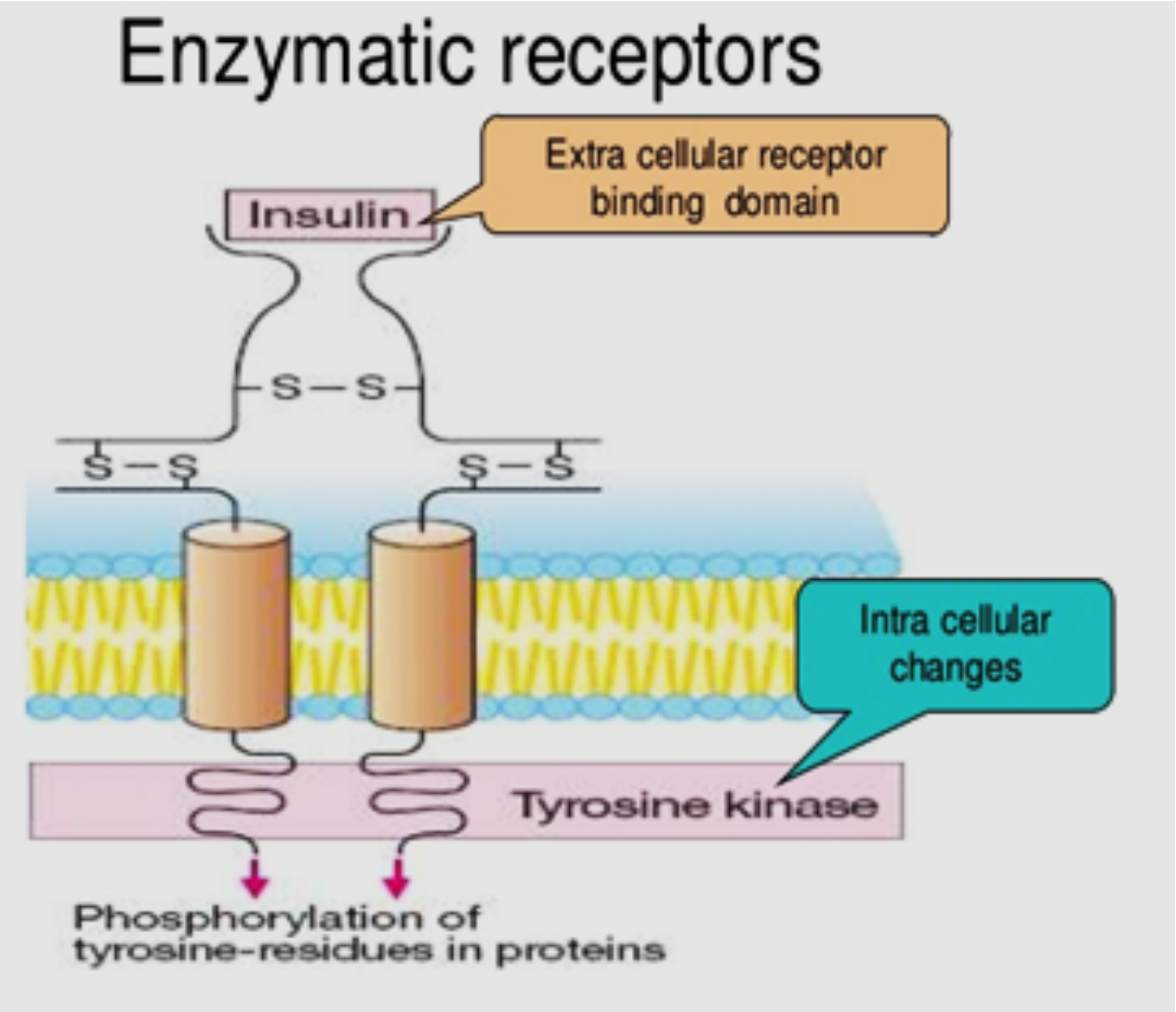
(Tyrosine Kinase-linked receptor)

- 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)

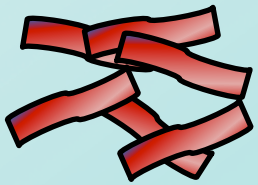
- **Activation of Type III receptors results in**
  - Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.
  - **E.g. Insulin receptors**

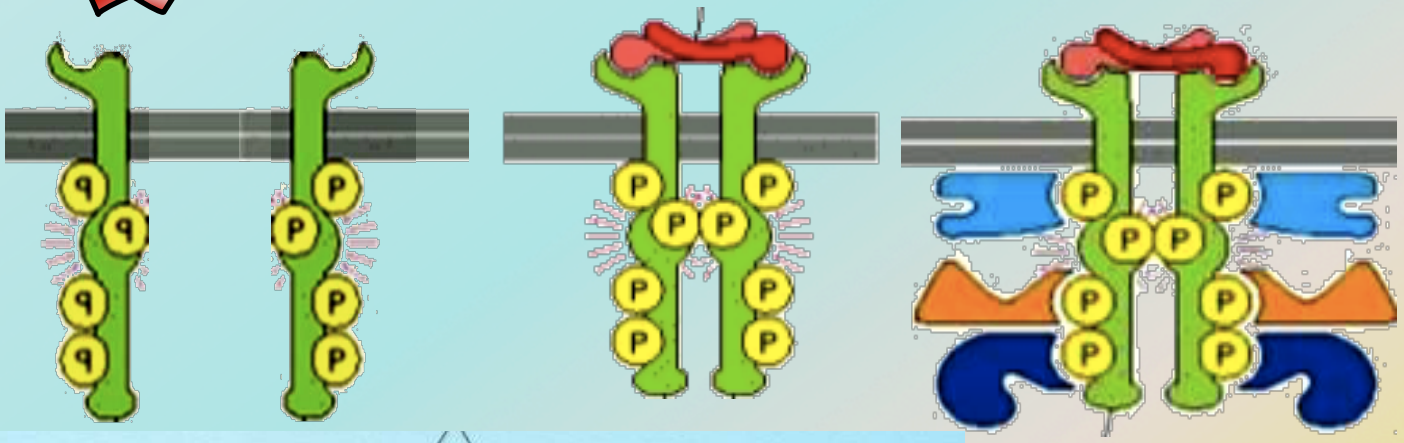
Insulin receptors

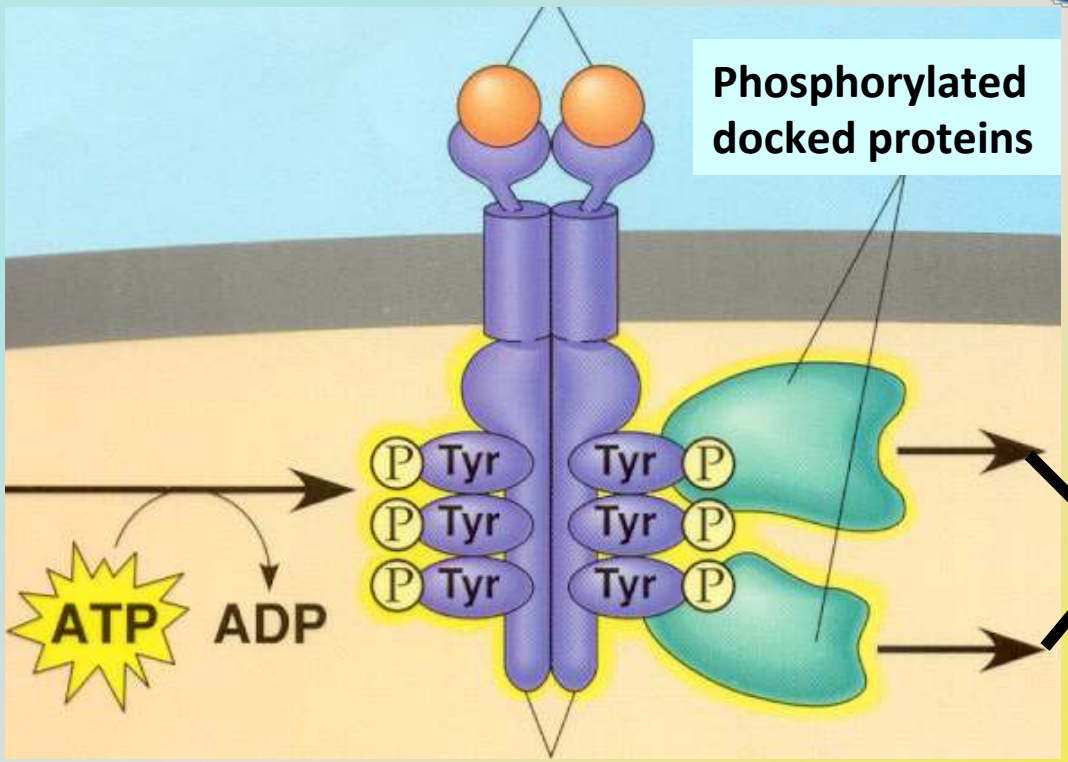


3 Enzyme-Linked Receptors

Tyrosine Kinase-Linked Receptors







Phosphorylate other proteins that it docks

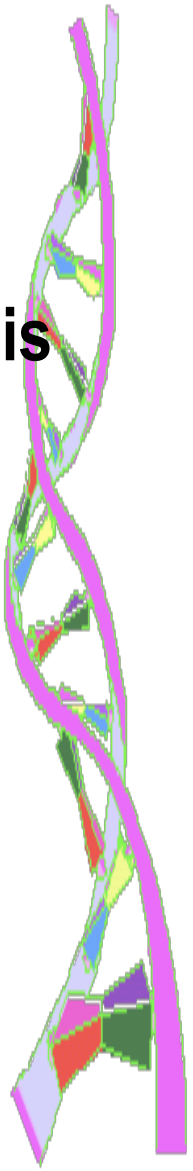
Example
Insulin Receptor

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.

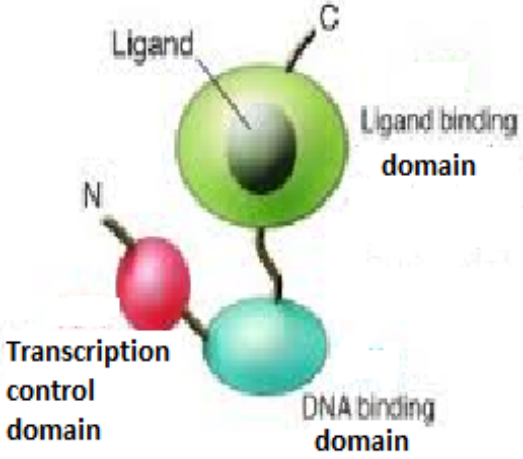
Type IV: Gene transcription receptors

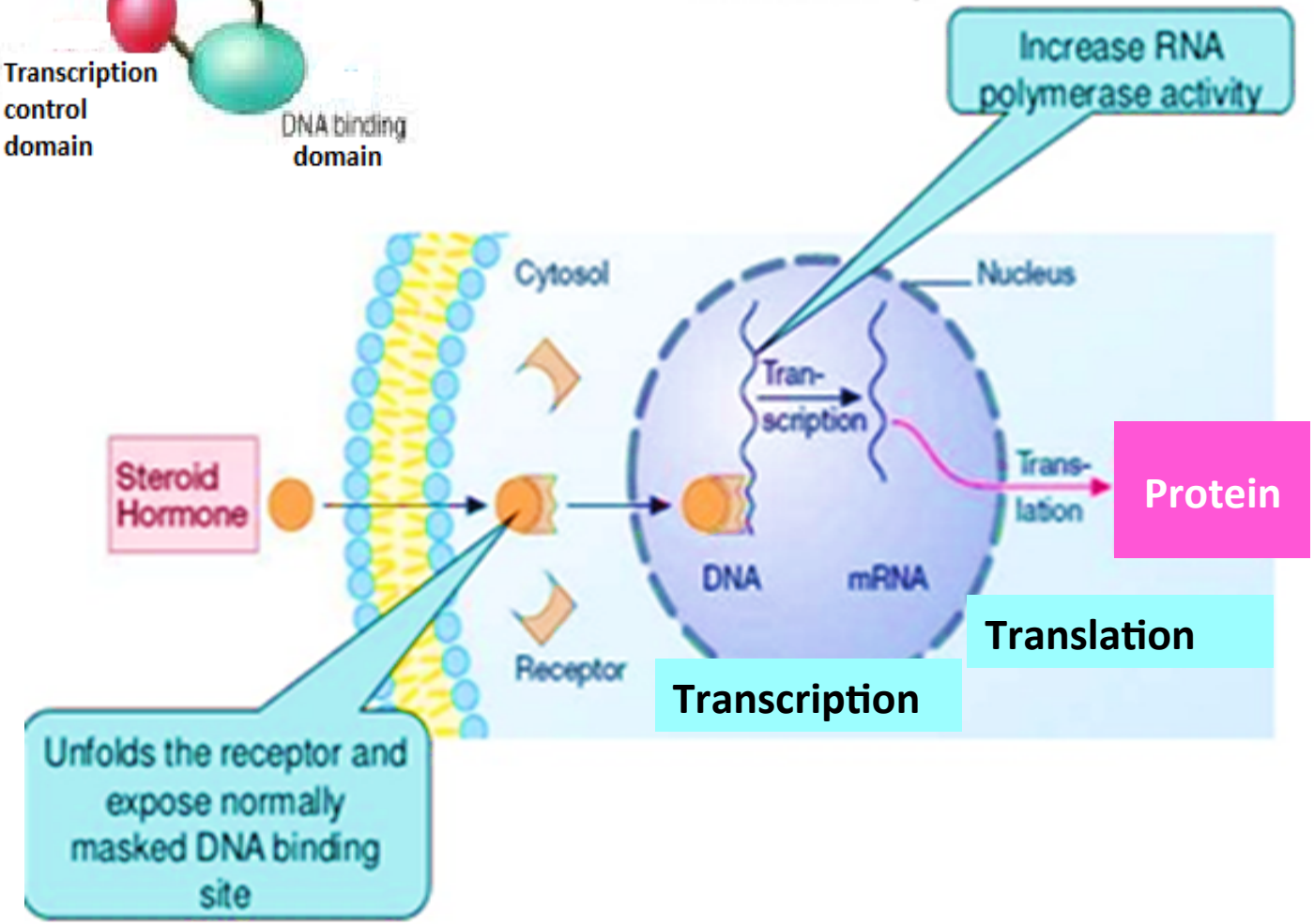


▶They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE] .

▶This means that the activated receptors are acting as TRANSCRIPTION FACTORS [TF] → expressing or repressing target genes.

Type IV: Gene transcription receptors

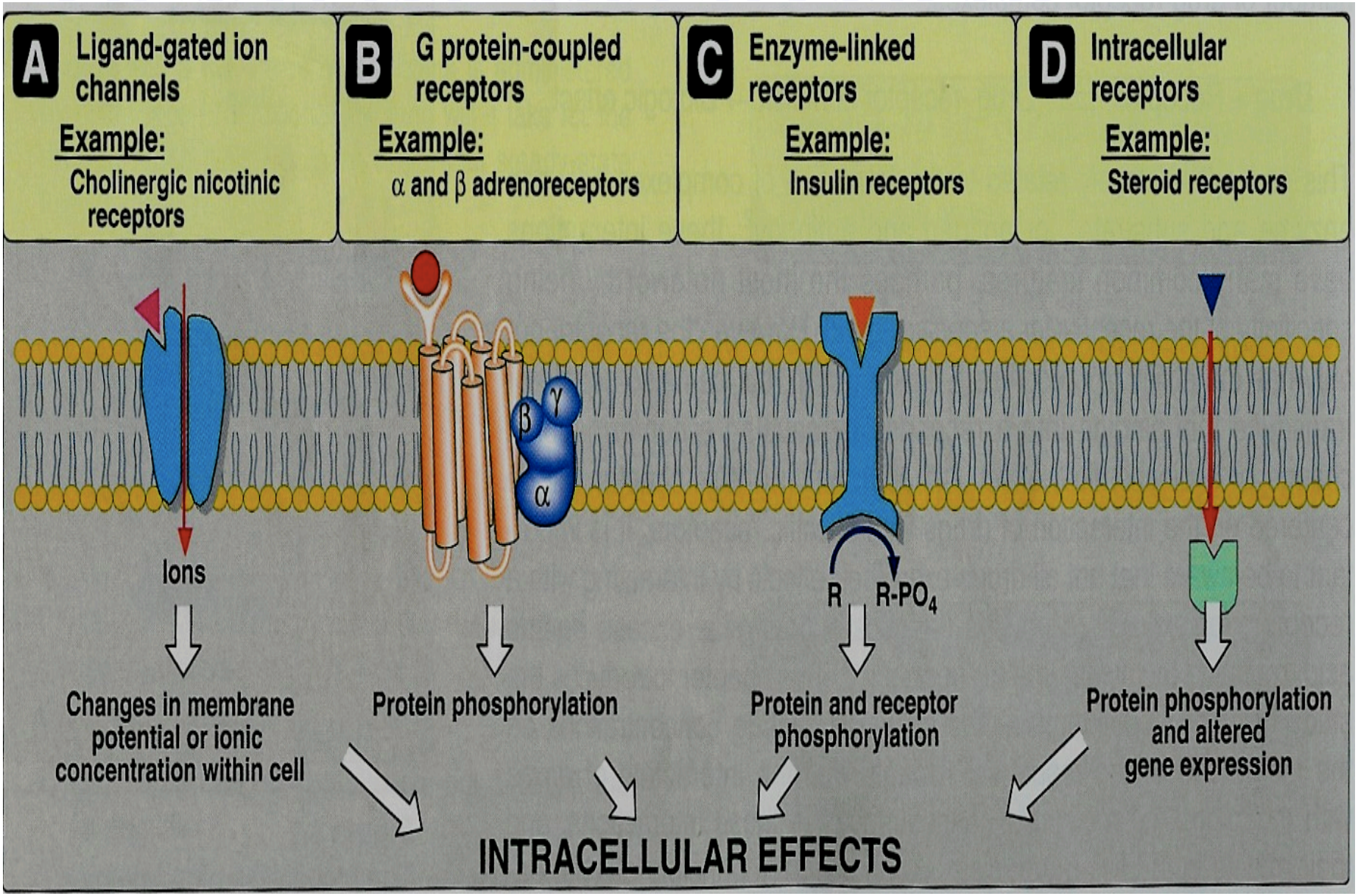


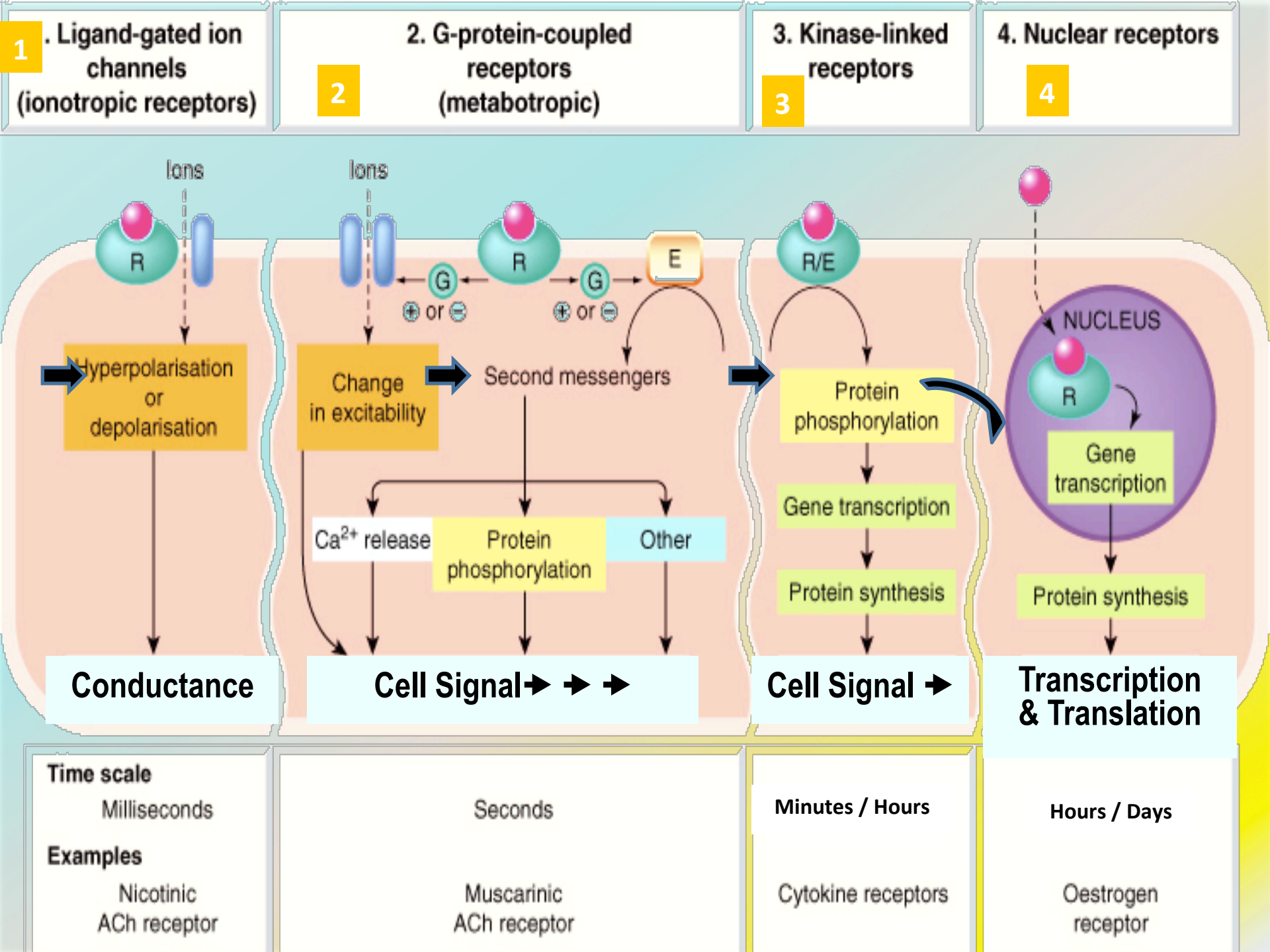


RECEPTOR FAMILIES

	Type I	Type II	Type III	Type III
Location	Membrane	Membrane	Membrane	Nucleus
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