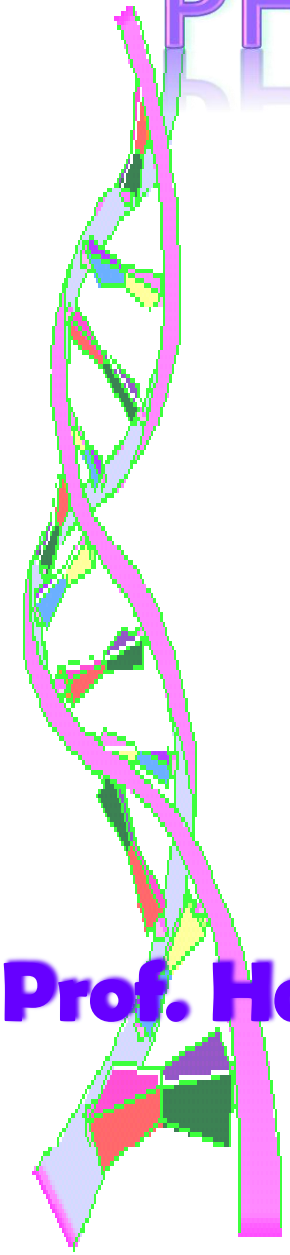
PHARMACODYNAMICS III

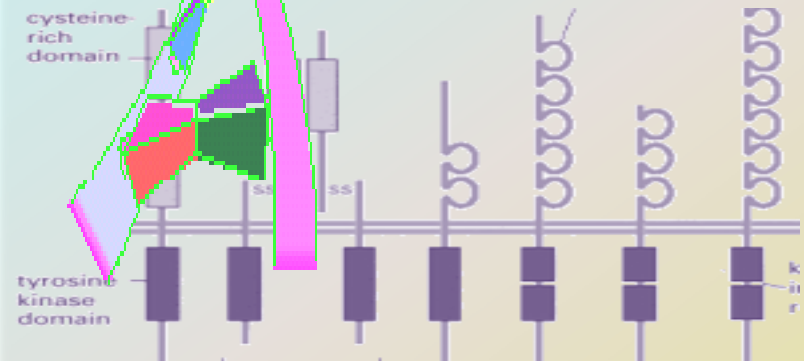


RECEPTOR FAMILIES

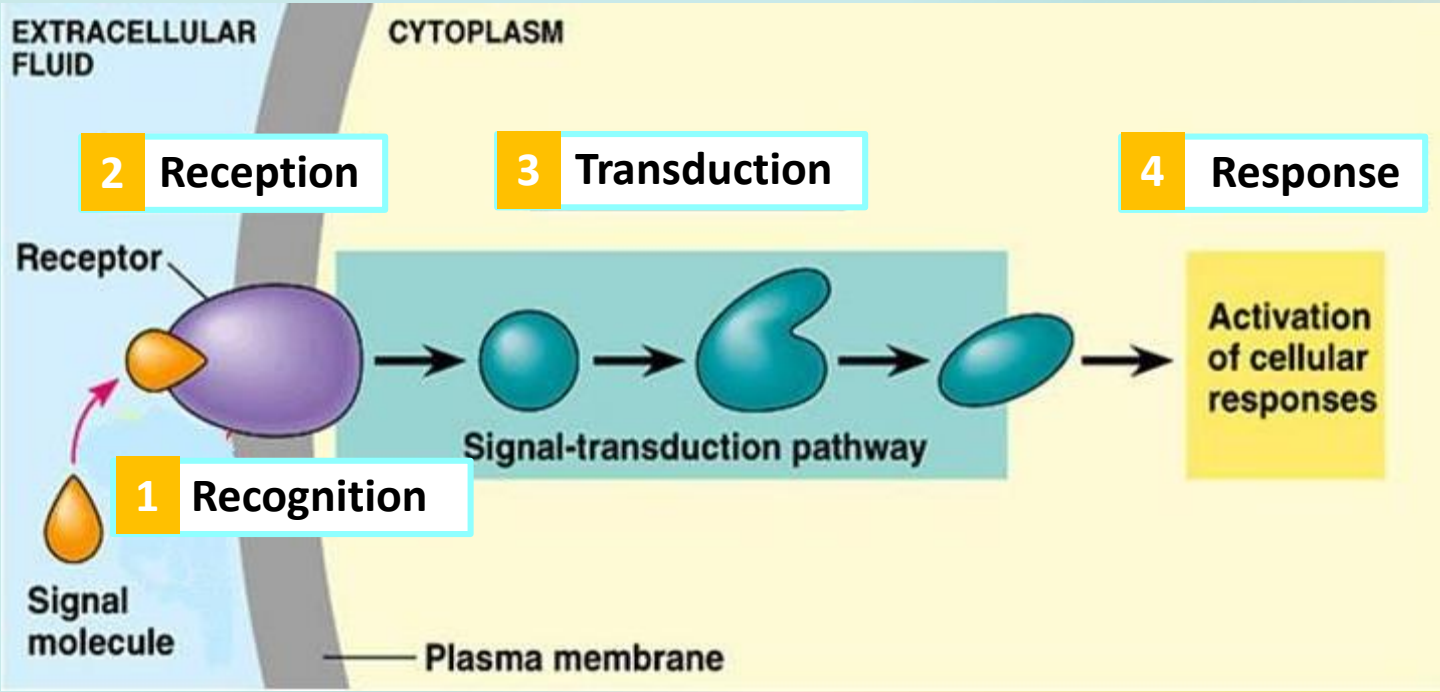
Prof. Hanan Hagar **ASSO.Prof Osama Yousif**

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

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

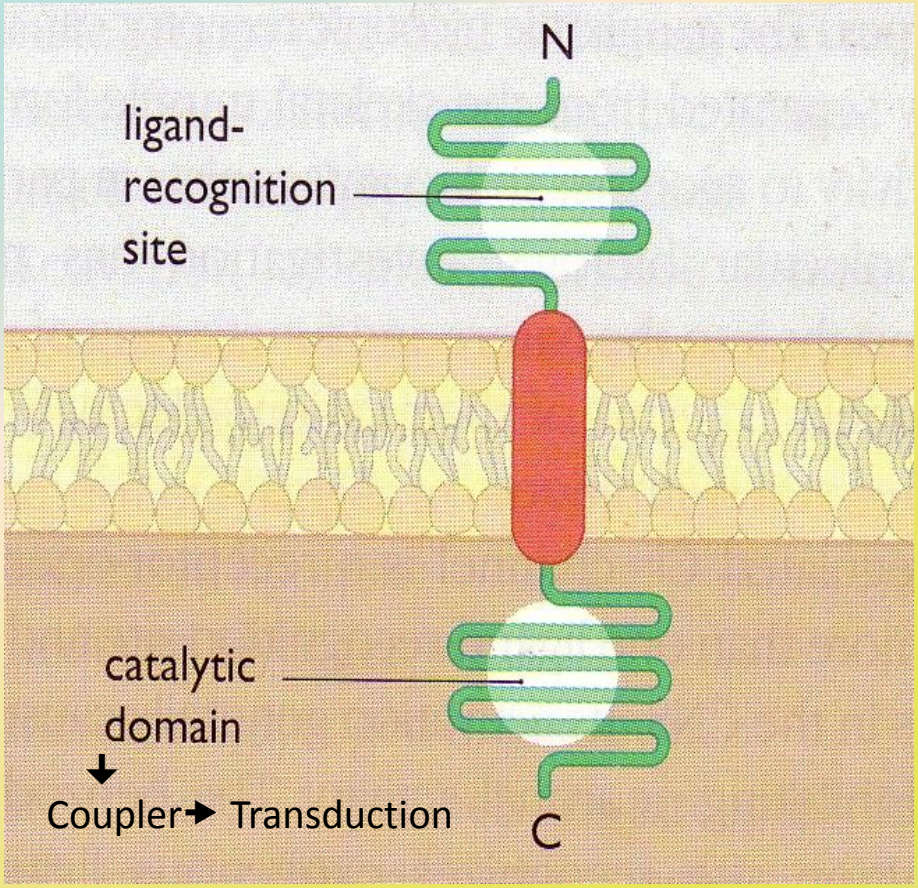


A RECEPTOR


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

A RECEPTOR structure

- Ligand recognition site
- Inner catalytic domain



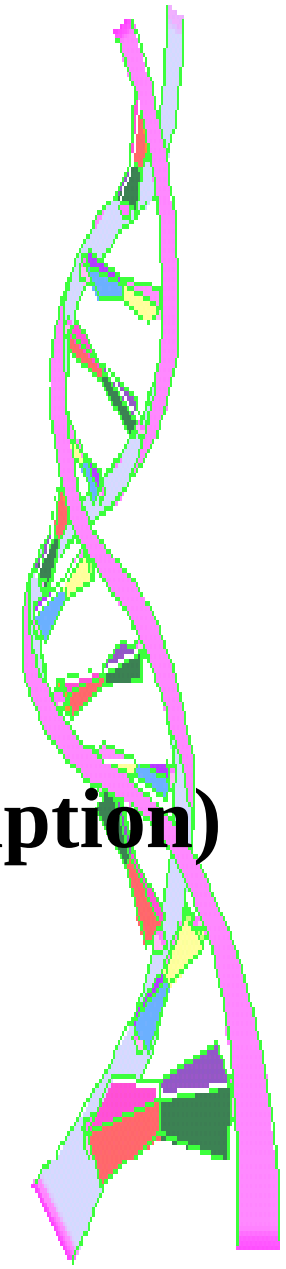
RECEPTOR FAMILIES

Type I **(Ion Channel-Linked receptors)**

Type II **(G-Protein coupled receptors)**

Type III **(Enzyme-Linked receptors)**

Type IV **(Receptors linked to gene transcription)**



TYPE I : Ion Channel-Linked receptors
Ligand gated ion channels
Ionotropic receptors

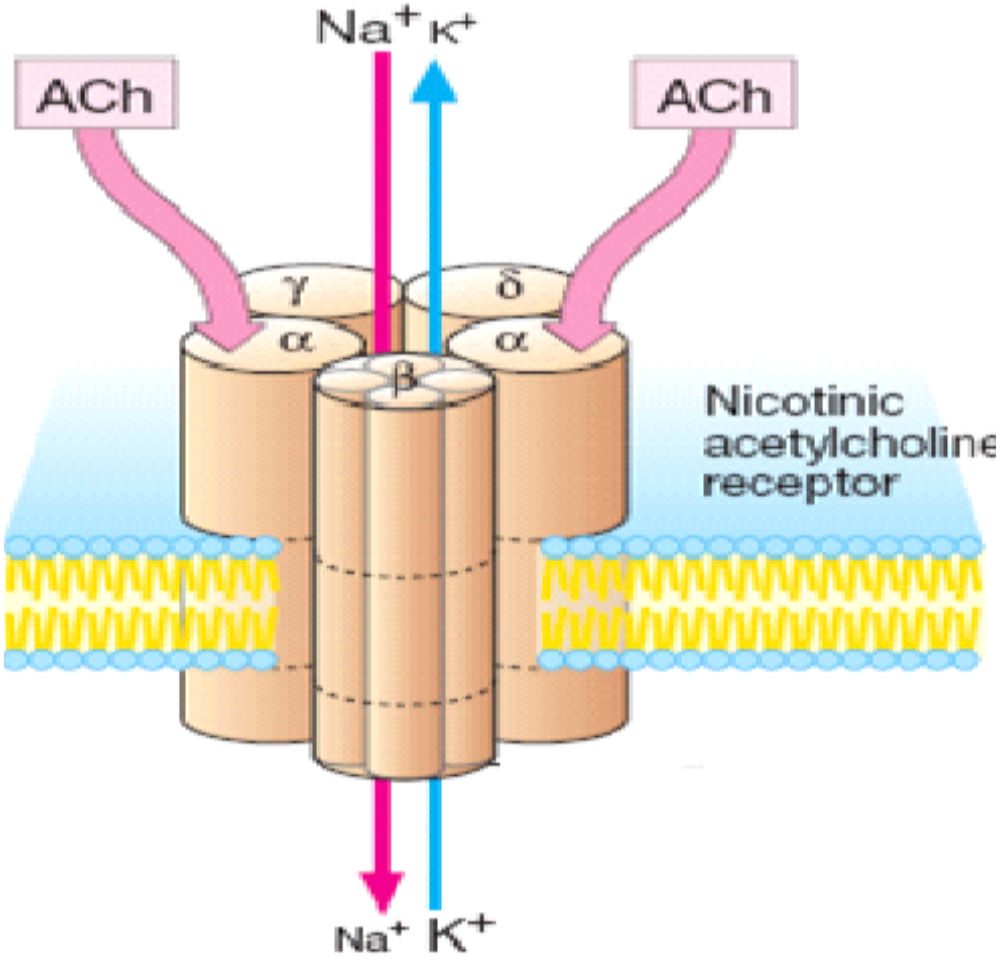
- Located at cell membrane
- Directly activated by ligand binding
- Involved in fast synaptic transmission.
- Directly related to channels.
- Response occurs in milliseconds.
- E.g. Nicotinic receptors activated by acetylcholine

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.

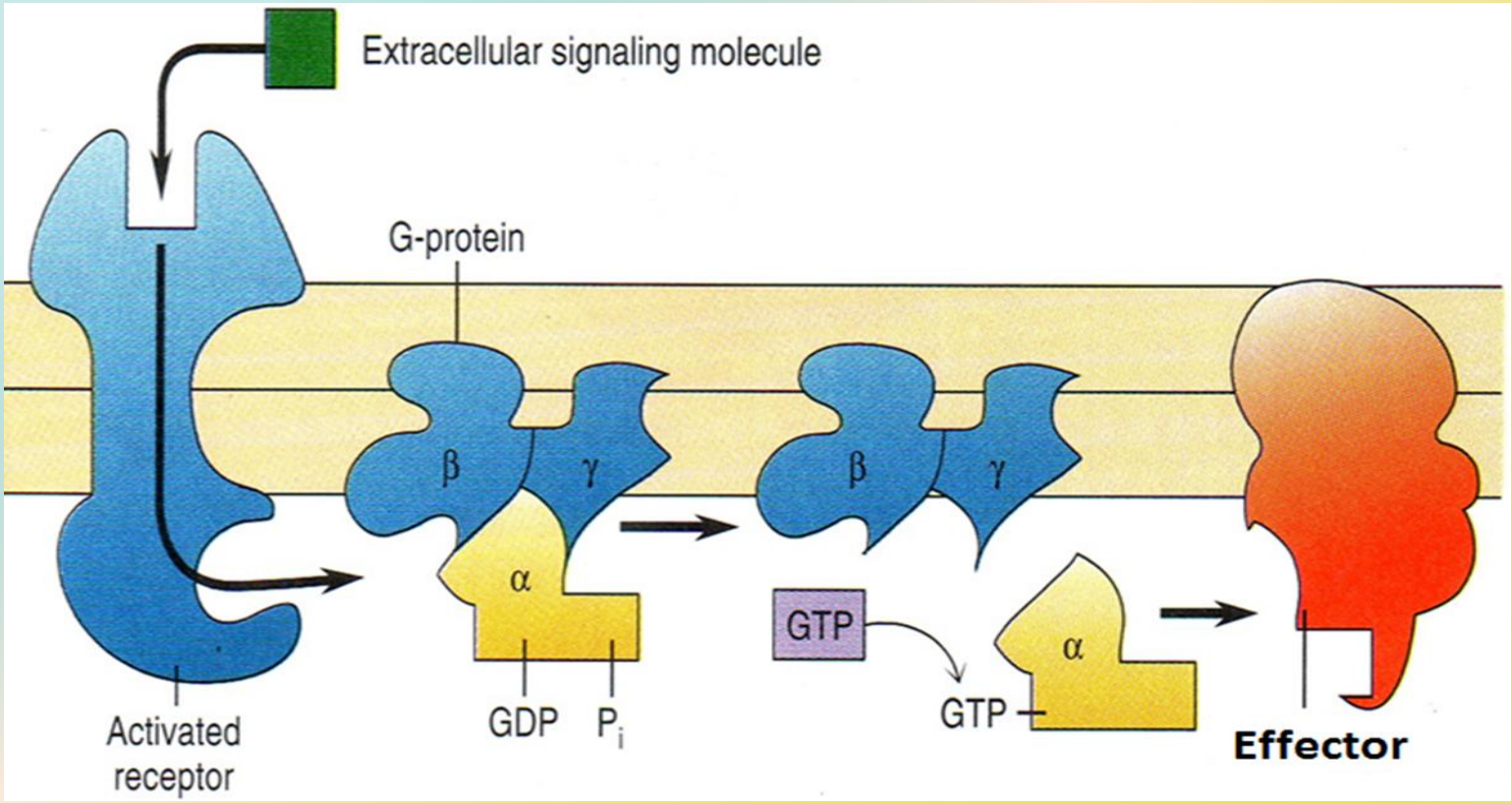


Type II: G-Protein coupled receptors
Metabotropic Receptor

- The largest family that accounts for many known drug targets
- Located at cell membrane
- Coupled to **G-protein**
- Response through ion channels or enzymes.
- Involved in rapid transduction
- Response occurs in seconds.
- **E.g. Muscarinic receptors of Ach**
- **Adrenergic receptors of Noradrenaline**

G-Protein → Is composed of 3 subunits [α β γ] & Guanyle Di-Phosphate [GDP]

- Agonist occupancy dissociates [α] subunit so GTP replaces GDP & go to activate effector.
- Agonist loss cleaves GTP by GTPase with return of GDP so [α β γ] bind again.



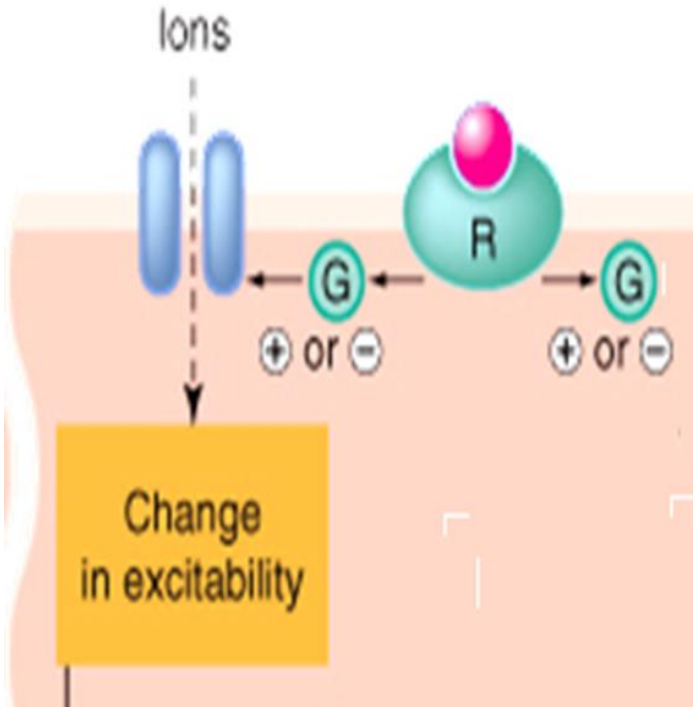
G-protein

- GTP-binding regulatory proteins
- Regulate guanine nucleotides GDP, GTP.
- Comprise of three subunits ($\alpha\beta\gamma$), α subunits possess GTPase activity
- **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.

Targets for G-proteins

Ion channels

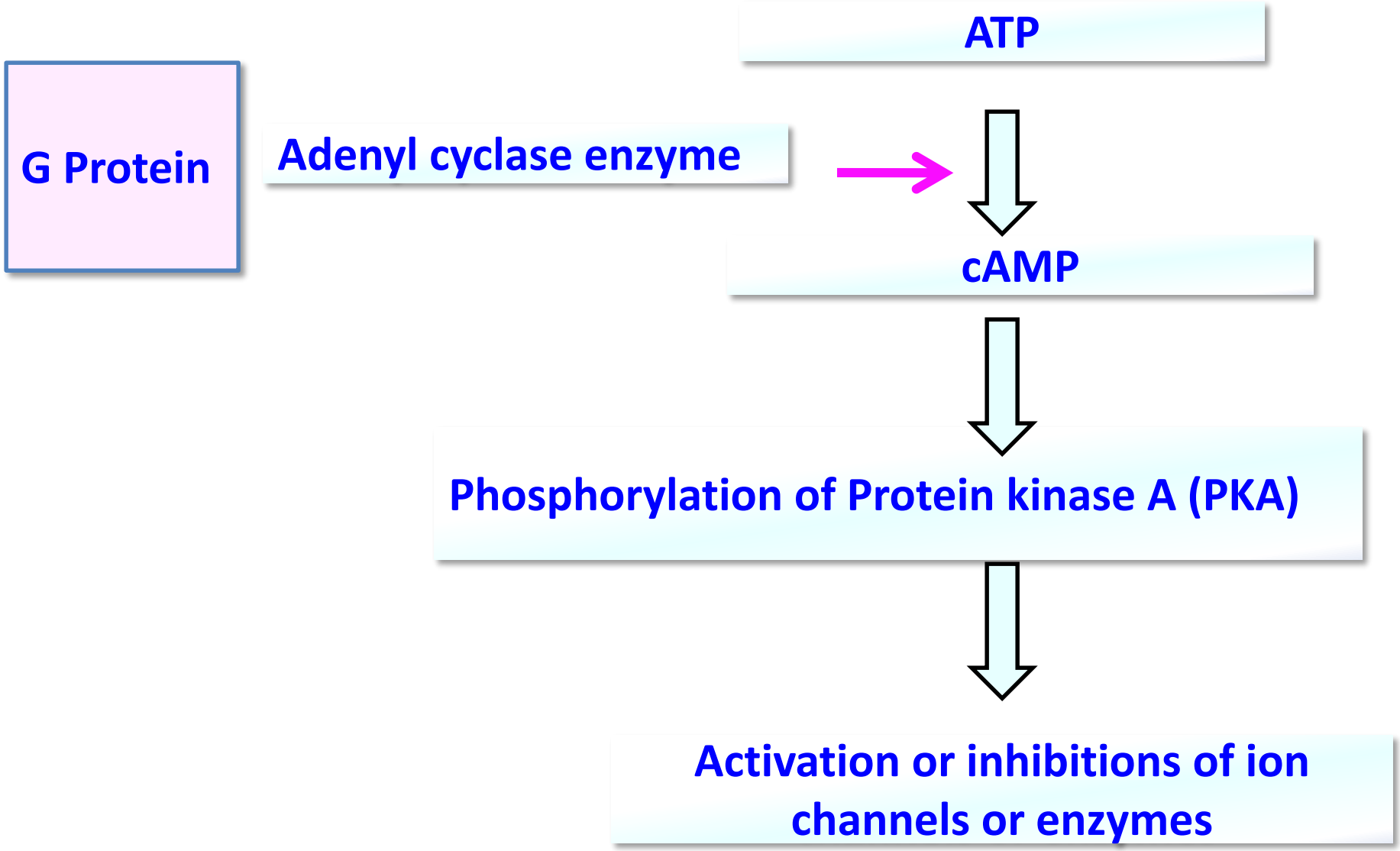
Muscarinic receptors in heart (K-channel), decrease heart rate.



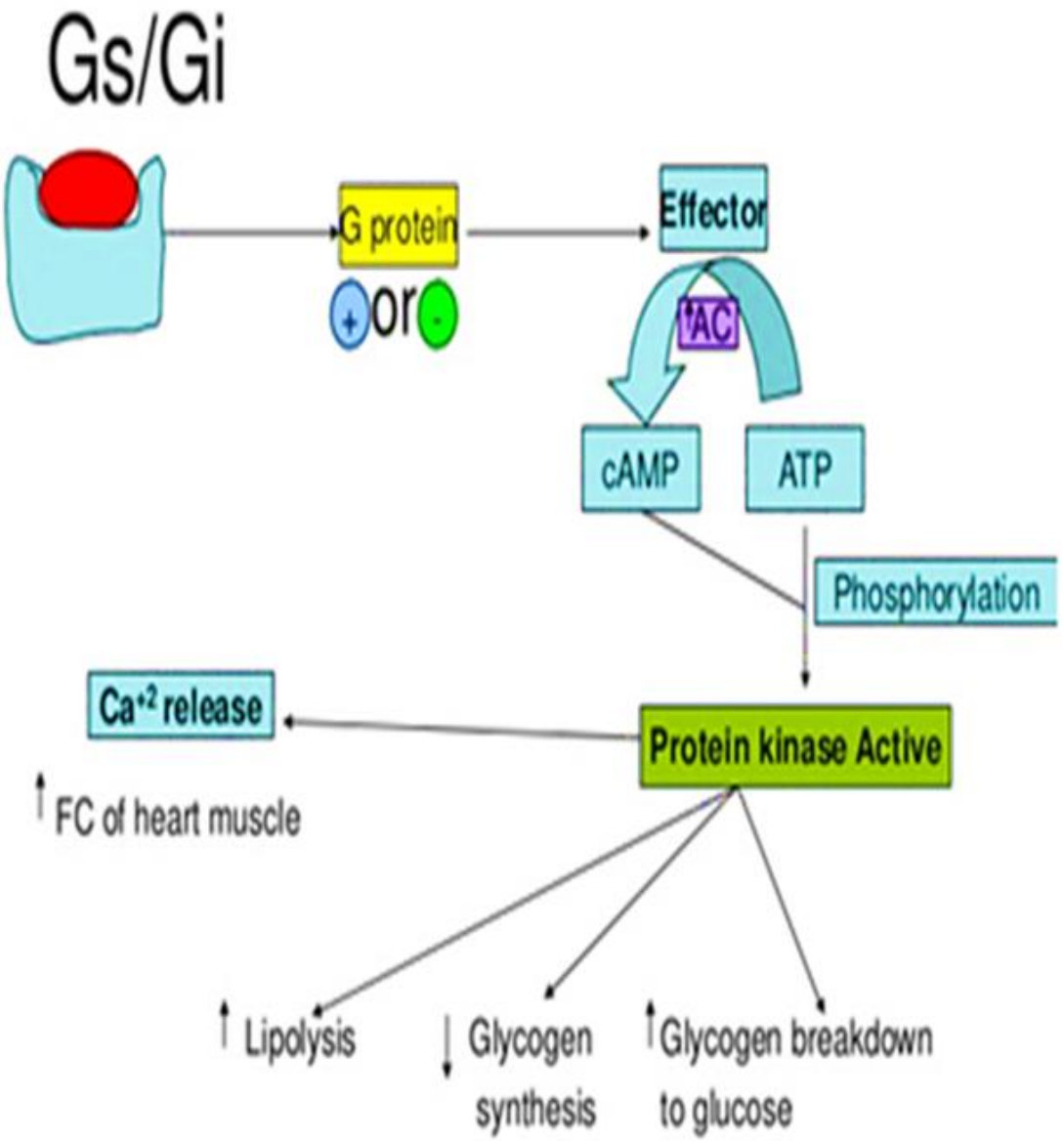
second messengers

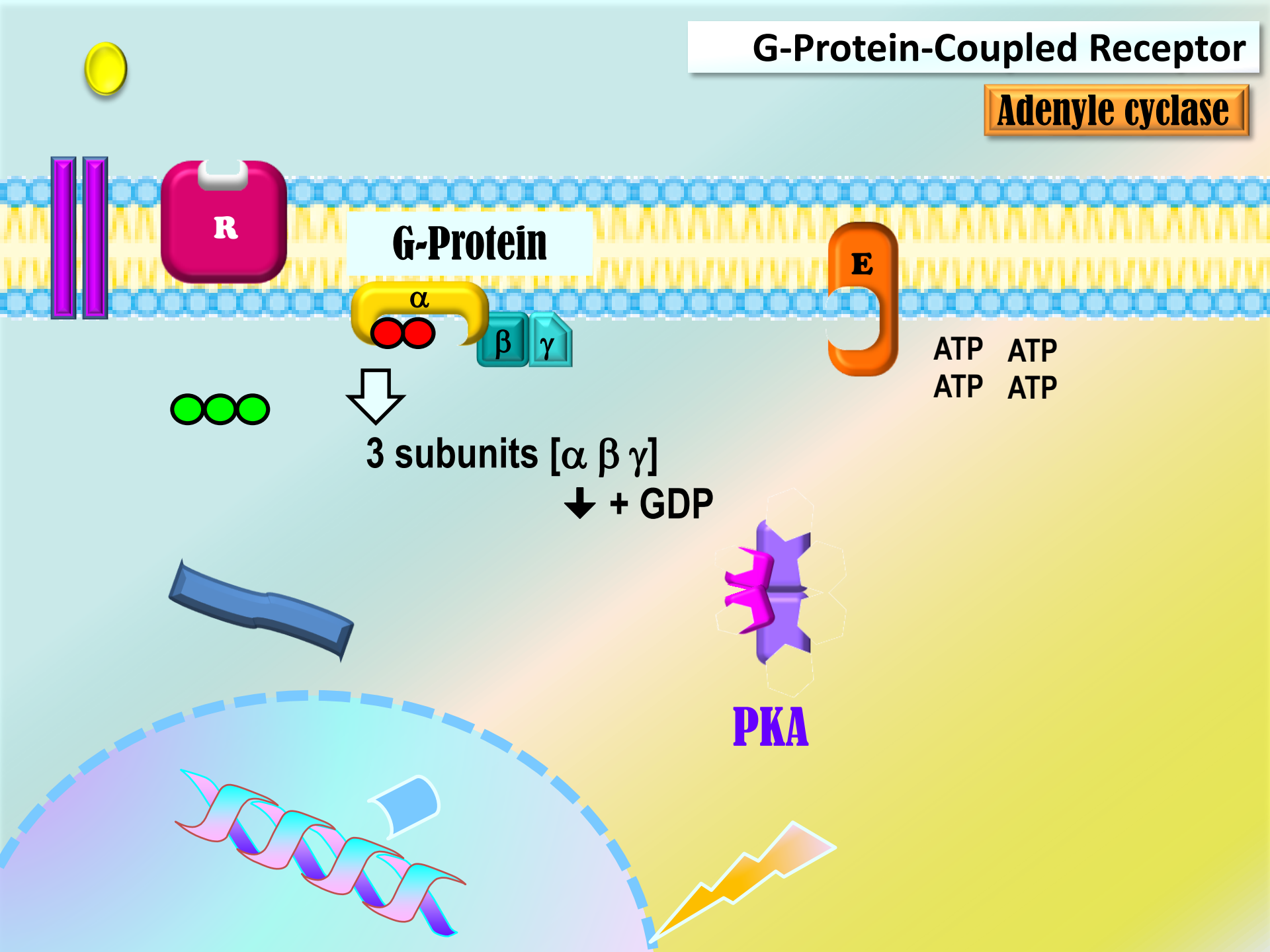
- Cyclic AMP system (cAMP)
- Inositol phosphate system (IP3+DAG)

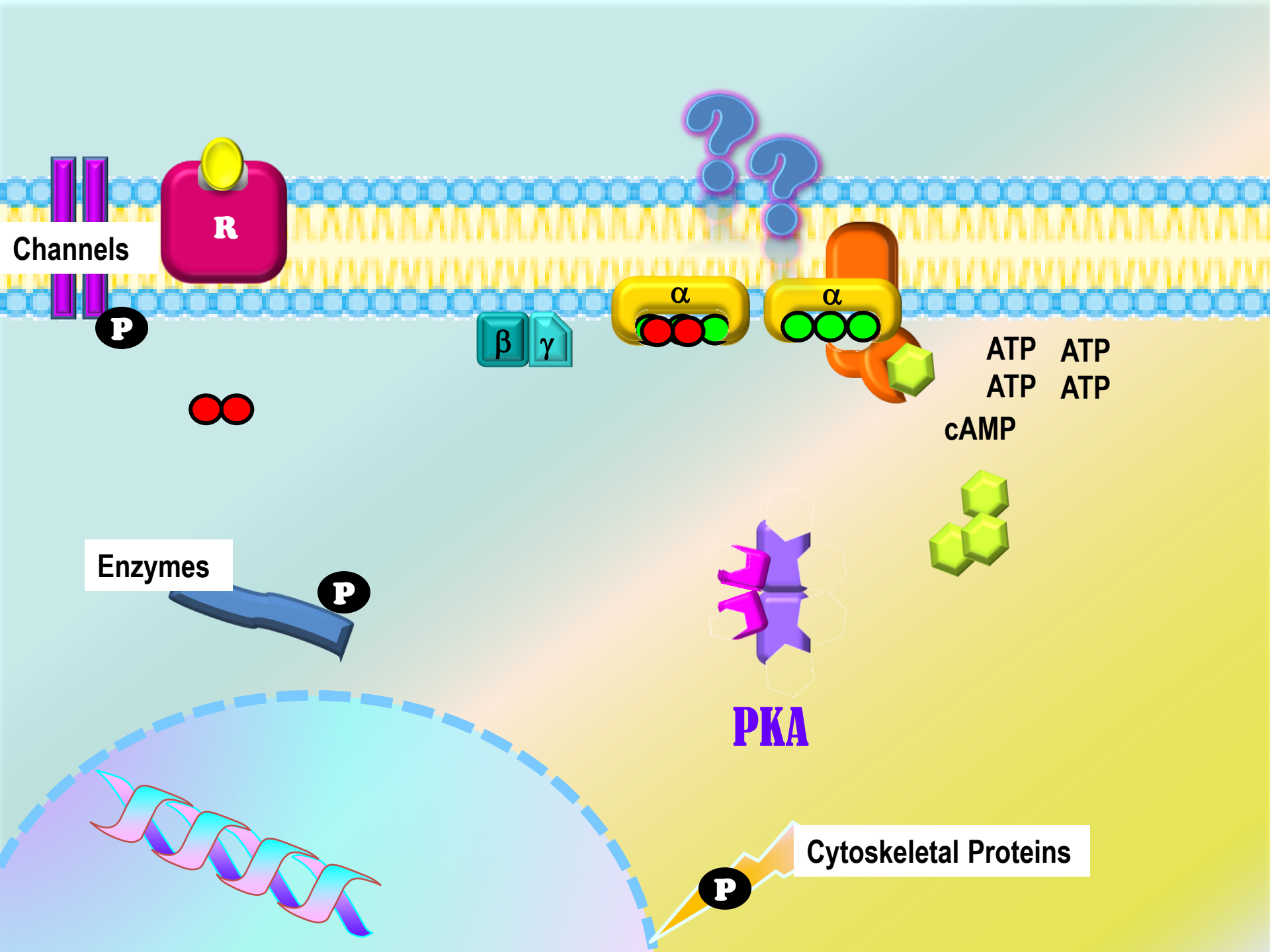
Cyclic AMP system (cAMP)



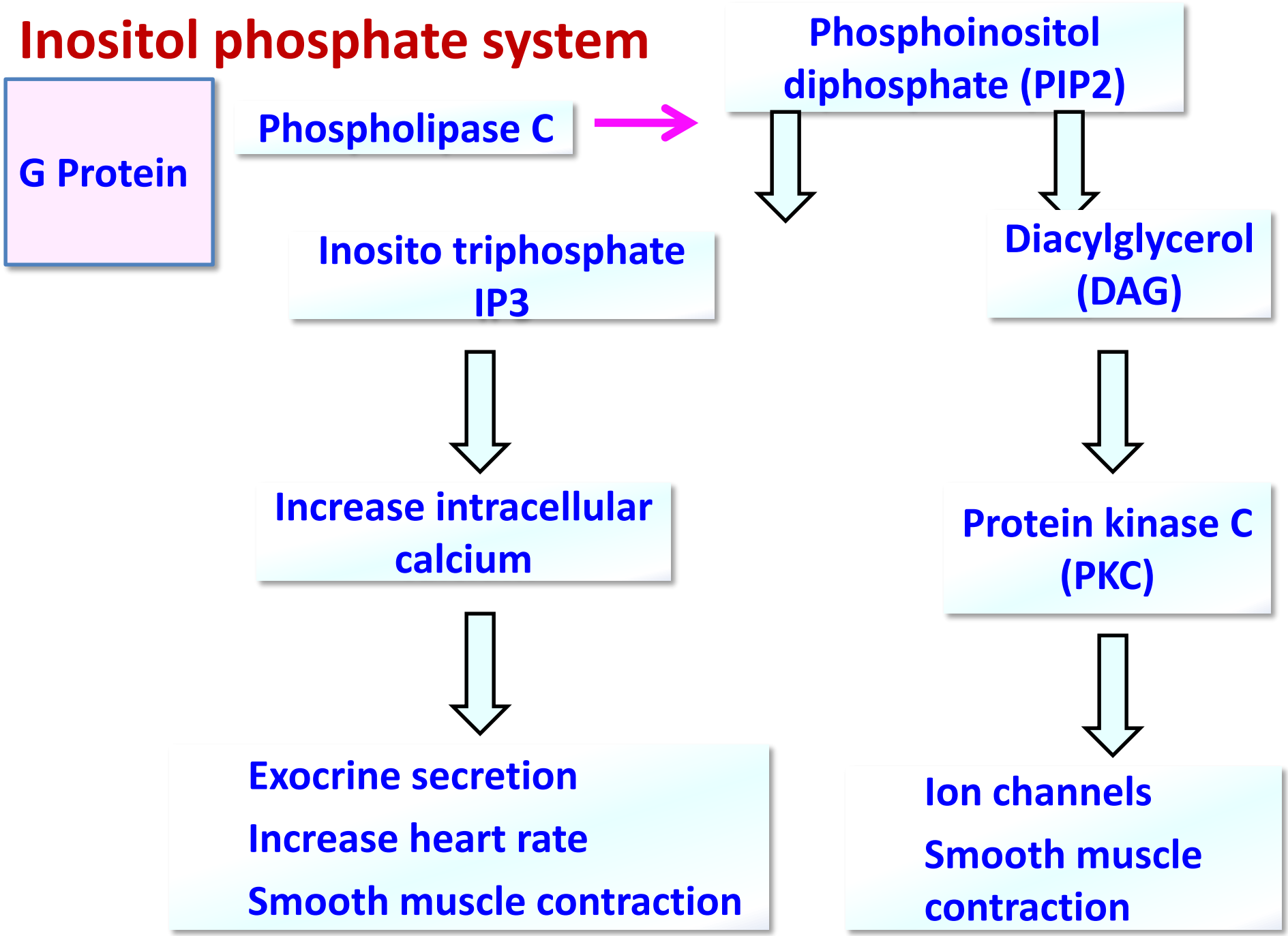
Cyclic AMP system (cAMP)

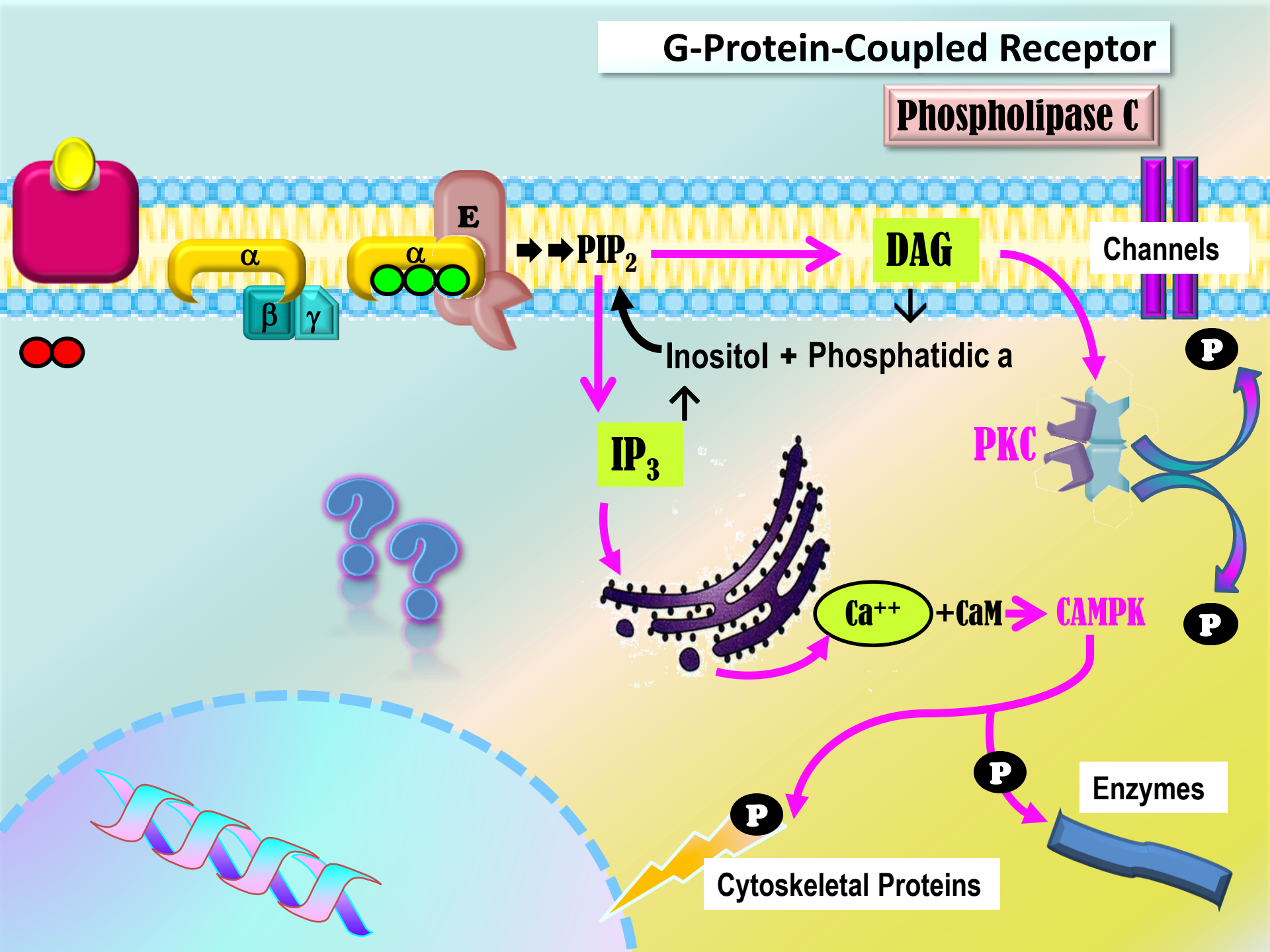



G-Protein-Coupled Receptor
Adenyle cyclase
R
G-Protein
α
β
γ
E
ATP ATP
ATP ATP
3 subunits [α β γ]
+ GDP
PKA

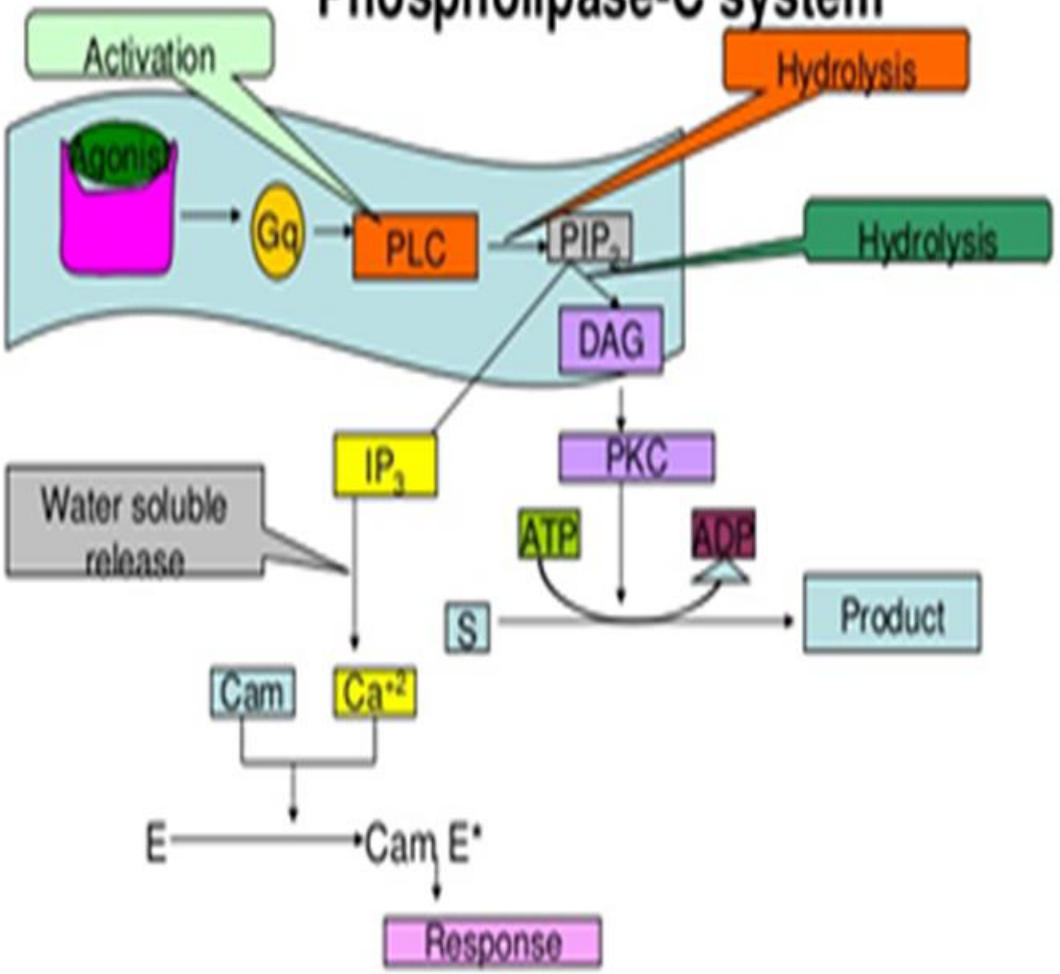

Channels
R
P
α
α
β
γ
ATP ATP
ATP ATP
cAMP
Enzymes
P
PKA
Cytoskeletal Proteins
P

Inositol phosphate system




G-Protein-Coupled Receptor
Phospholipase C
α
β
γ
α
E
PIP2
DAG
Channels
Inositol + Phosphatidic a
IP3
PKC
P
Ca++
+CaM
CAMPK
P
P
P
Enzymes
Cytoskeletal Proteins

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

Ach R → m Adrenergic R → 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

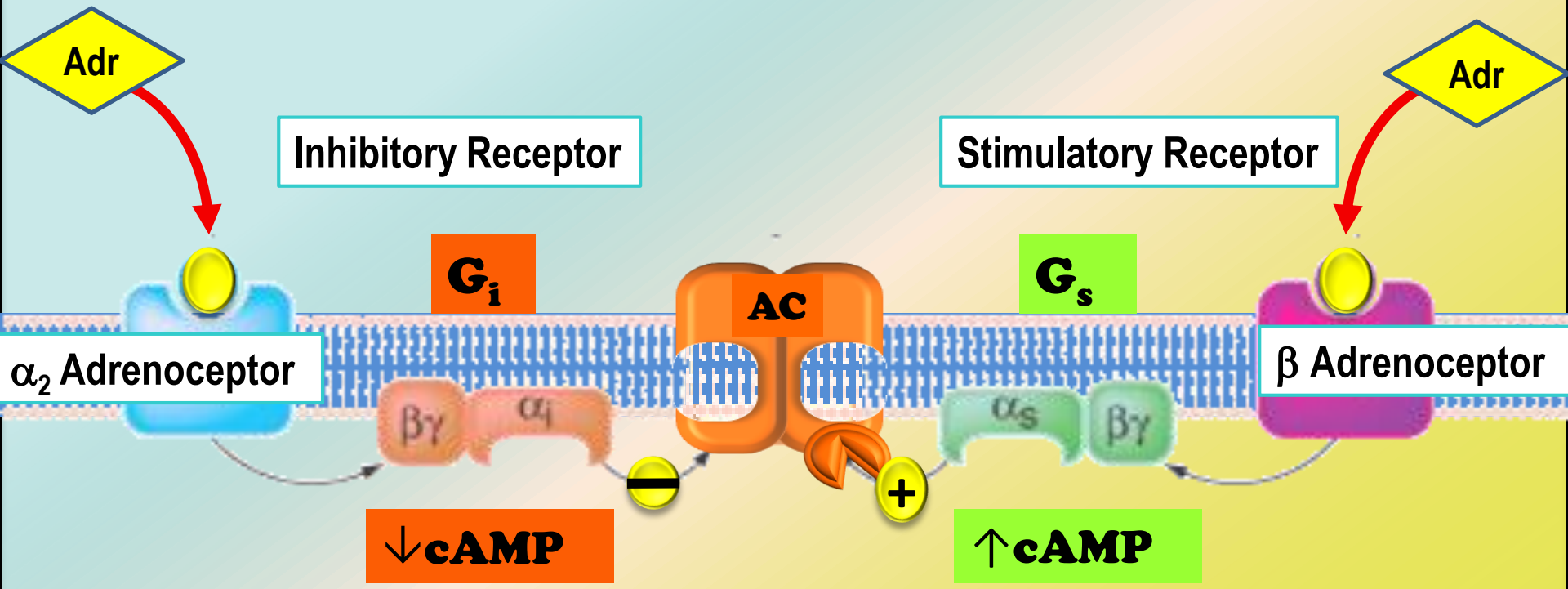
Divided according to their α-subunits into G_s, G_i and G_q

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

G_q is linked to activation of PLC-IP_3-Ca^{++} CaM & PKC

ADRENOCEPTORS

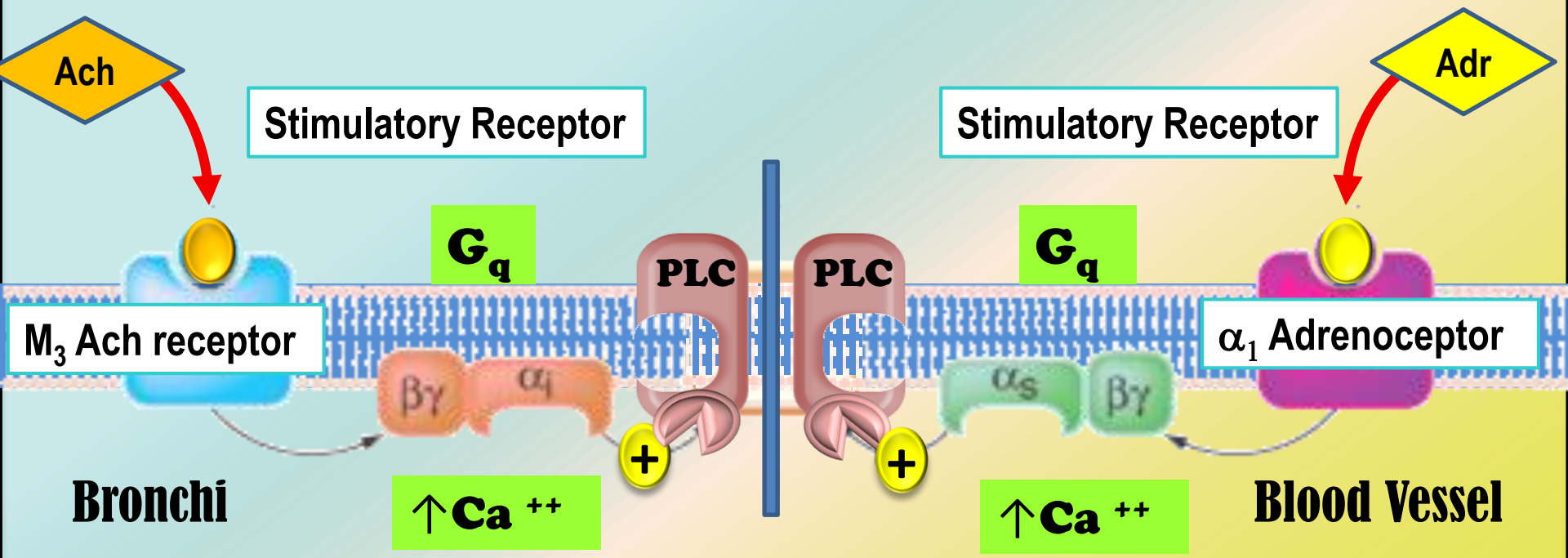
α_1 Adrenoceptors couple to G_q to stimulate PLC.
α_2 Adrenoceptors couple to G_i to inhibit AC.
$\beta_{1\&2}$ Adrenoceptors couple to G_s to stimulate AC



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)

(Kinase-linked receptor)

- Located at cell membrane with intrinsic enzymatic activity
- **Activation of receptors results in**
  - Activation of protein 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**

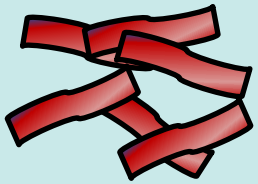
Type III (Enzyme-Linked receptors)

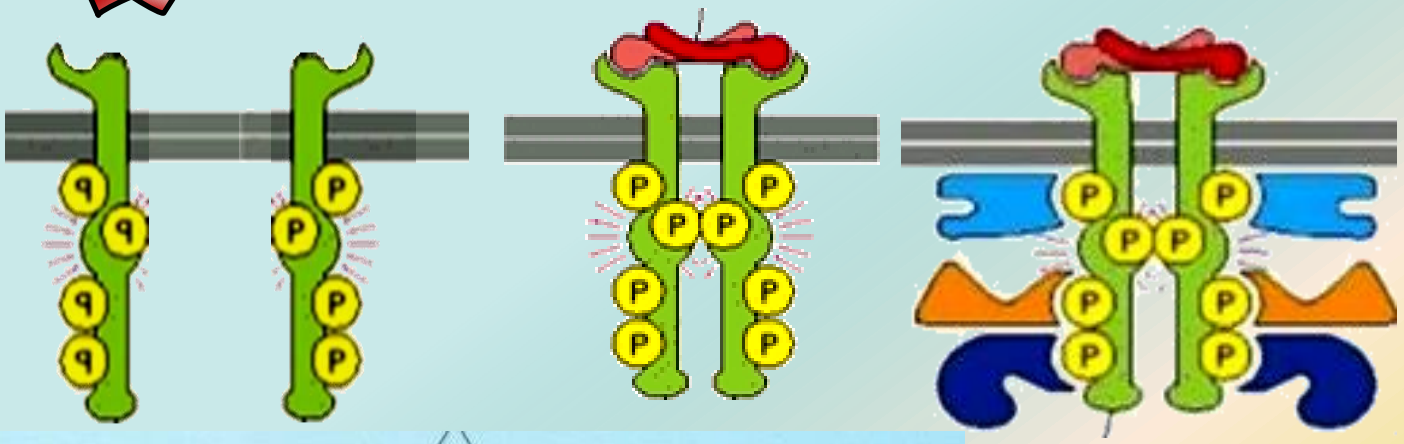
(Kinase-linked receptor)

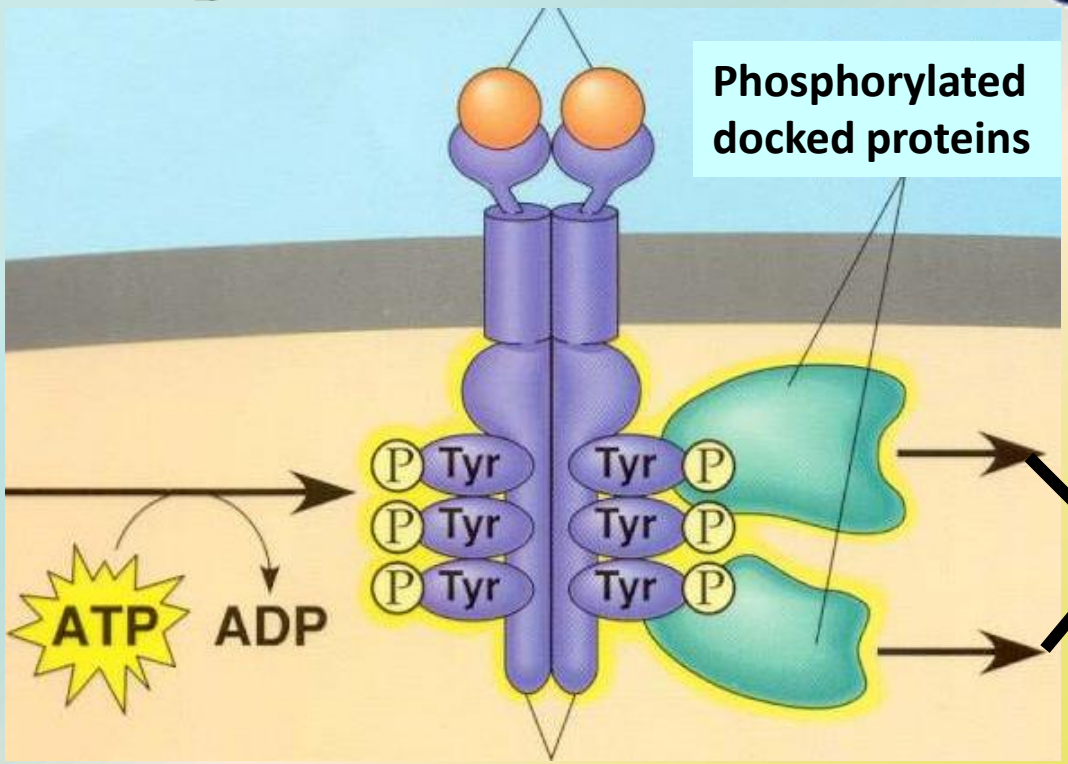
- Involved in response to hormones, growth factors.
- Response occurs in minutes to hours.
- They control many cellular functions as metabolism and growth.

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

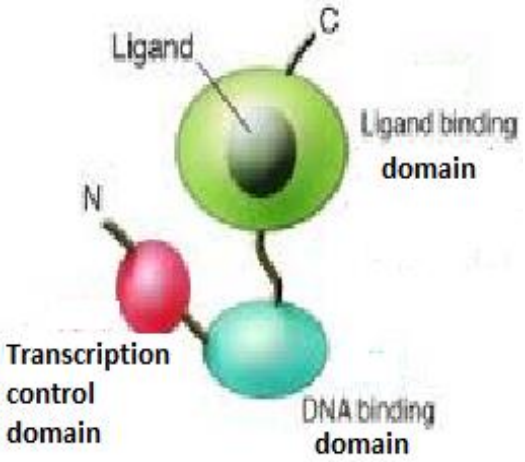
- Located intracellularly
- Directly related to DNA (Gene transcription).
- Activation of receptors either increase or decrease protein synthesis
- Response occurs in hours or days and persists longer.
- Their natural ligands are lipophylic hormones; steroids, thyroids, estrogen.

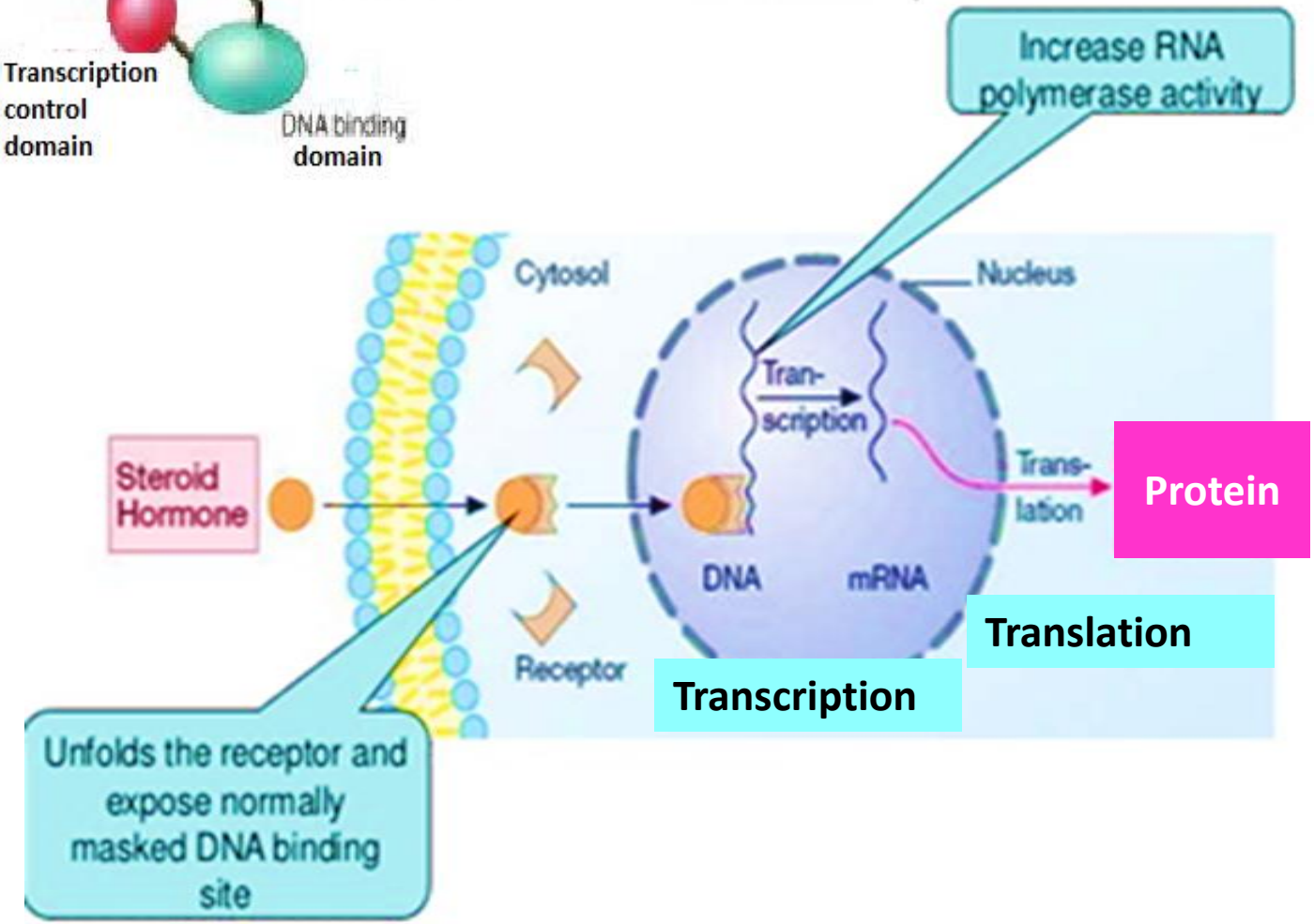
Type IV: Gene transcription receptors

▶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.

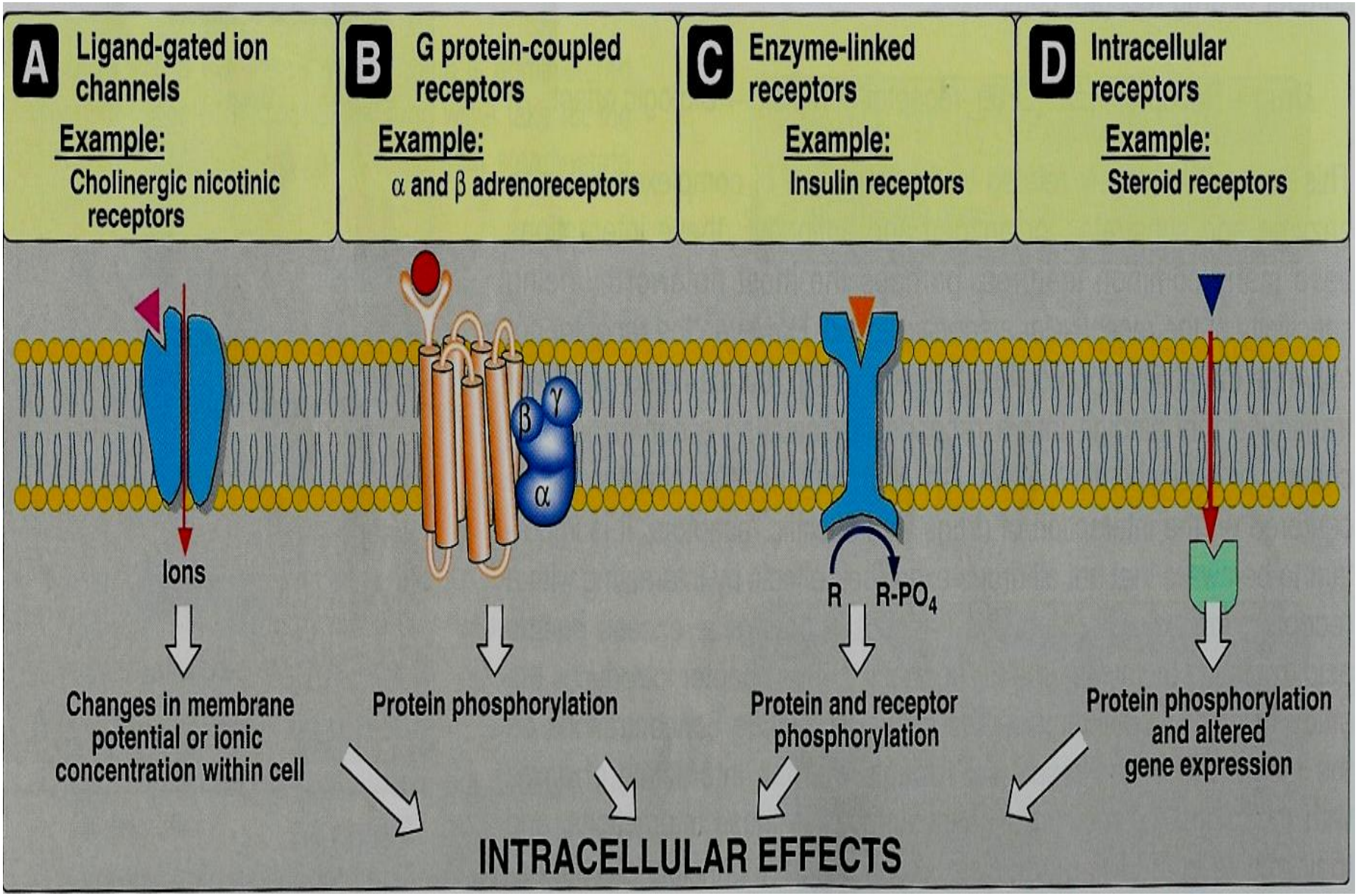
Type IV: Gene transcription receptors

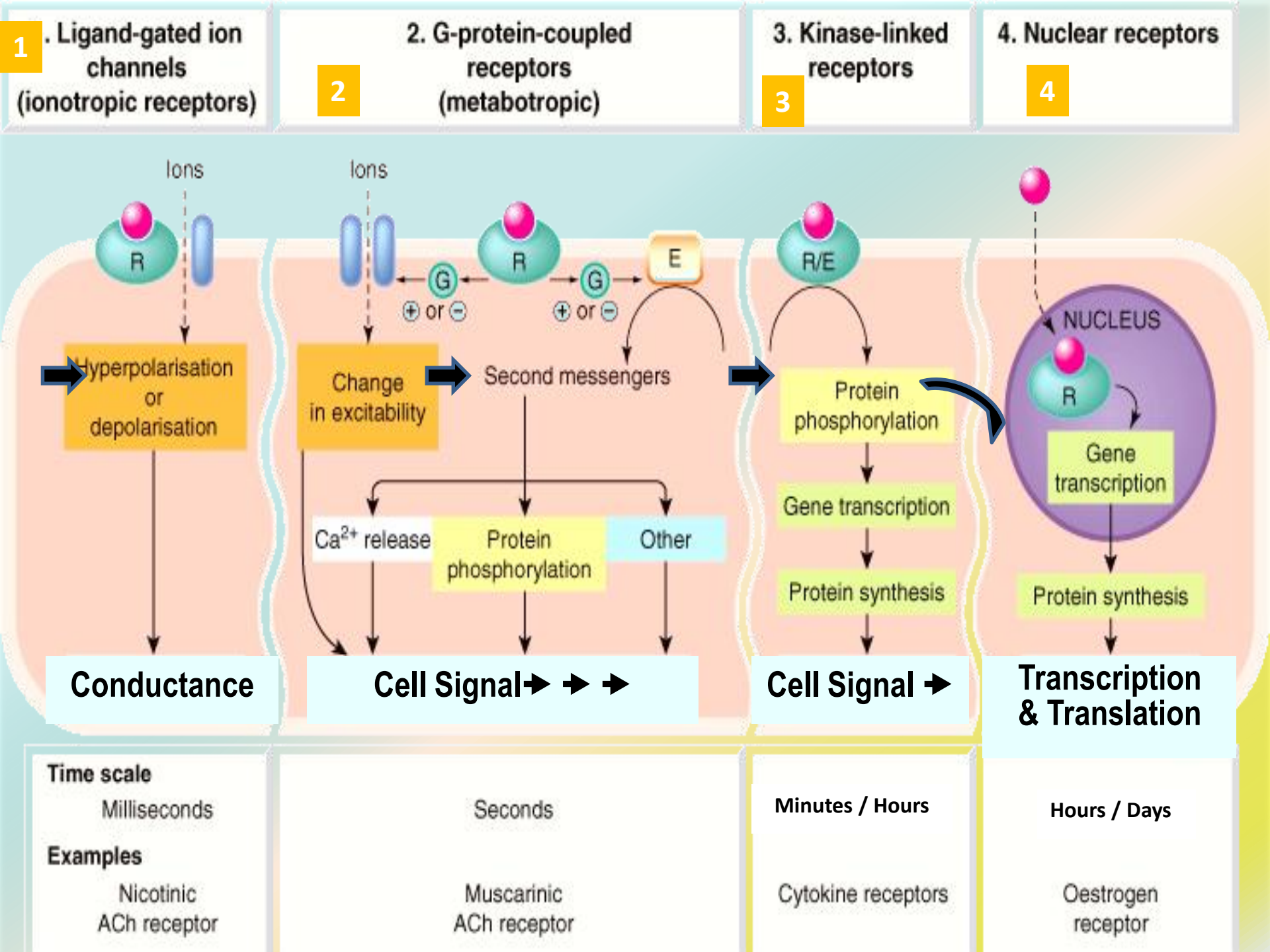




	Type I	Type II	Type III	Type III
Location	Membrane	Membrane	Membrane	Nucleus
Coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	Muscarinic receptors	Insulin receptors	Estrogen Steroid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