

PHARMACODYNAMICS III



RECEPTOR FAMILIES

ILOS

➤ **Classify receptors into their main families**

➤ **Recognize their different transduction mechanism**

➤ **Identify the nature & time frame of their response**



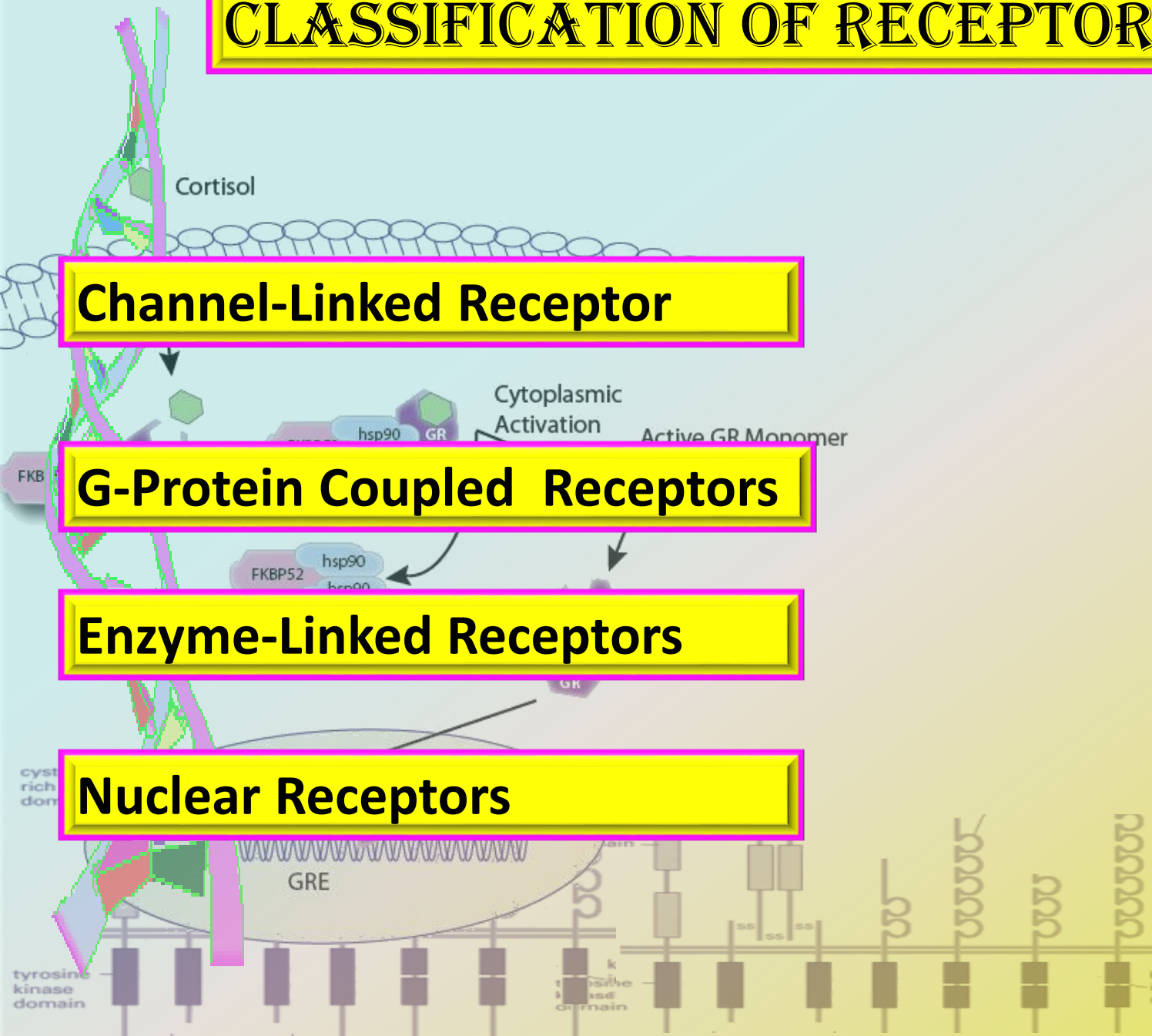
CLASSIFICATION OF RECEPTORS

Channel-Linked Receptor

G-Protein Coupled Receptors

Enzyme-Linked Receptors

Nuclear Receptors



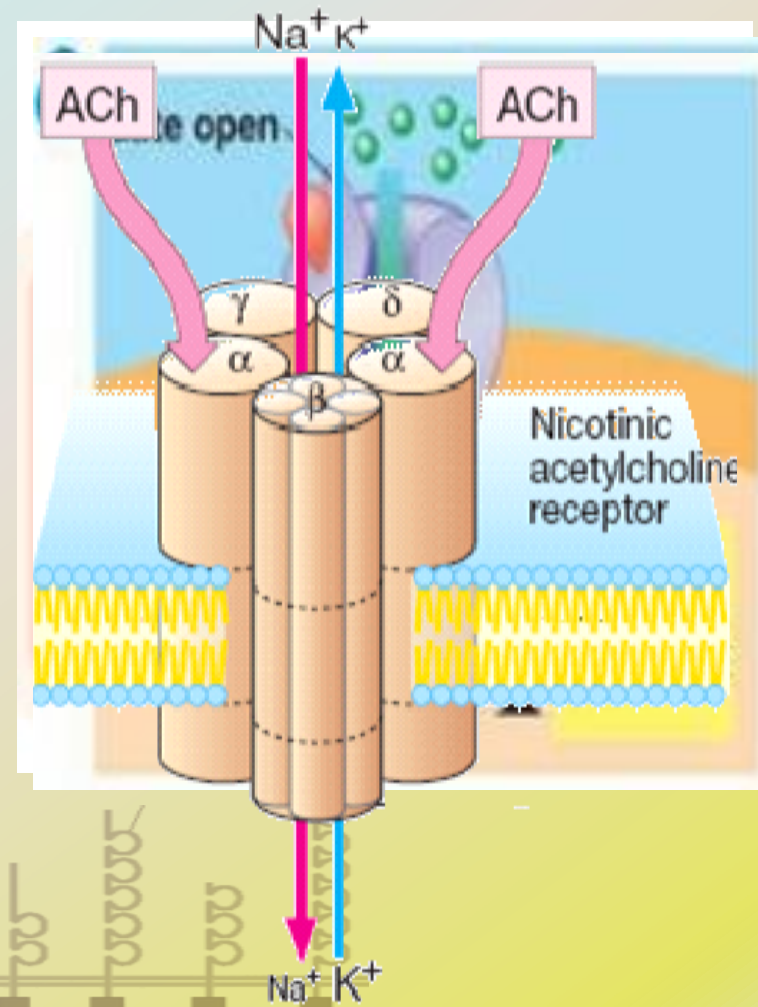
CHANNEL-LINKED RECEPTORS

Ionotropic

Involved in fast synaptic neurotransmission, ligand binding & opening occur in milli seconds

Membrane receptors coupled directly to ion channels

e.g. nicotinic Ach

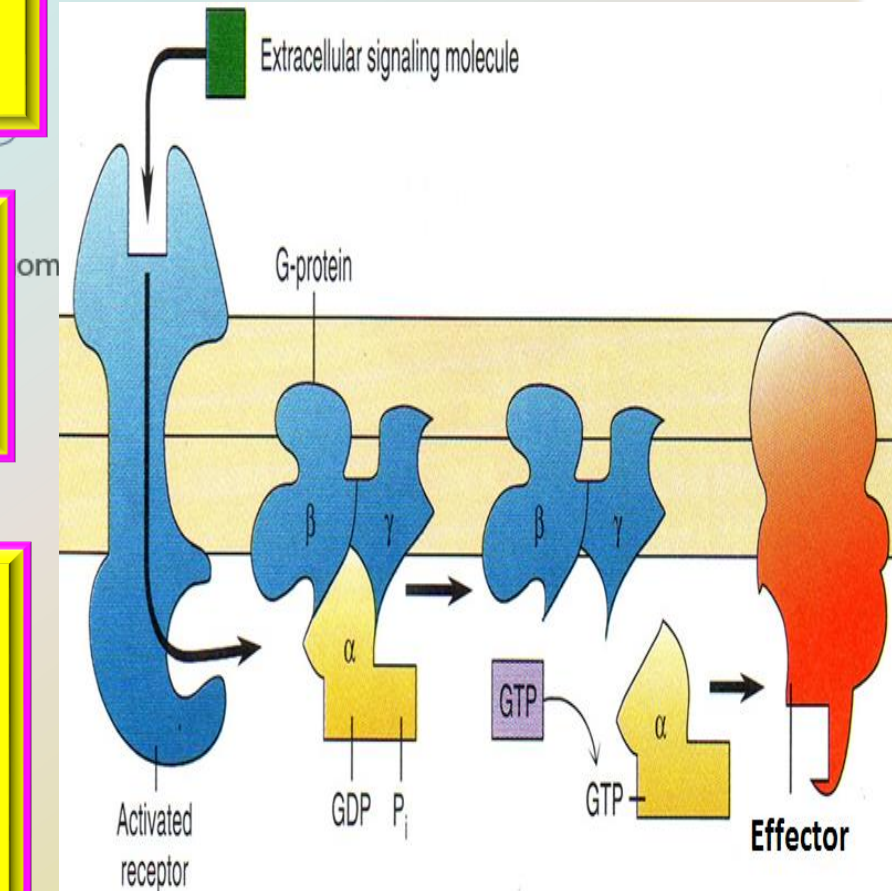


G-PROTEIN COUPLED RECEPTORS

Membrane receptors, coupled to intracellular effector system via G protein

The G- protein comprises 3 subunits $[\alpha\beta\gamma]$, the α - subunit possesses **GTPase** activity

When the trimer binds to agonist- occupied receptor , **the α -subunit dissociates** & is then free to activate an effector

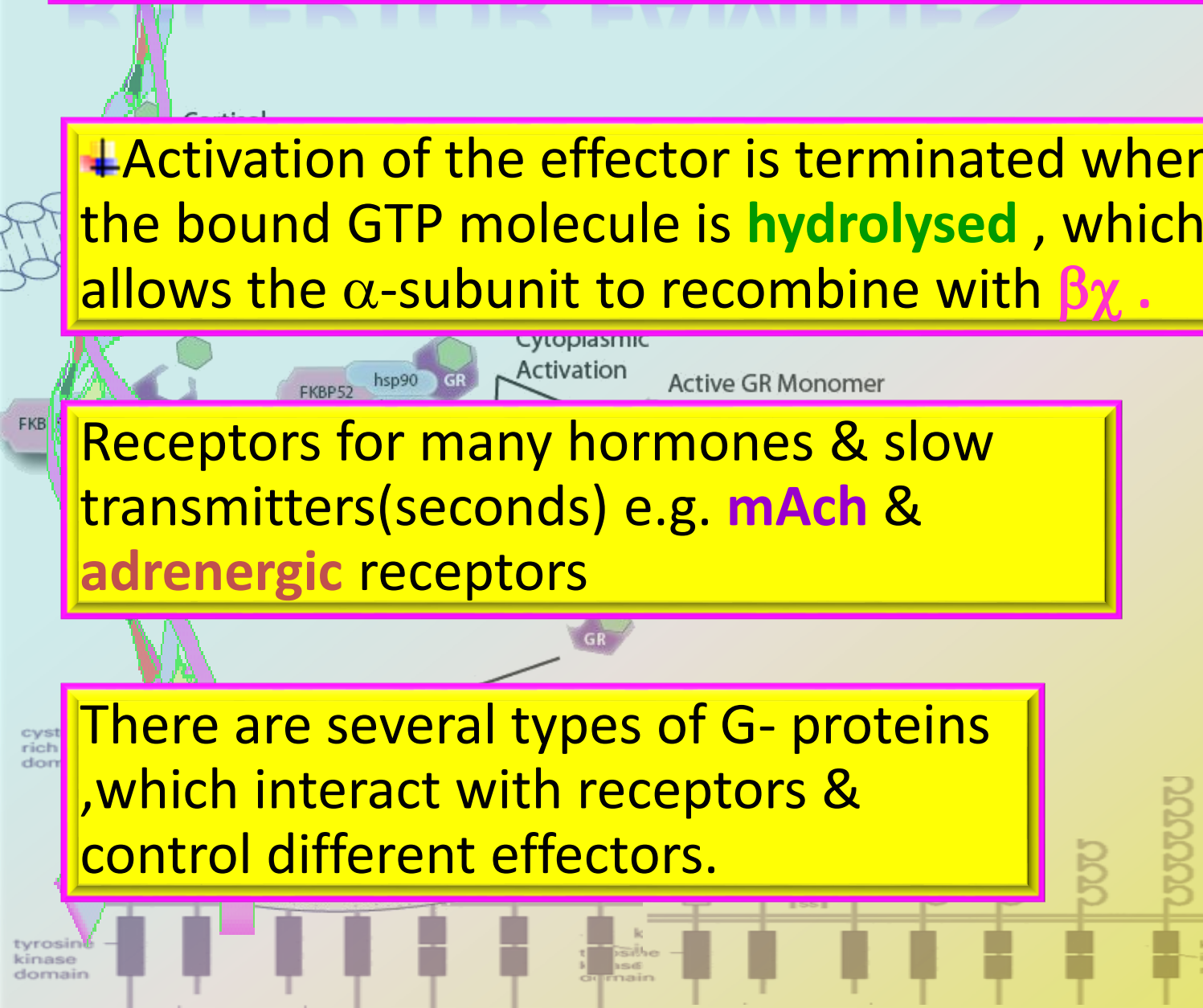


G-PROTEIN COUPLED RECEPTORS

Activation of the effector is terminated when the bound GTP molecule is **hydrolysed**, which allows the α -subunit to recombine with $\beta\gamma$.

Receptors for many hormones & slow transmitters (seconds) e.g. **mACh** & **adrenergic** receptors

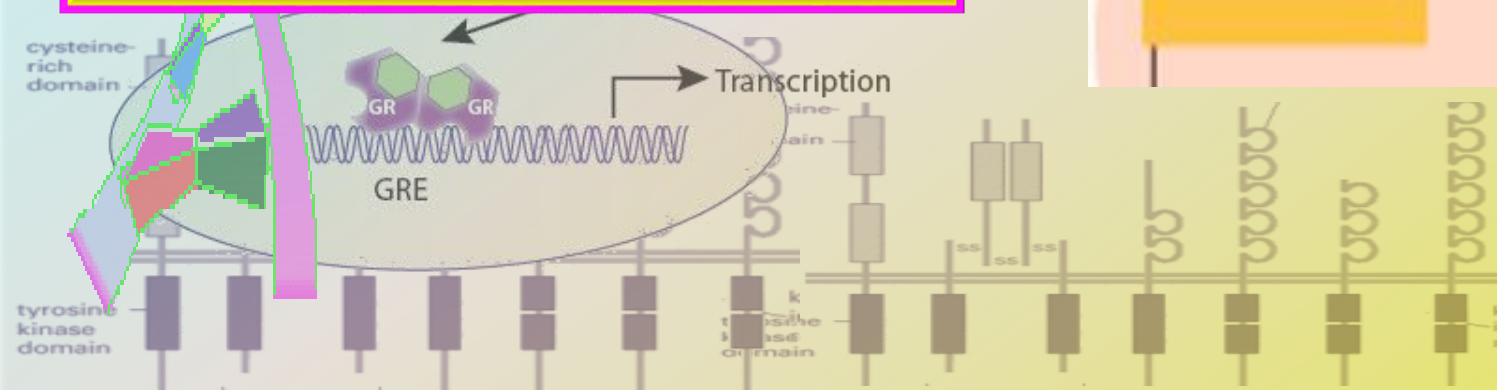
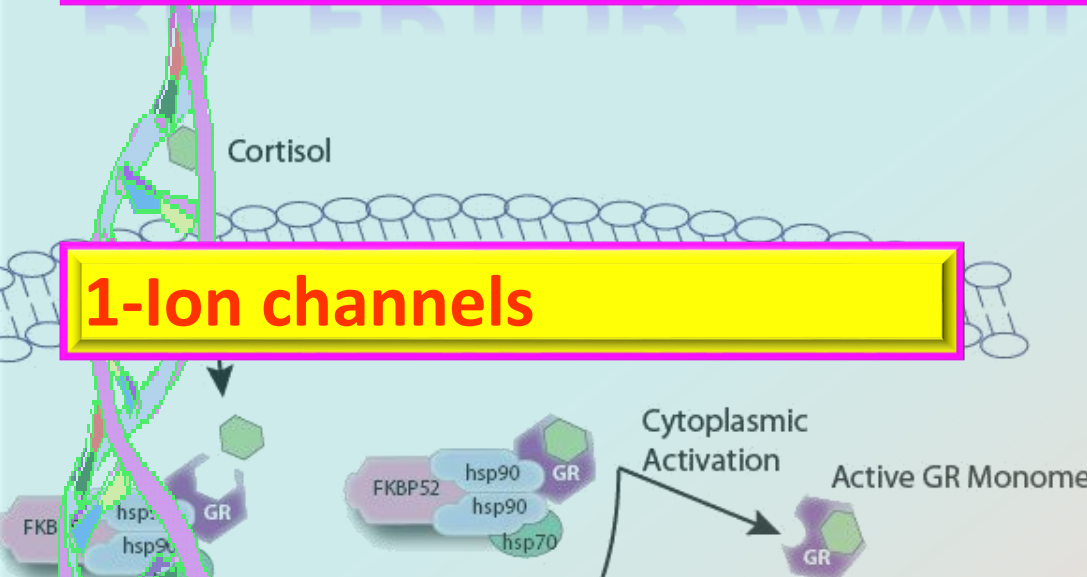
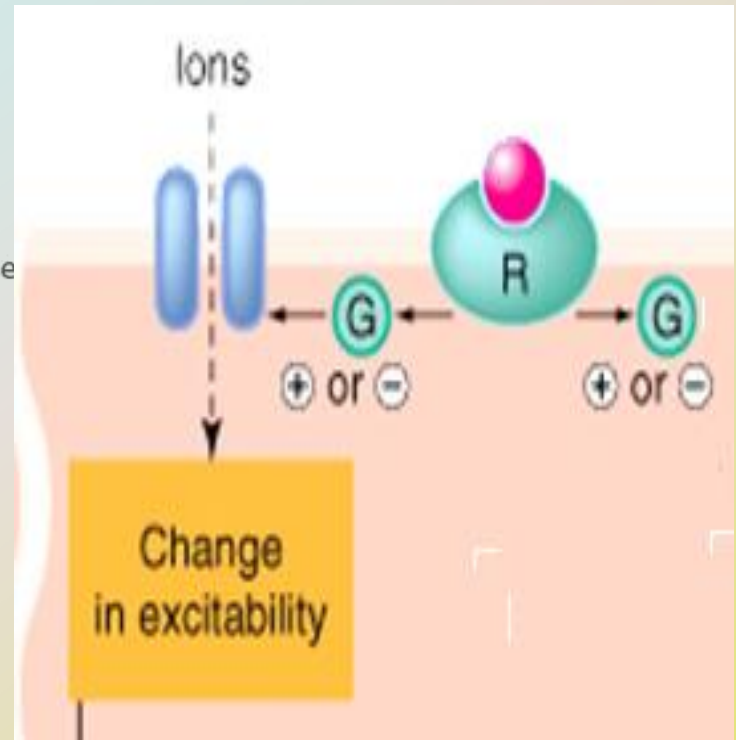
There are several types of G-proteins, which interact with receptors & control different effectors.



EFFECTORS FOR G-PROTEINS

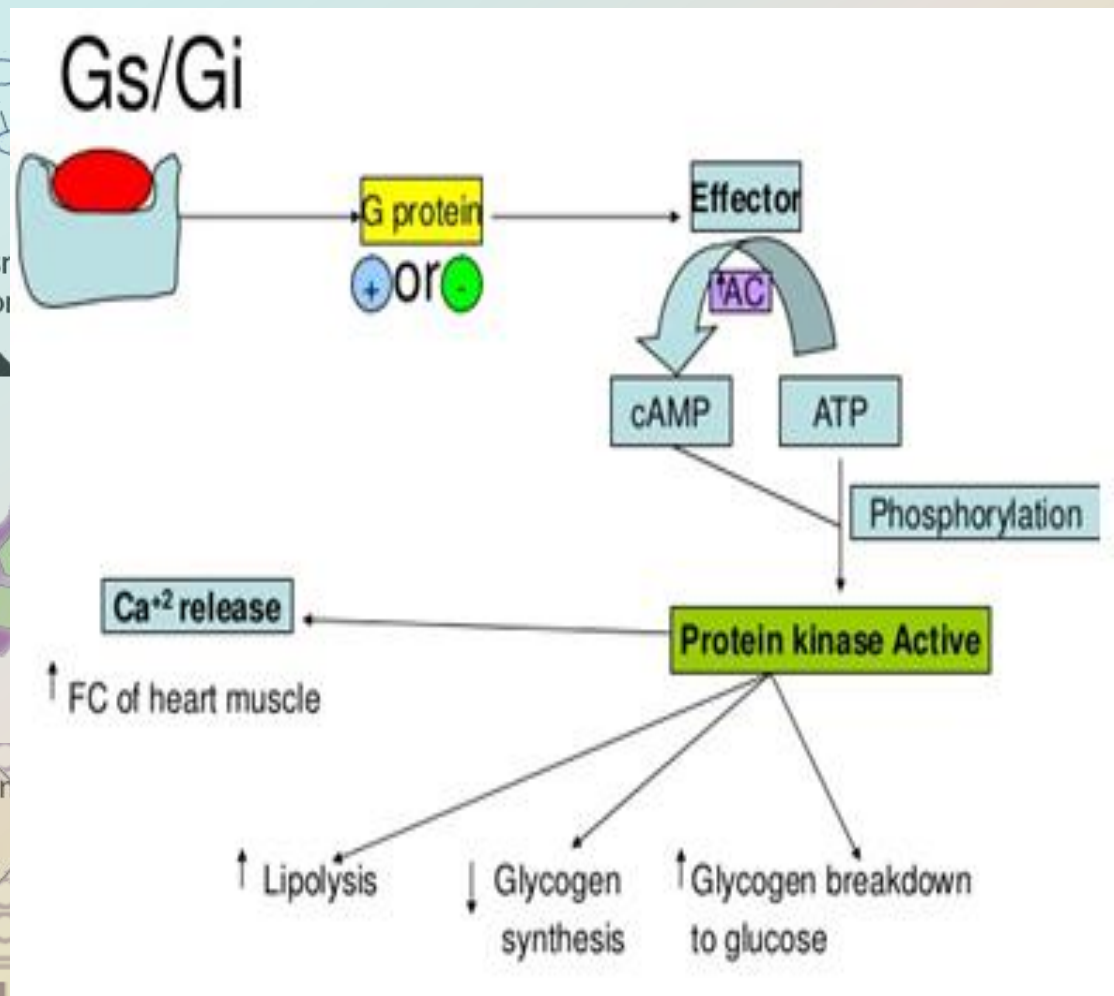
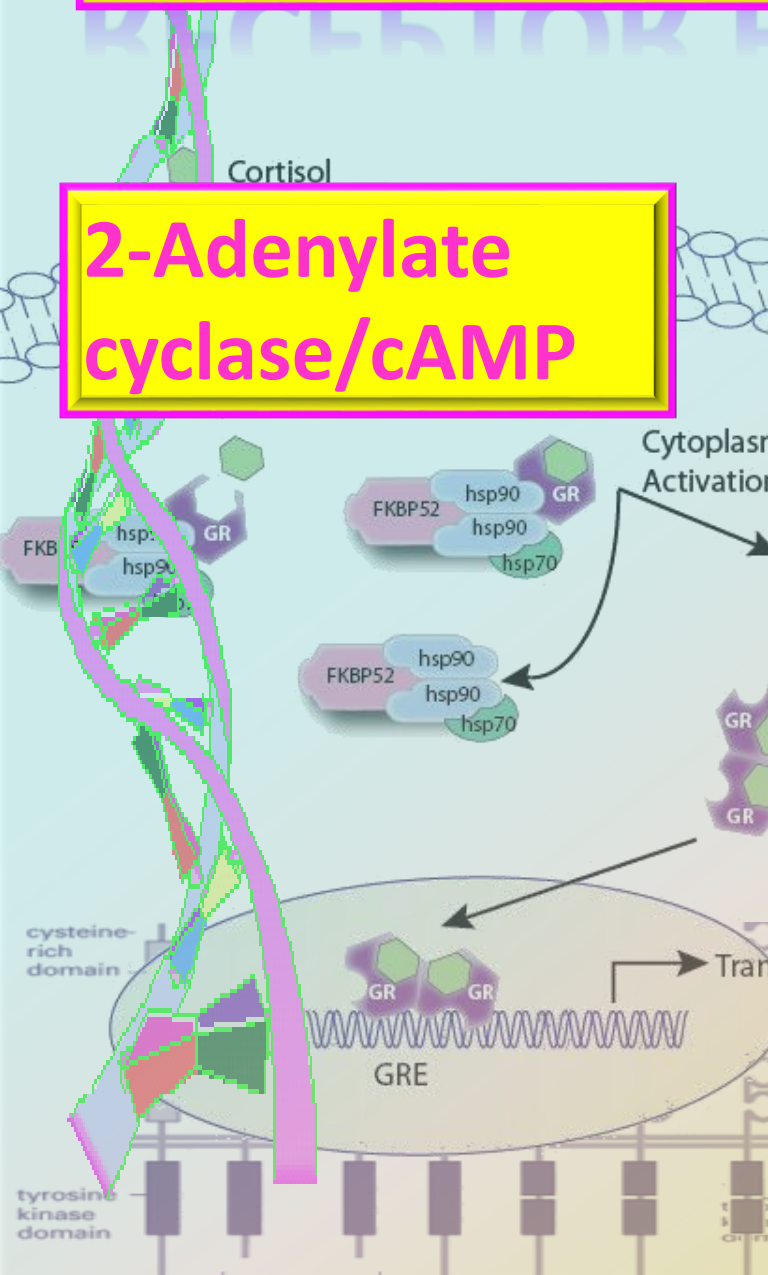
1-Ion channels

e.g. K^+ , Ca^{++} thus affecting membrane excitability, transmitter release,



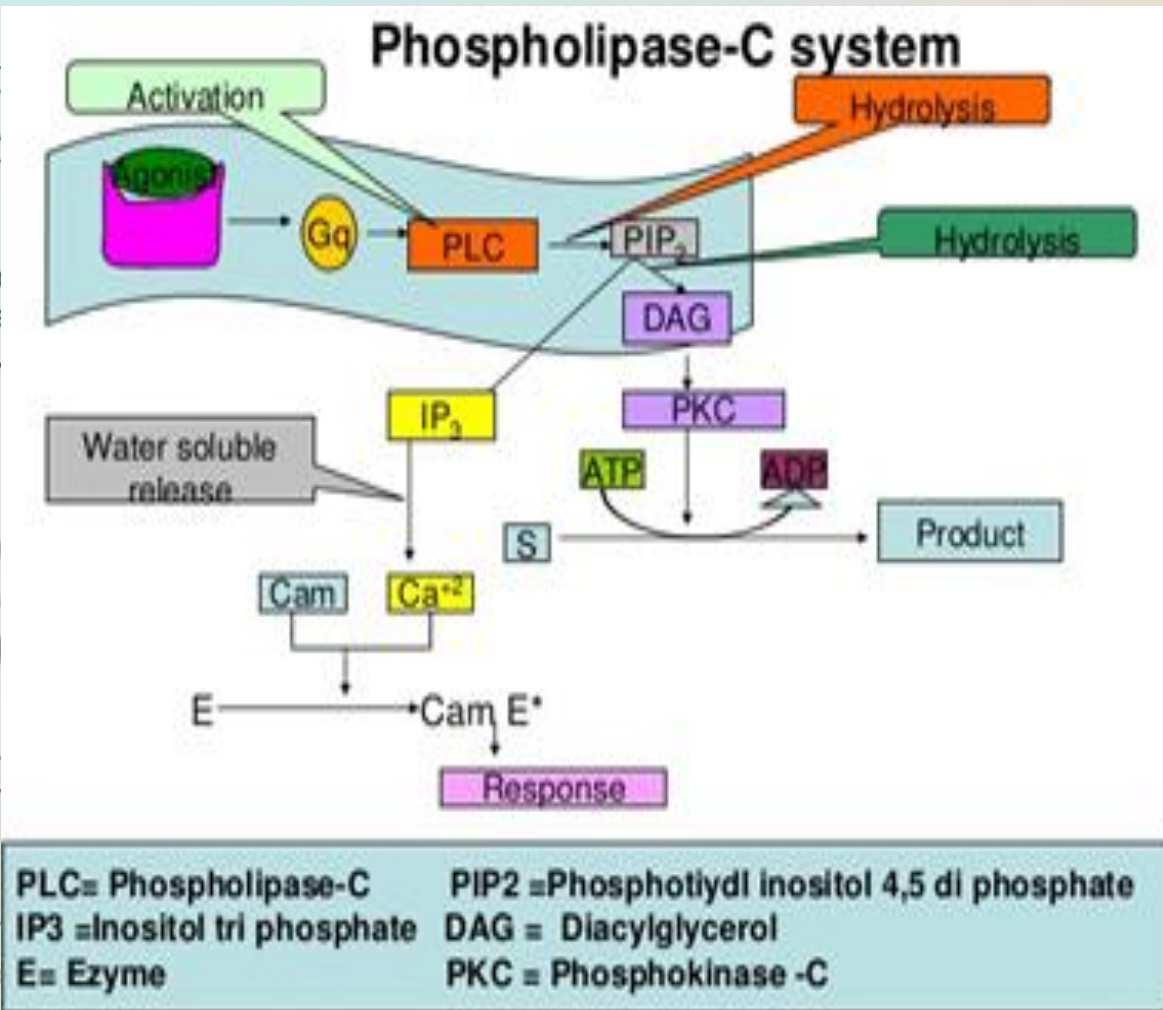
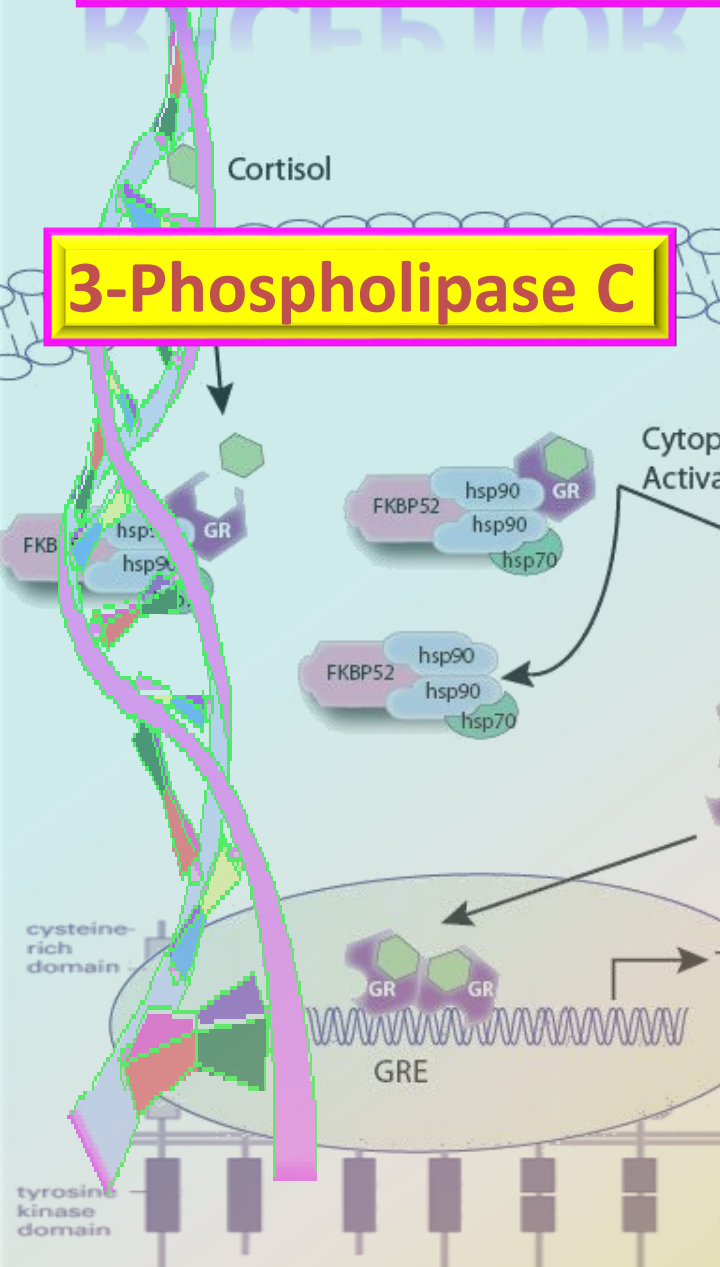
EFFECTORS FOR G-PROTEINS

2-Adenylate cyclase/cAMP



EFFECTORS FOR G-PROTEINS

3-Phospholipase C



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

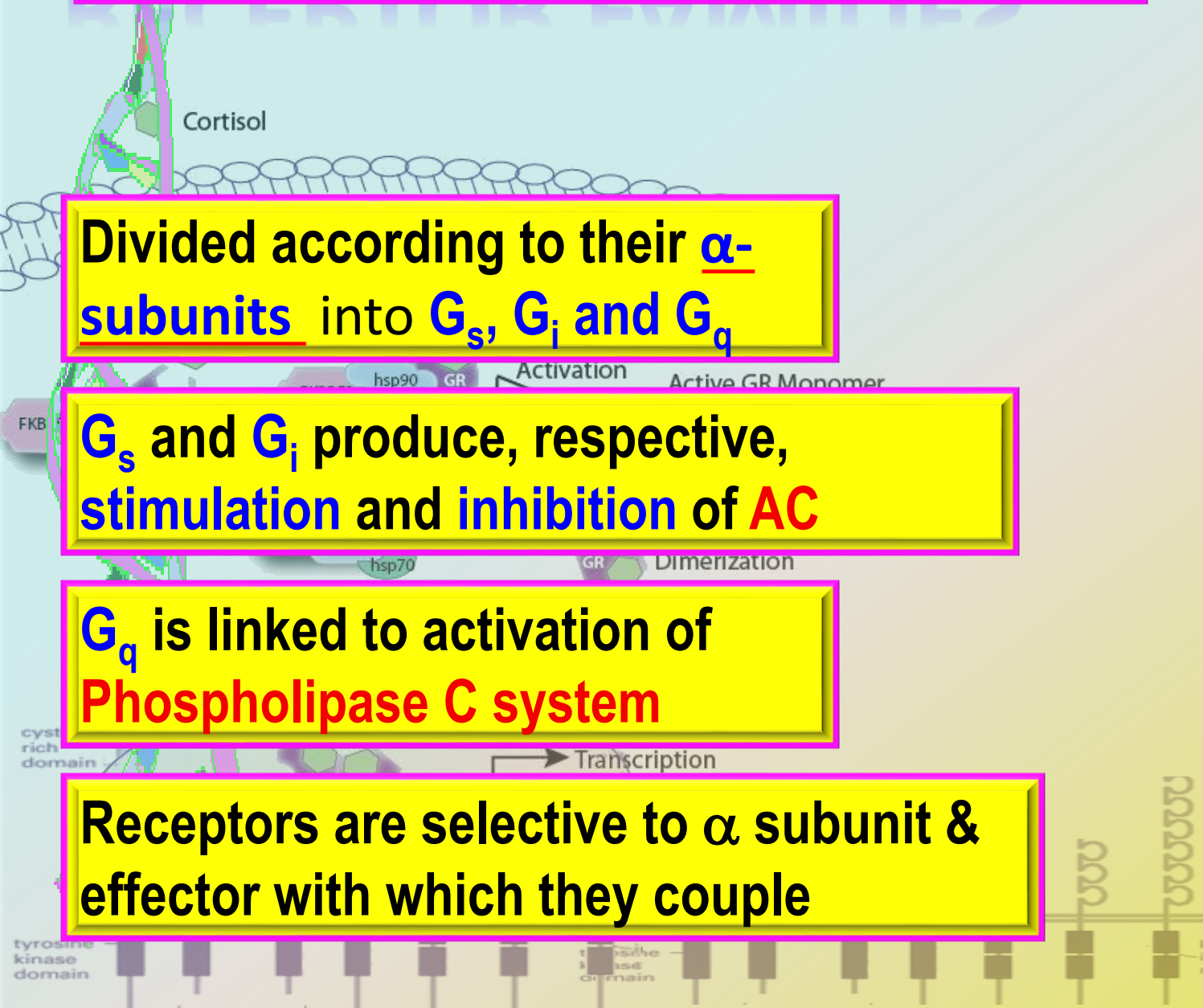
CLASSES OF G PROTEIN

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

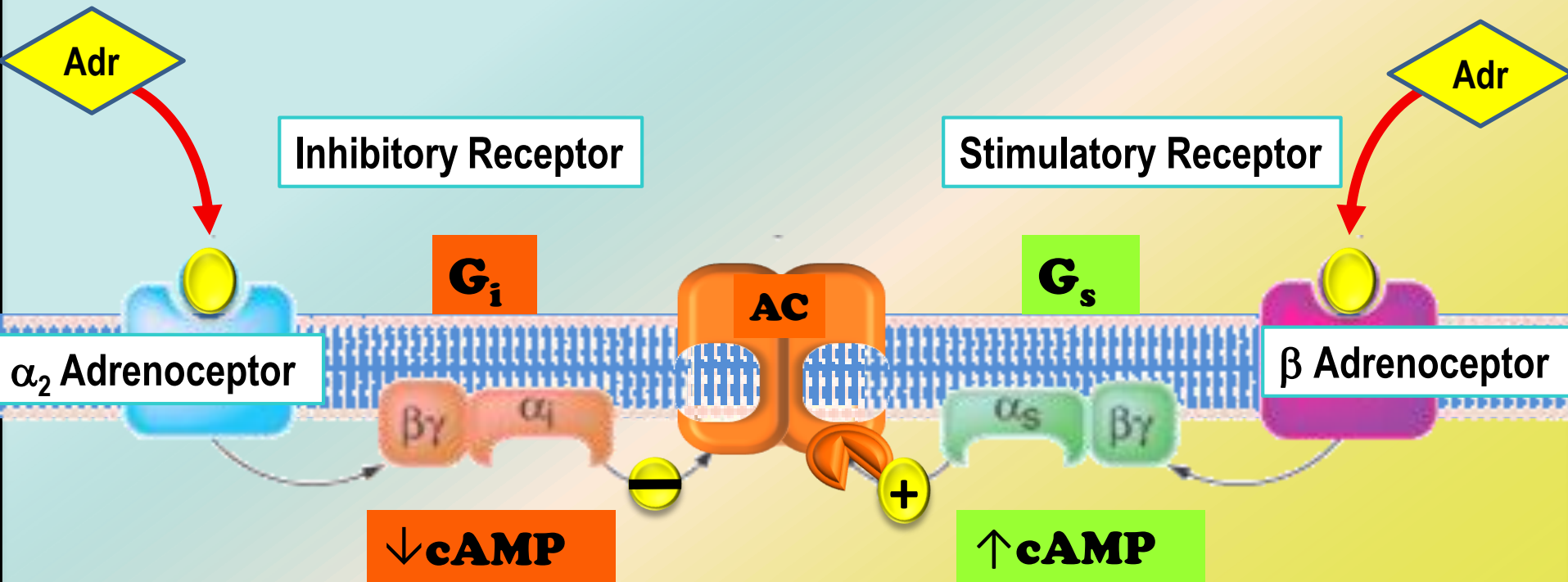


ADRENOCEPTORS

α_1 Adrenoceptors couple to G_q to stimulate PLC.

α_2 Adrenoceptors couple to G_i to inhibit AC.

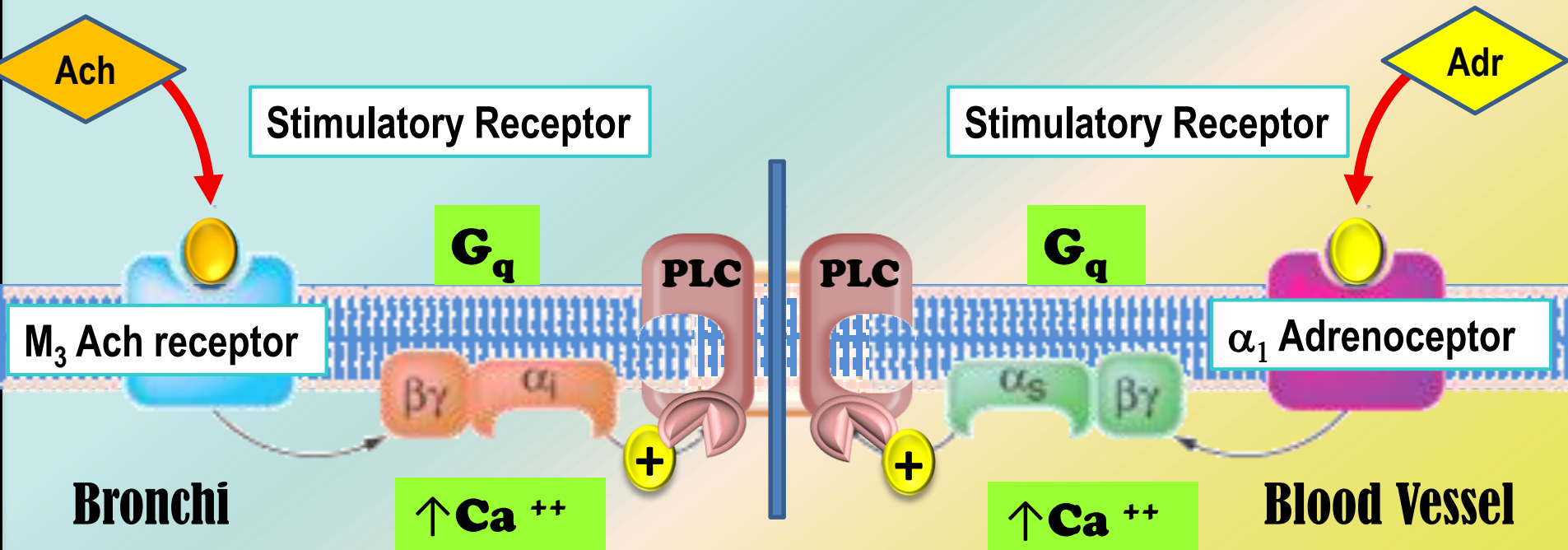
$\beta_{1\&2}$ Adrenoceptors couple to G_s to stimulate AC



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



ENZYME-LINKED RECEPTORS

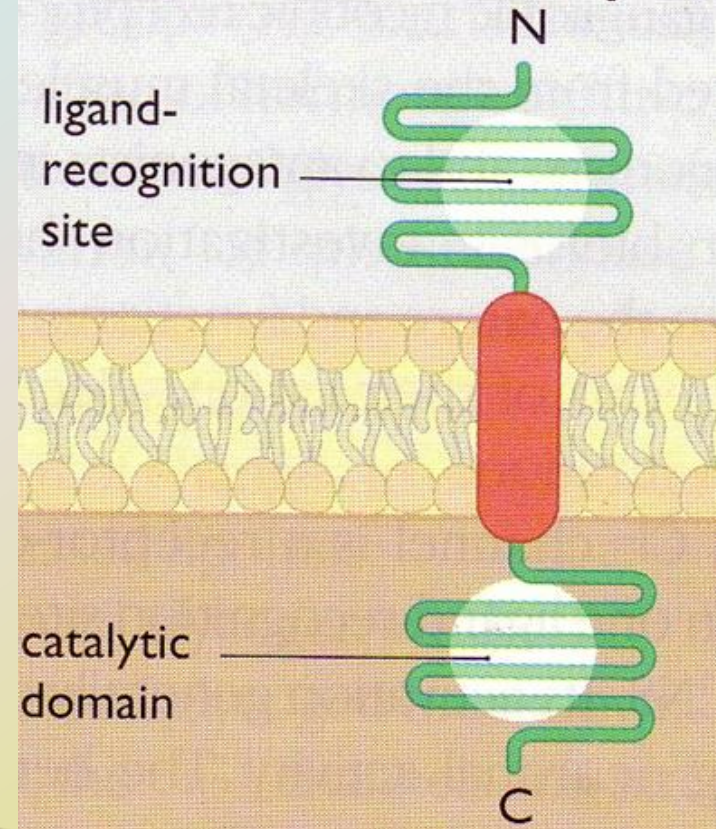
• The receptors have a large **extracellular ligand-binding** domain connected via a single α -helix to the **intracellular domain**

Some have intrinsic tyrosine kinase activity

Receptors for various **hormones**
e.g insulin , growth factors

• They are involved mainly in events controlling cell growth & differentiation

Receptor that is an enzyme

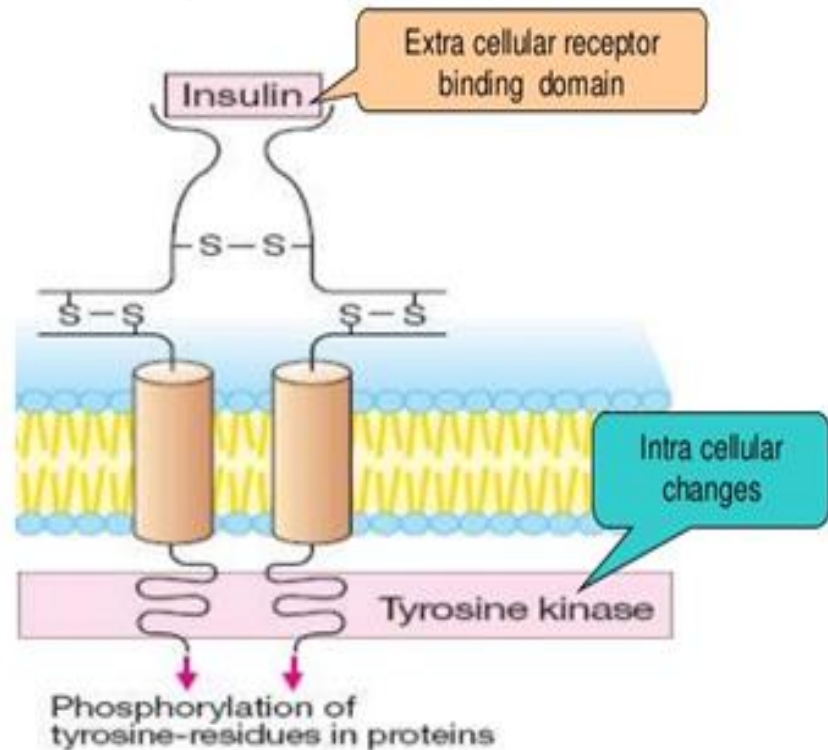


ENZYME-LINKED RECEPTORS

Signal transduction involves **autophosphorylation** of tyrosine residue which acts as acceptor of SH2 domain of various proteins, thereby allowing control of various cell functions.

This usually require many intracellular signaling steps that take time to process (minutes to hours).

Enzymatic receptors

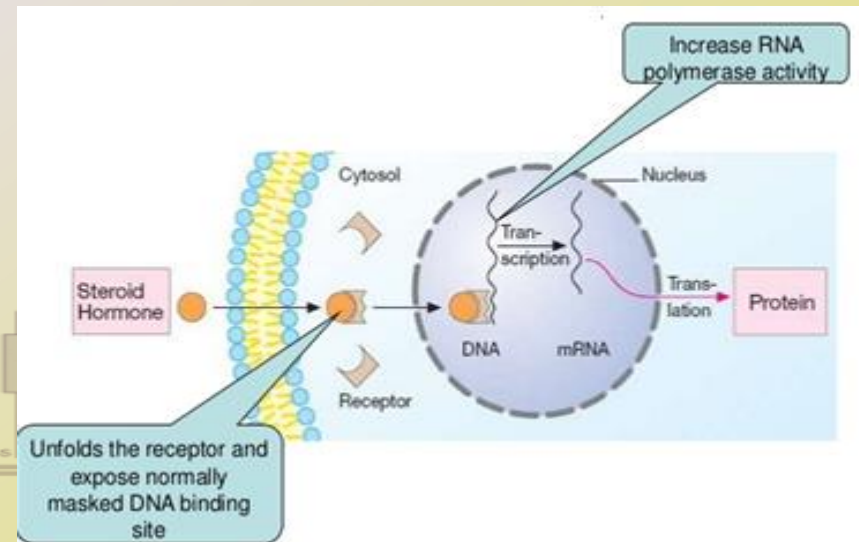
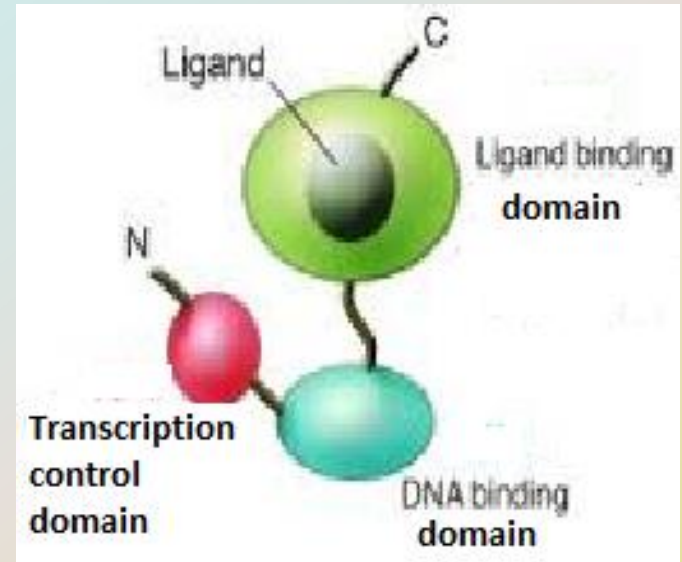


NUCLEAR RECEPTORS

Receptors are **intracellular proteins**

Receptors consist of a conserved DNA-binding domain attached to variable **ligand-binding & transcription control domains**.

DNA-binding domain recognizes specific base sequences (response element), thus **promoting or repressing** particular genes.



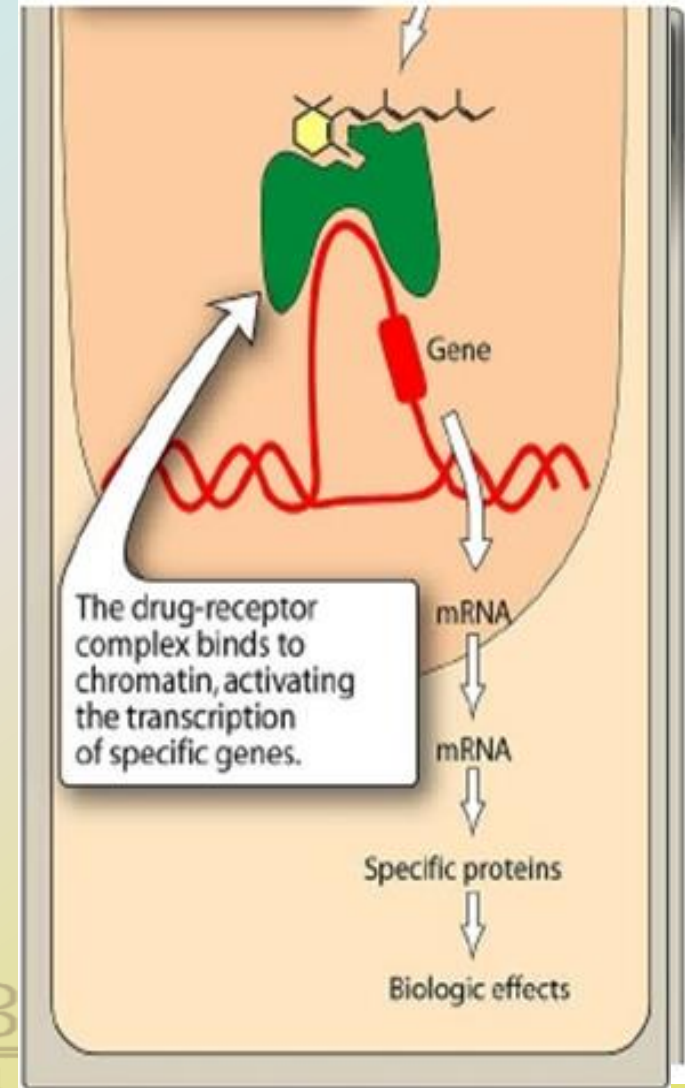
NUCLEAR RECEPTORS

They react as **TRANSCRIPTION FACTORS** expressing or epressing target genes.

Effects are produced as a result of **protein synthesis**, thus they are slow in onset(hours & days).

Pattern of gene activation depends on both **cell type & nature of ligands**

ligands include **steroid hormones, vitamin D & thyroid hormone**



SYNOPSIS

Characteristics of receptor families

	Ligand gated	G-protein coupled	Enzymatic	Nuclear
Location	Membrane	Membrane	Membrane	Intracellular
Effector	Ion channel	Ion Channel or enzyme	Enzyme	Gene
coupling	Direct	G-protein	Direct	Via DNA
Example	Nicotinic	Muscarinic	Insulin	Steroid , hormone
Time scale	mseconds	seconds	min/hou	hou/days