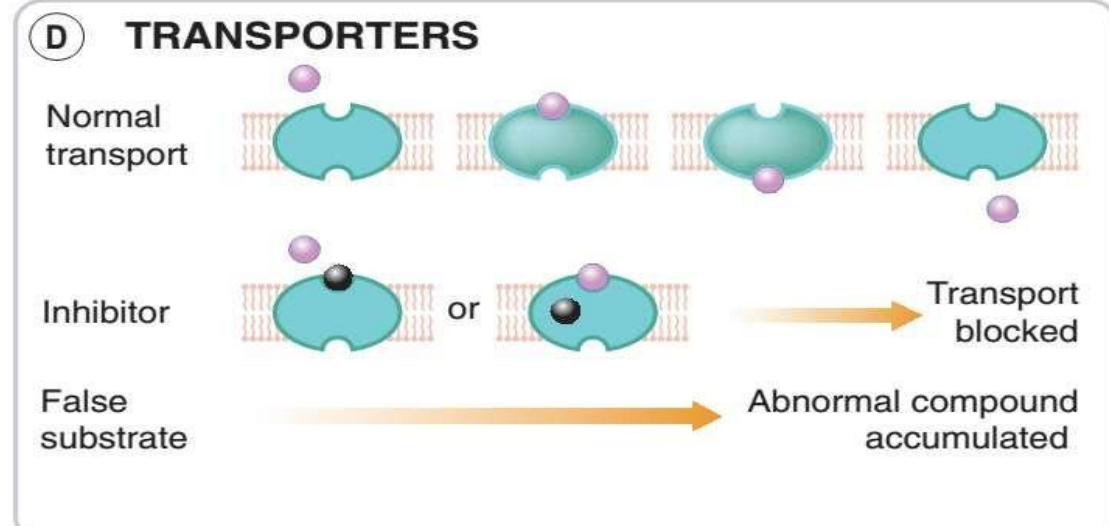
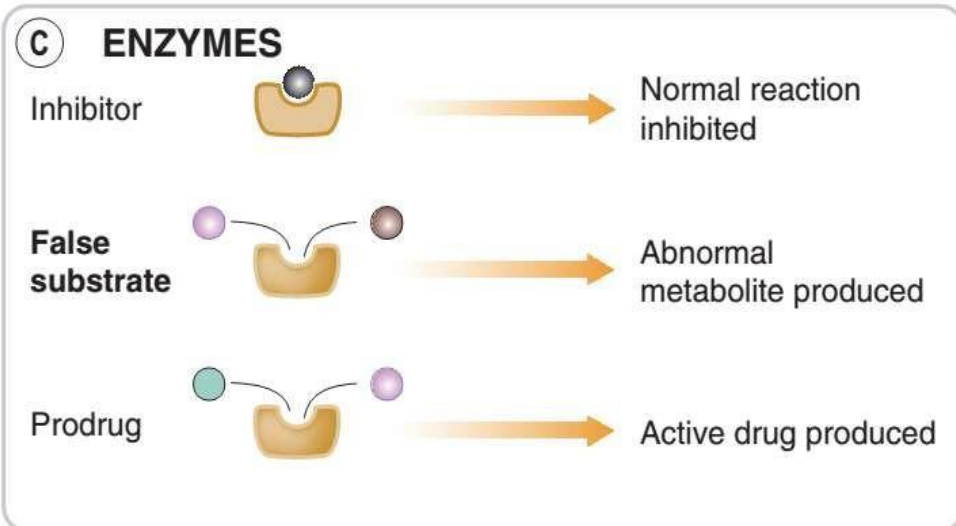
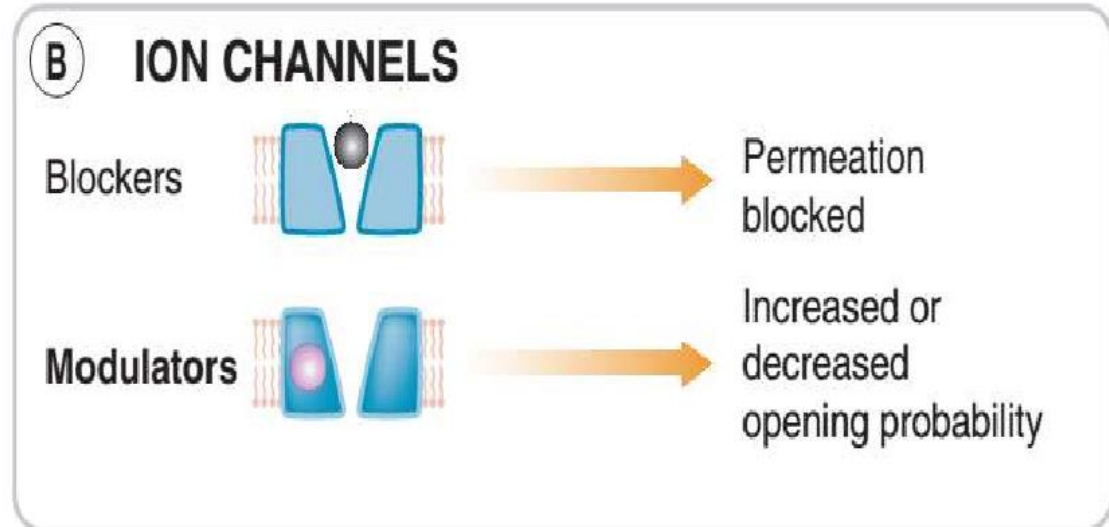
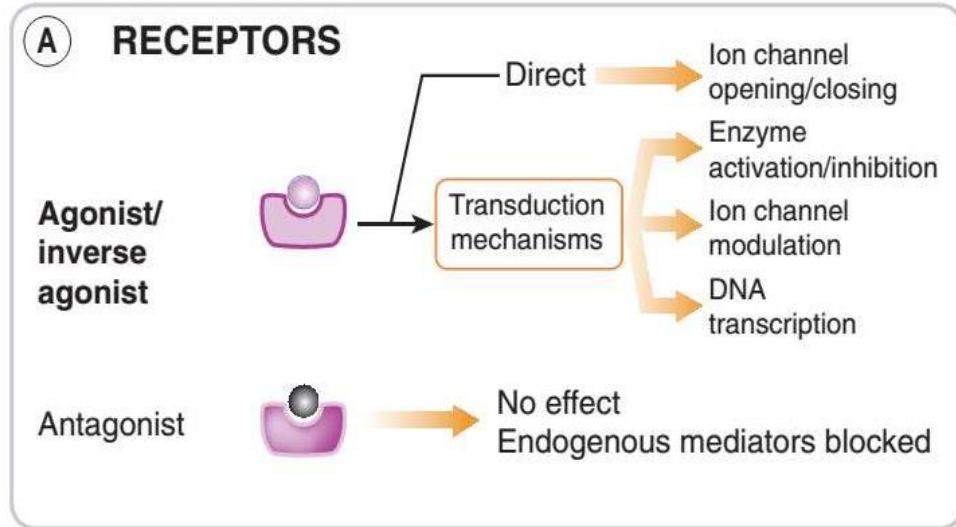


TYPES OF RECEPTORS

OUTLINE

- Definition
- History
- Receptor Theories
- Criteria for classifying receptors
- Types of Receptors :
 - Ligand Gated Ion Channels
 - G-Protein Coupled Receptors
 - Enzyme Linked Receptors
 - Nuclear Receptors
- Summary

TARGETS FOR DRUG ACTION



- Agonist/substrate
- Antagonist/inhibitor
- Abnormal product
- Prodrug

What are receptors?

- Receptor is a cellular macromolecule, whose function is to recognize and respond to chemical signals

HISTORY

- 1878 – **John Langley** proposed 'receptive substance'
- 1905 - Receptive substance on surface of skeletal muscle mediate drug action.
Different in different species
- **Paul Ehrlich** designated 'receptor' to be anchoring group of the protoplasmic molecule for the administered compound
- Envisaged molecules extending from cells that the body could use to distinguish and mount an immune response to foreign objects
- 1948 - **Ahlquist** showed the differential action of adrenaline & demonstrated its effects on two distinct receptor populations & the theory of receptor-mediated drug interactions gained acceptance

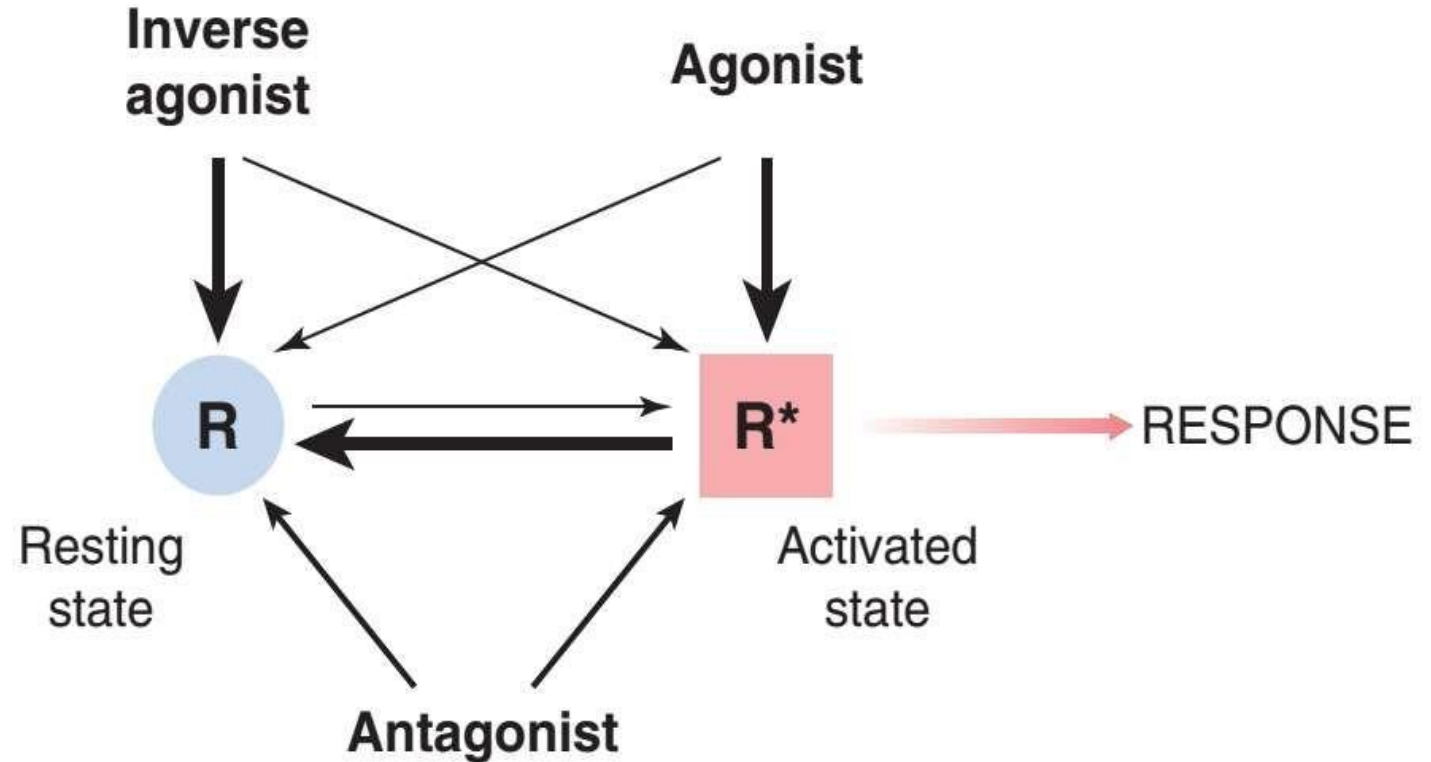
- 1970s - Pharmacology entered a new phase following the development of receptor-labelling techniques
- Multiple subtypes of receptors now known, which has paved the way for clinically superior drugs

CRITERIA FOR CLASSIFYING RECEPTORS

- Pharmacological Criteria
- Tissue Distribution
- Ligand Binding
- Transducer Pathway
- Molecular Cloning

RECEPTOR THEORIES

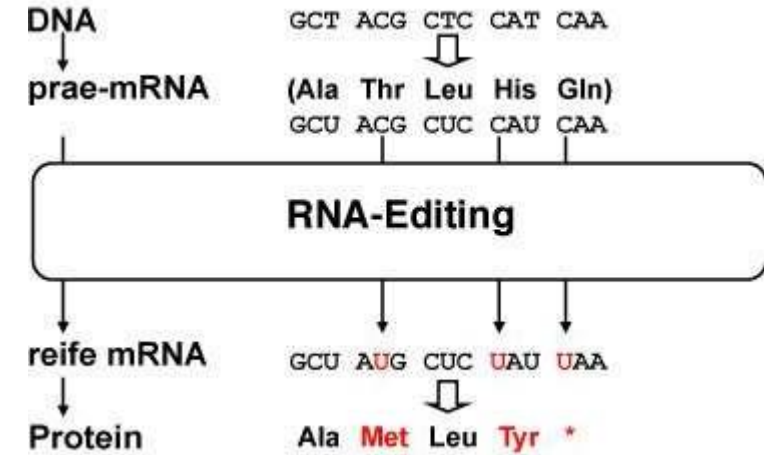
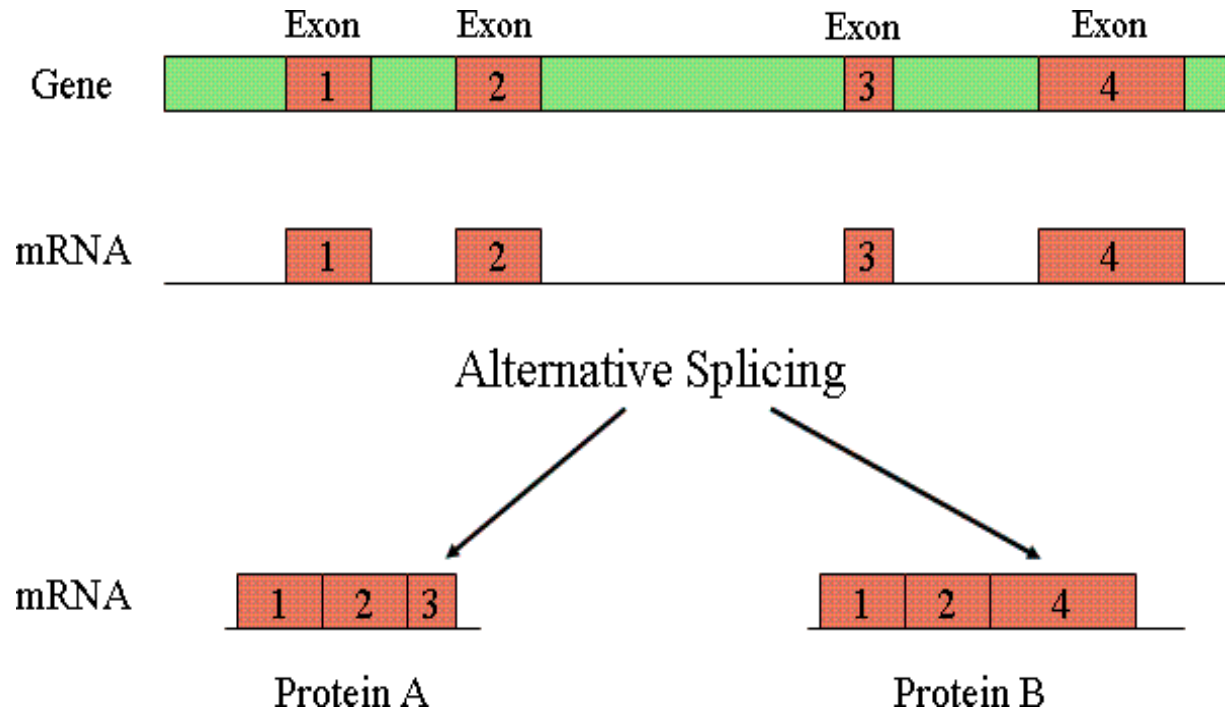
- Occupation theory (1937)
- Rate theory (1961)
- Two State Receptor Theory (1983)



TYPES OF RECEPTORS

- Ligand Gated Ion Channels
- G-Protein Coupled receptors
- Enzyme Linked receptors
- Nuclear receptors

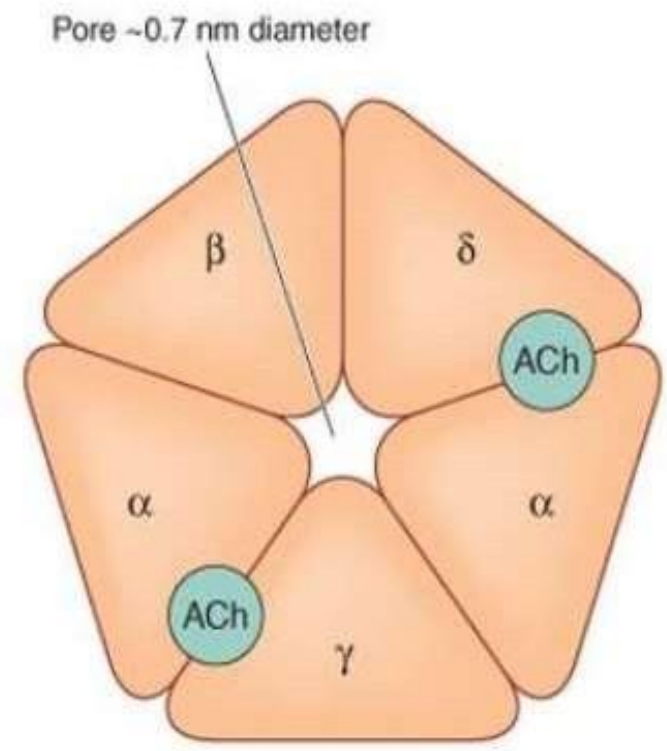
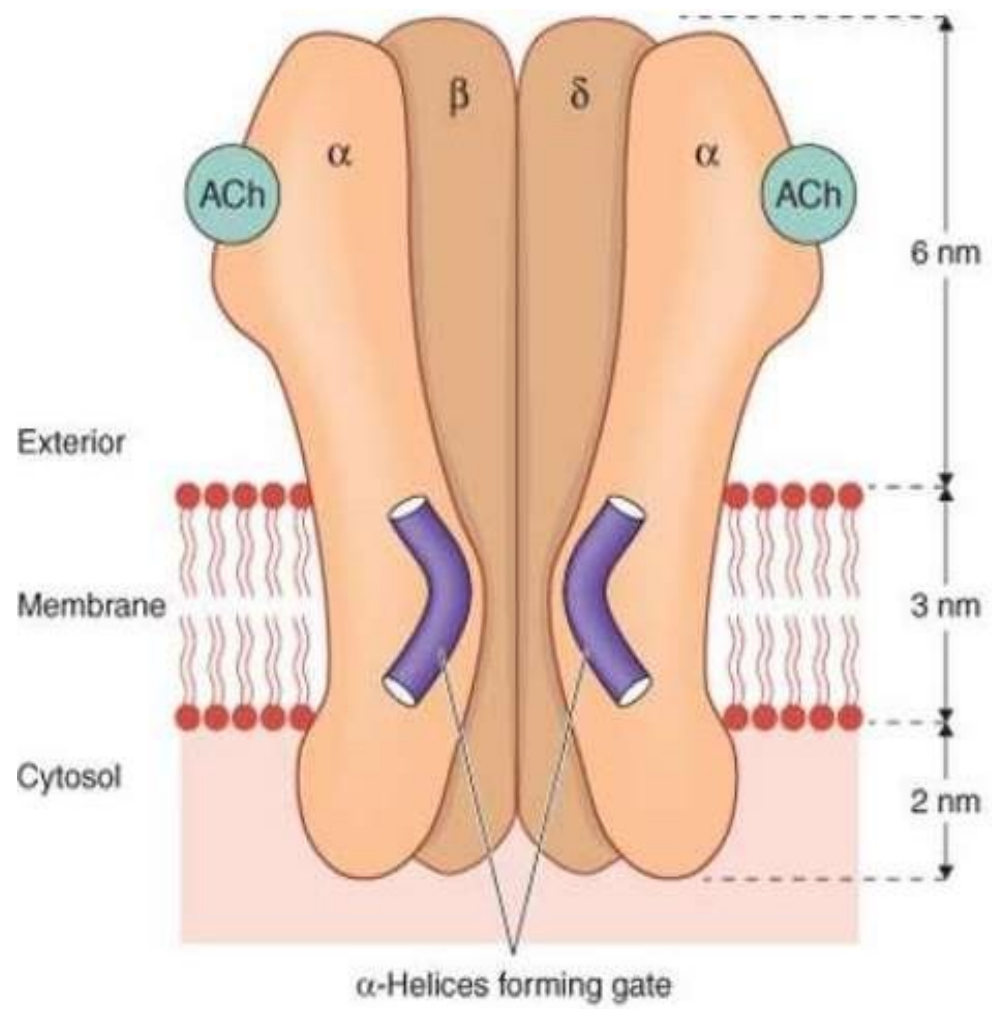
RECEPTOR SUBTYPES & NOMENCLATURE



IUPHAR- International Union of Basic and Applied Pharmacology

TYPE 1 : LIGAND GATED ION CHANNELS

- Ionotropic Receptors
- Typically receptors on which neurotransmitters act
- Timescale : Milliseconds
- Localization : Membrane
- Effector : Ion Channel
- Coupling : Direct
- Examples : Nicotinic Ach Receptor, GABA_A Receptor, Glutamate Receptor, Glycine receptor, 5 Hydroxytryptamine type 3 (5 – HT₃)



MOLECULAR STRUCTURE

- Nicotinic Ach receptor studied in great detail
- Pentameric Assembly of 4 types of subunits α , β , γ and δ
- 4 membrane spanning α -helices inserted into membrane
- 2 Ach binding sites, both must bind Ach molecules for receptor activation
- Lining of central transmembrane pore formed by helical segments of each subunit (negatively charged AA). 5 helices sharply kinked inwards halfway, forming a constriction

GATING MECHANISM

- Ach molecules bind, twists the α subunits, kinked helices either straighten out or swing out of the way, opening channel pore
- Conductance produced by different Ach like agonists is the same whereas mean channel lifetime varies
- Mutation of a critical residue in helix changes channel from being cation selective (excitatory) to being anion selective (typical of receptors for inhibitory transmitters like GABA)

- Most excitatory neurotransmitters cause
Increase in Na^+ and K^+ permeability



net inward current carried mainly by Na^+



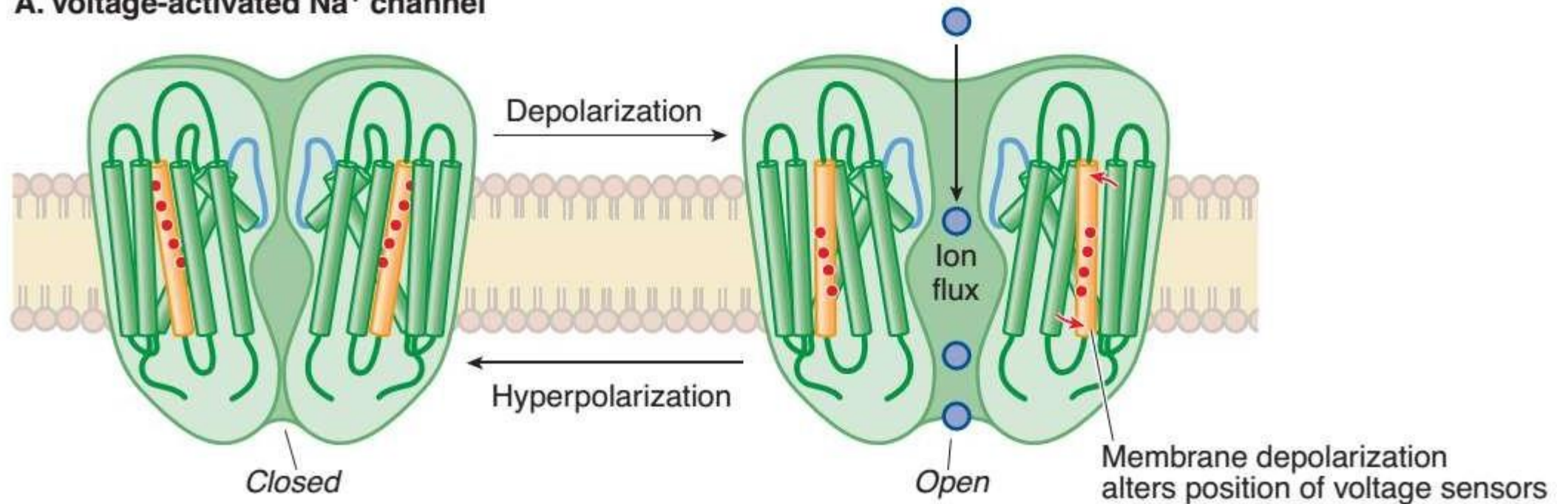
Depolarization of the membrane (probability to generate action potential)

- Speed of this response implies that coupling between the receptor and ionic channel is a direct one (no intermediate biochemical steps involved)

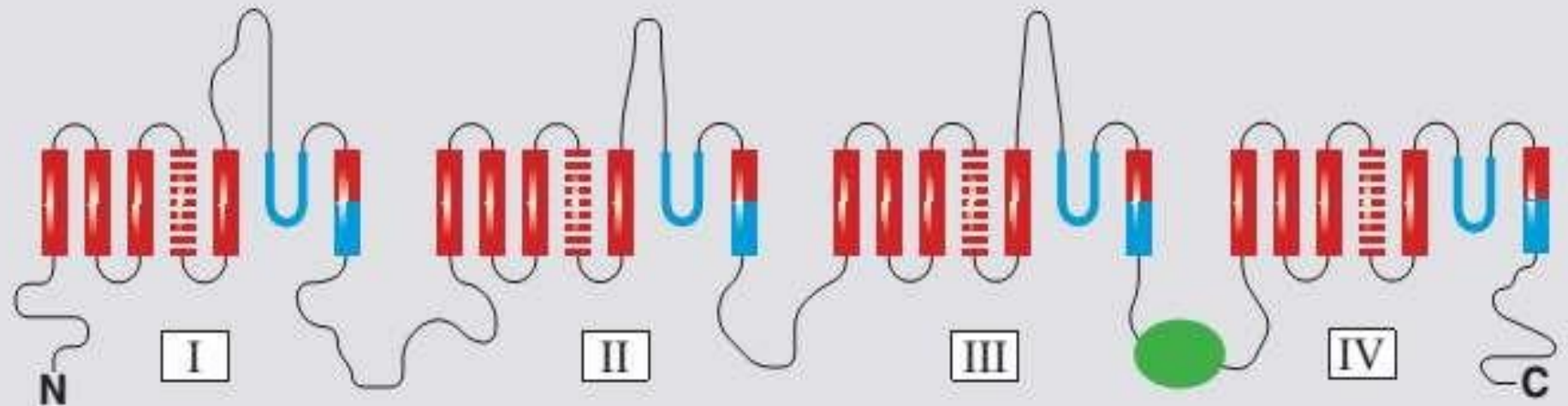
VOLTAGE OPERATED CHANNELS

- These channels open when the cell membrane is depolarised. They underlie the mechanism of membrane excitability
- Activation induced by membrane depolarisation is short lasting, even if the depolarisation is maintained
- The most important channels in this group are selective sodium, potassium or calcium channels

A. Voltage-activated Na⁺ channel



VOLTAGE-GATED SODIUM AND CALCIUM CHANNELS

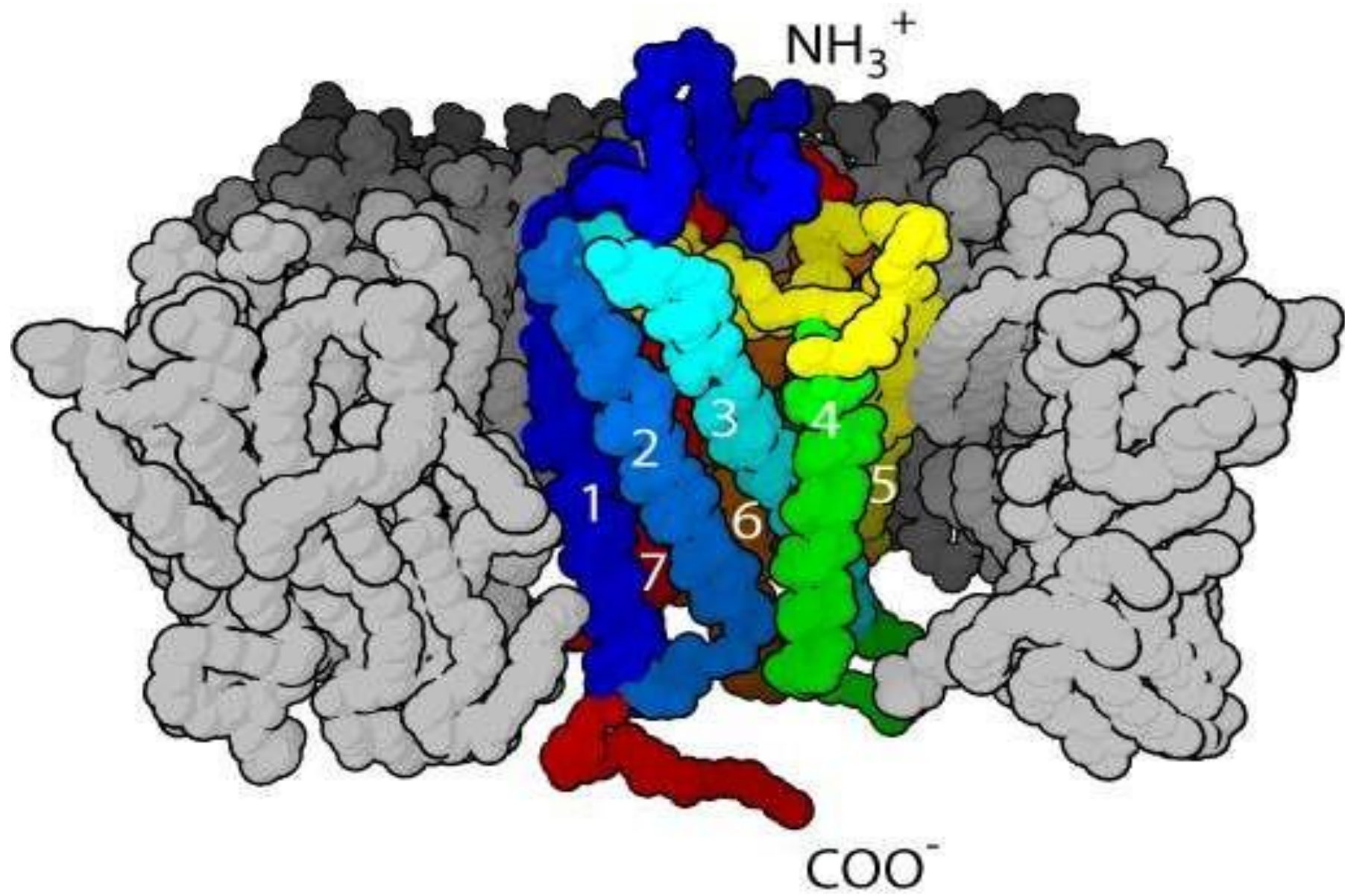


Ligand Gated receptors v/s VOCs

- ROCs appear to assume only two states whereas VOCs undergo a third state called refractory (inactivated) state.
- Voltage gated channels have no major endogenous modulator (like Ach)

TYPE 2 : G – PROTEIN – COUPLED RECEPTORS

- Alfred Goodman Gilman & Martin Rodbell (1994)
- Metabotropic or 7 – Transmembrane/ Heptahelical receptors
- Largest family
- Timescale : Seconds
- Location : Membrane
- Effector : Channel or Enzyme
- Coupling : G- Protein
- Examples : adrenoceptors, Muscarinic Ach, histamine, serotonin, opioid, cannabinoid, amine, peptide, prostanoid receptors



MOLECULAR STRUCTURE

- Single polypeptide chain 1100 residues. 7 Transmembrane α -helices, an extracellular N-terminal domain and intracellular C-terminal domain
- 3rd cytoplasmic loop couples to the G- Protein

| G-protein-coupled receptor families ^a | | |
|---|---|--|
| Family | Receptors ^b | Structural features |
| A: rhodopsin family | The largest group. Receptors for most amine neurotransmitters, many neuropeptides, purines, prostanoids, cannabinoids, etc. | Short extracellular (N terminal) tail. Ligand binds to transmembrane helices (amines) or to extracellular loops (peptides) |
| B: secretin/ glucagon receptor family | Receptors for peptide hormones, including secretin, glucagon, calcitonin | Intermediate extracellular tail incorporating ligand-binding domain |
| C: metabotropic glutamate receptor/ calcium sensor family | Small group Metabotropic glutamate receptors, GABA _B receptors, Ca ²⁺ -sensing receptors | Long extracellular tail incorporating ligand-binding domain |

G-PROTEINS AND THEIR ROLE

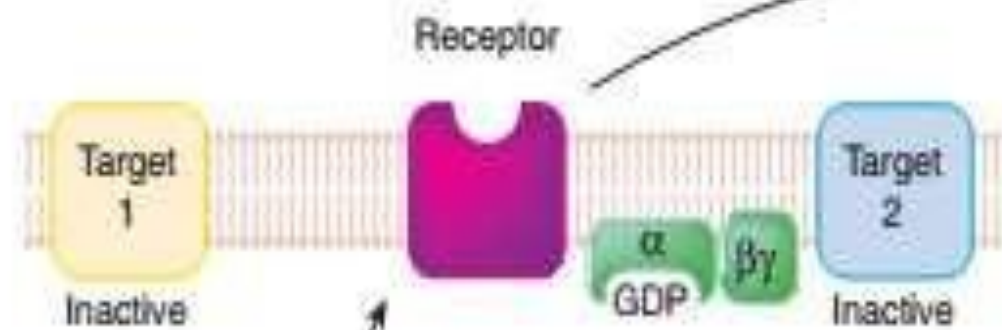
- Family of membrane-resident proteins whose function is to **recognize activated GPCRs** and **pass on the message to the effector systems** that generate a cellular response

- Function of G-Protein:

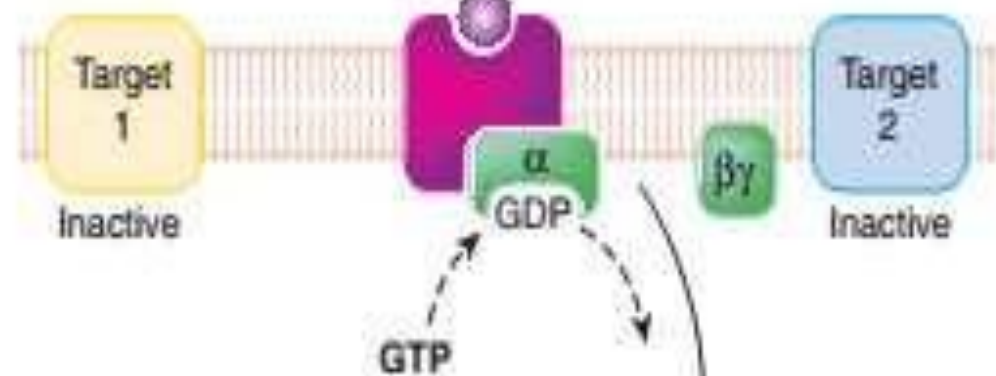
3 subunits (α , β , γ) are anchored to the membrane through attached lipid residues

Coupling of the α subunit to an agonist-occupied receptor causes bound GDP to exchange with intracellular GTP; α -GTP complex dissociates from receptor and from $\beta\gamma$ complex

Resting state



Receptor occupied by agonist



GTP hydrolysed



Target proteins activated



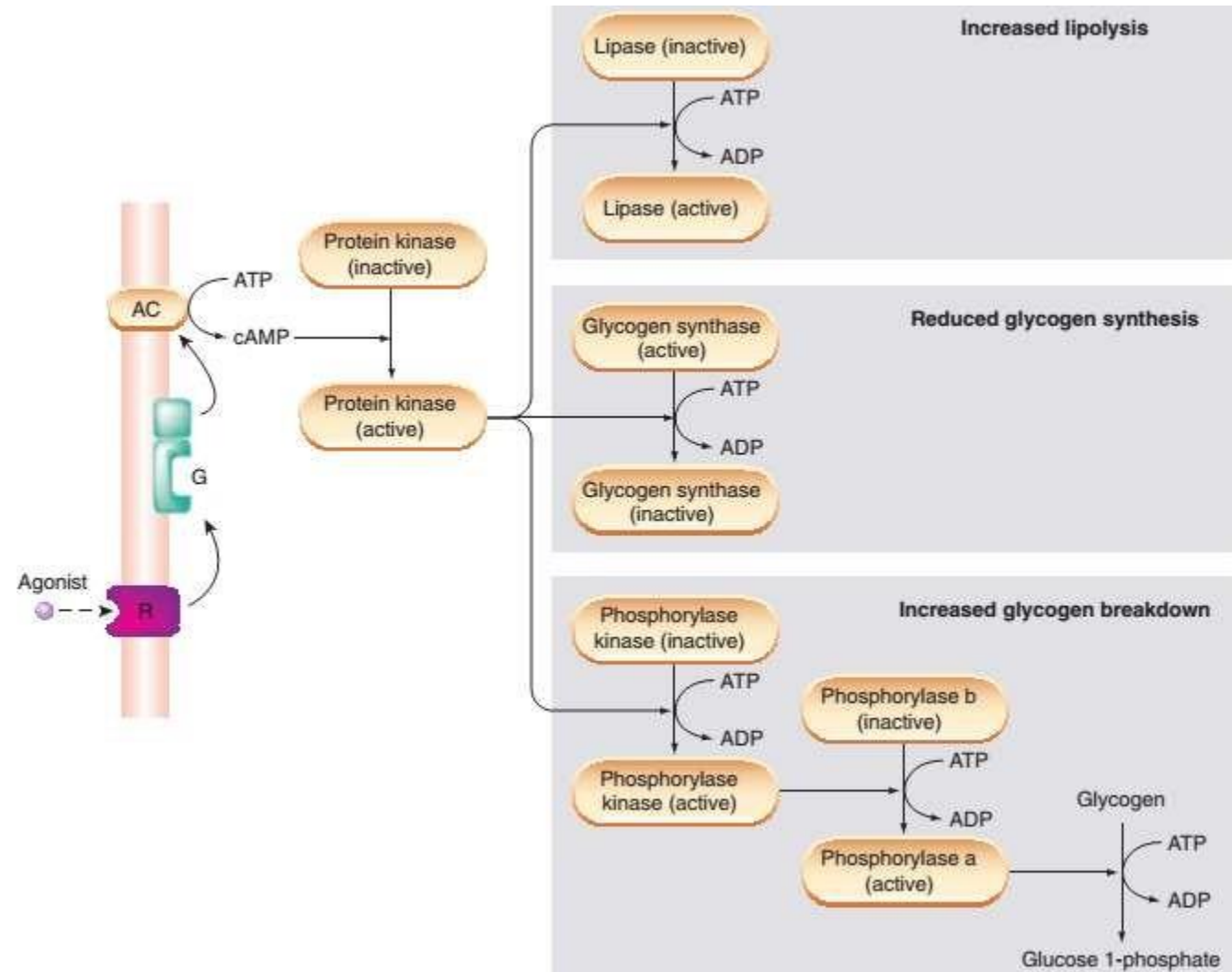
- Amplification : A single agonist–receptor complex can activate several G-protein molecules, each of these can remain associated with the effector enzyme for long enough to produce many molecules of product (Second messenger)
- Four main classes of G-protein (Gs, Gi, Go and Gq) show selectivity with respect to both the receptors and the effectors with which they couple
- Cholera toxin and pertussis toxin

| Subtypes | Associated receptors | Main effectors |
|--------------------------------------|--|--|
| Gα subunits | | |
| G α_s | Many amine and other receptors (e.g. catecholamines, histamine, serotonin) | Stimulates adenylyl cyclase, causing increased cAMP formation |
| G α_i | As for G α_s , also opioid, cannabinoid receptors | Inhibits adenylyl cyclase, decreasing cAMP formation |
| G α_o | As for G α_s , also opioid, cannabinoid receptors | ?Limited effects of α subunit (effects mainly due to $\beta\gamma$ subunits) |
| G α_q | Amine, peptide and prostanoid receptors | Activates phospholipase C, increasing production of second messengers inositol trisphosphate and diacylglycerol |
| G $\beta\gamma$ subunits | All GPCRs | As for G α subunits (see above). Also: <ul style="list-style-type: none"> • activate potassium channels • inhibit voltage-gated calcium channels • activate GPCR kinases (GRKs, • activate mitogen-activated protein kinase cascade |

Targets for G-Proteins

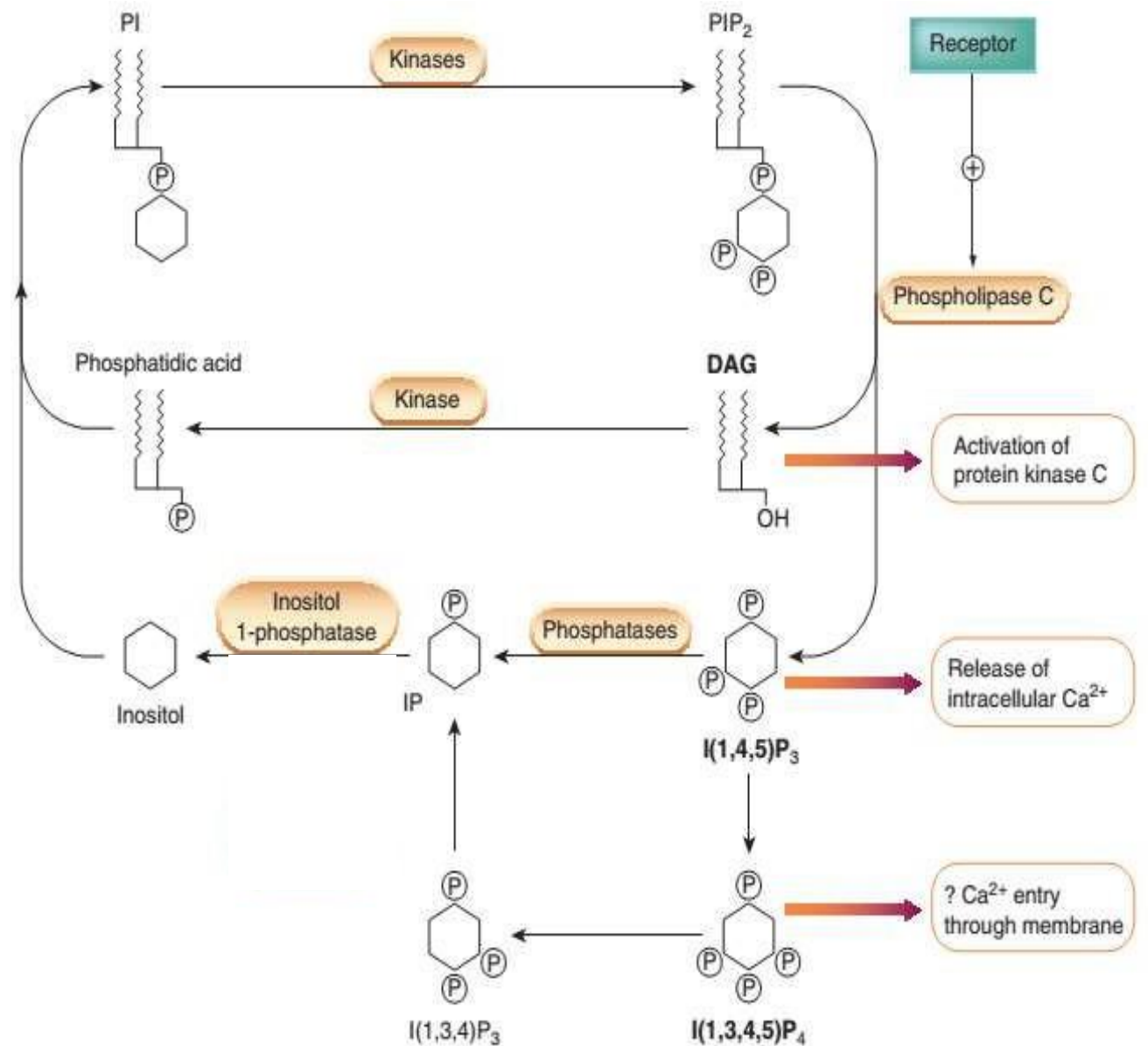
➤ Adenylate cyclase

- catalyses formation of the intracellular messenger cAMP
- cAMP activates various protein kinases that control cell function in many different ways by causing phosphorylation of various enzymes, carriers & other proteins



➤ Phospholipase C/IP3/DAG

- catalyzes the formation of IP3 and DAG from membrane phospholipid
- IP3 increases free cytosolic **Ca²⁺** (releasing Ca²⁺ from intracellular compartments) which initiates many events
- DAG activates **protein kinase C**, which controls many cellular functions by phosphorylating proteins



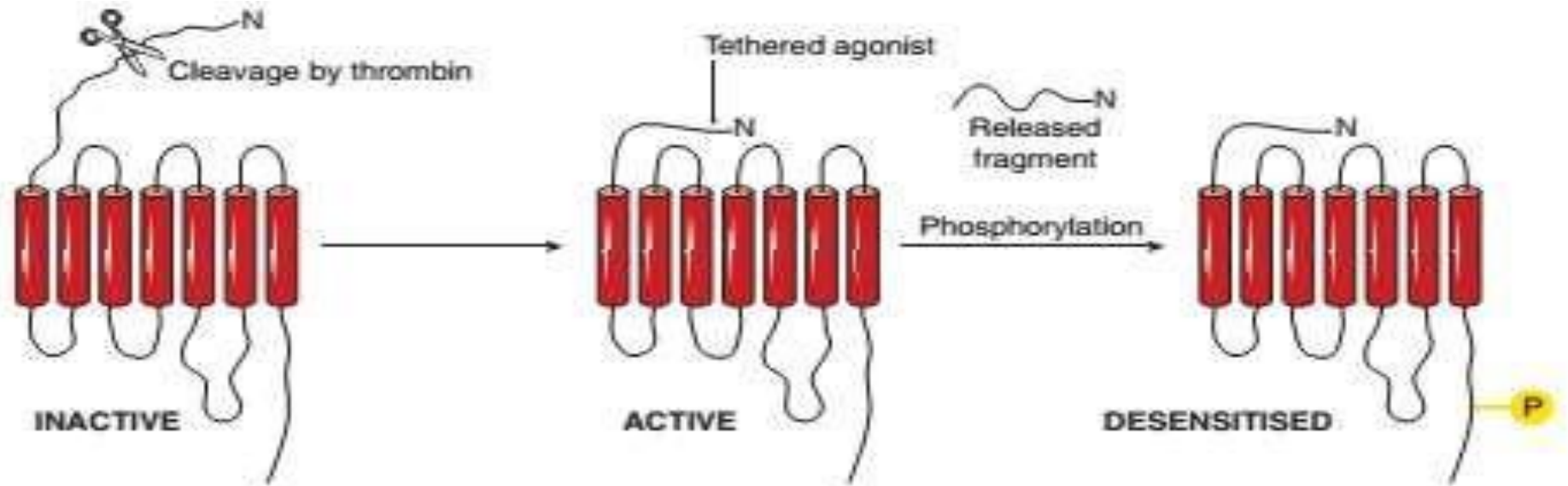
- Ion Channels appears to be general mechanism for controlling K^+ and Ca^{++} channels by direct interaction between the $\beta\gamma$ -subunit of G_0 and the channel
- Phospholipase A₂ (formation of arachidonic acid and eicosanoids)
- The Rho/Rho kinase system $G_{12/13}$ type G-protein. α subunit interacts with *guanosine nucleotide exchange factor*, which facilitates GDP–GTP exchange at another GTPase, Rho. On exchange Rho activated & activates Rho kinase - phosphorylates substrate proteins
- The MAP kinase system activated by cytokines and growth factors acting on kinase-linked receptors and by GPCR ligands. Controls processes involved in cell division, apoptosis and tissue regeneration

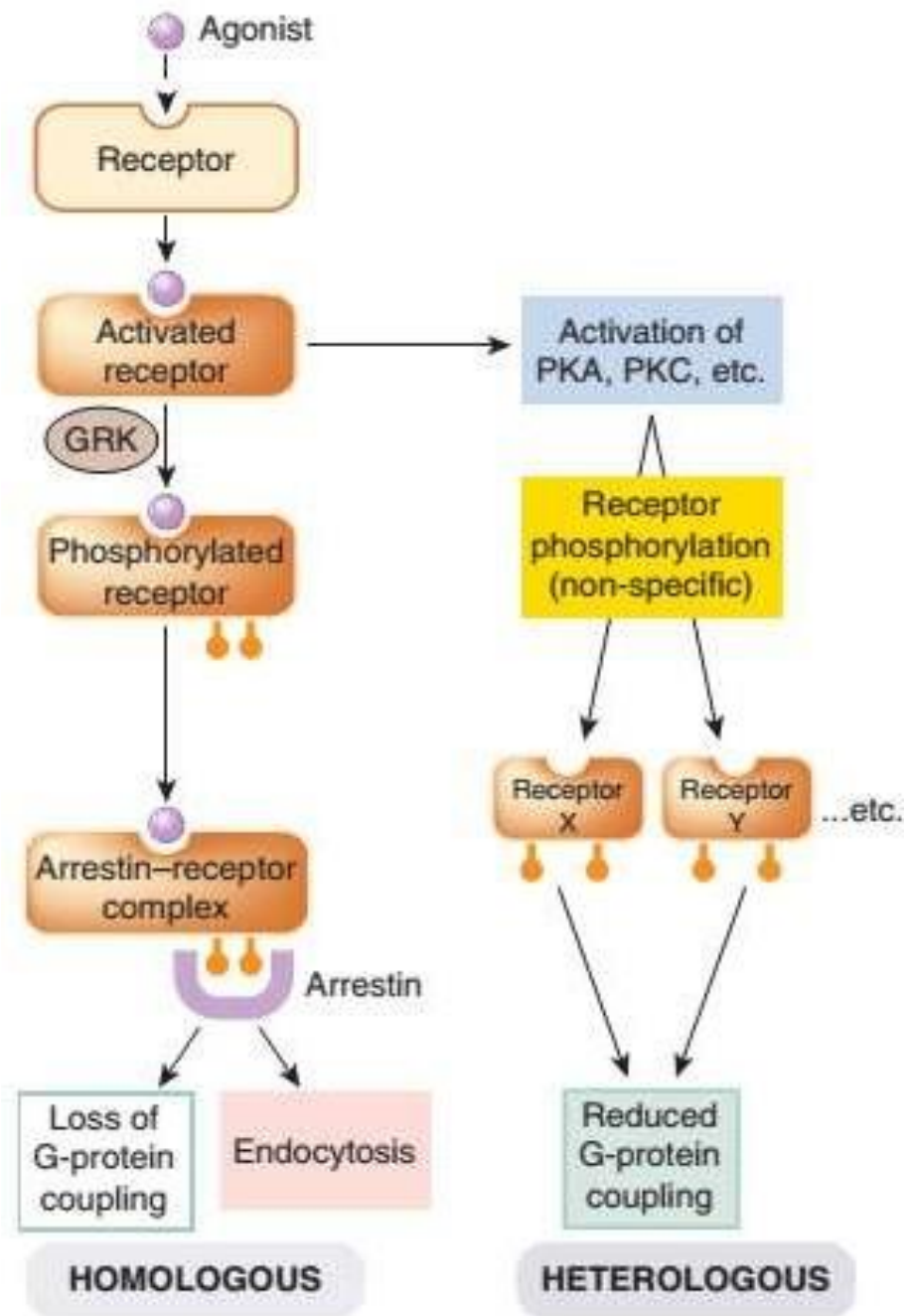
Protease Activated Receptors

End of extracellular N-terminal tail of the receptor snipped off to expose 5-6 N-terminal residues that bind to receptor domains in extracellular loops, functioning as 'tethered agonist'

A PAR molecule can be activated only once

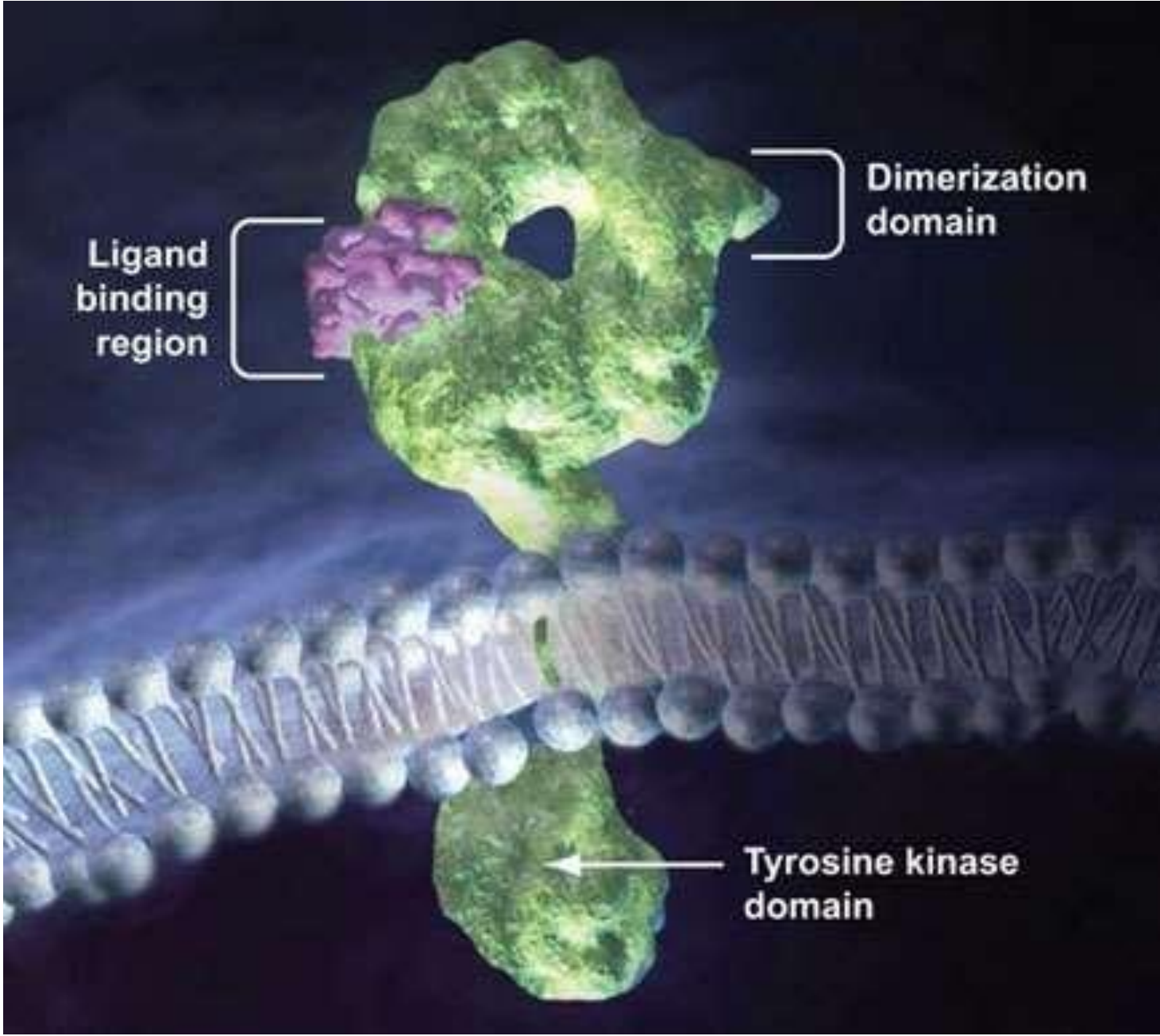
Inactivation by further proteolytic cleavage that frees tethered ligand, or by desensitization





TYPE 3 : KINASE LINKED AND RELATED RECEPTORS

- Large, heterogenous group responding mainly to protein mediators.
- Timescale : Hours
- Location : Membrane
- Effector : Protein Kinases
- Coupling : Direct
- Examples : Insulin, Growth Factors, Cytokine, ANF receptors




MOLECULAR STRUCTURE AND TYPES

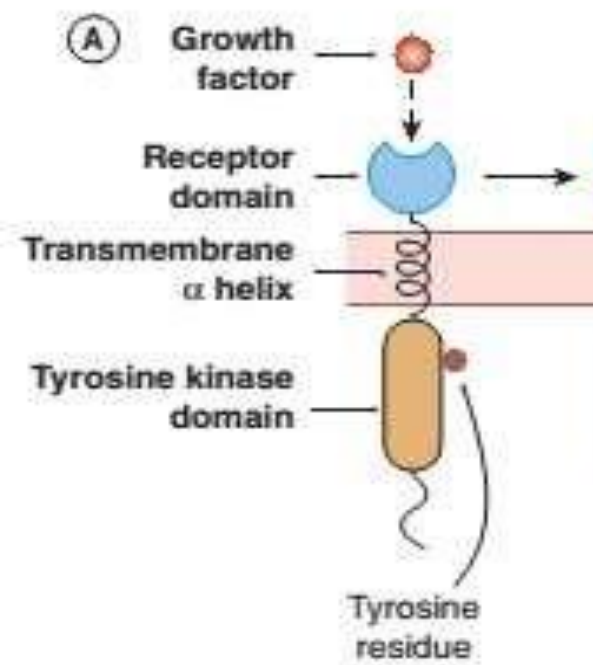
- Large proteins - single chain ~ 1000 residues, single membrane-spanning helical region, with a large extracellular ligand-binding domain, and an intracellular domain of variable size and function

Types –

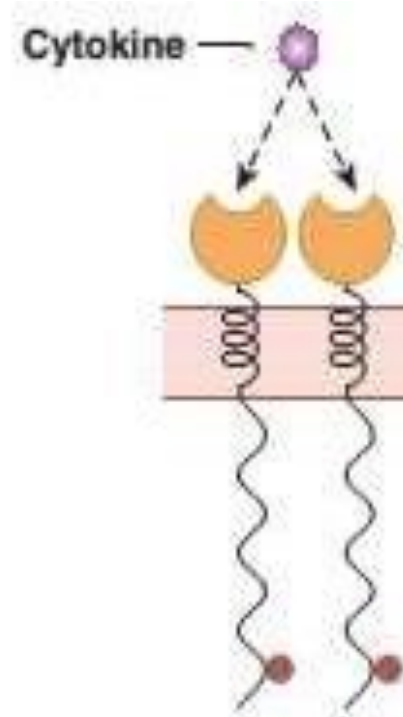
- Receptor tyrosine kinases (RTKs)
- Serine/threonine kinases
- Cytokine receptors. lack intrinsic enzyme activity. When occupied, they associate with and activate, a cytosolic tyrosine kinase, such as Jak (the Janus kinase)

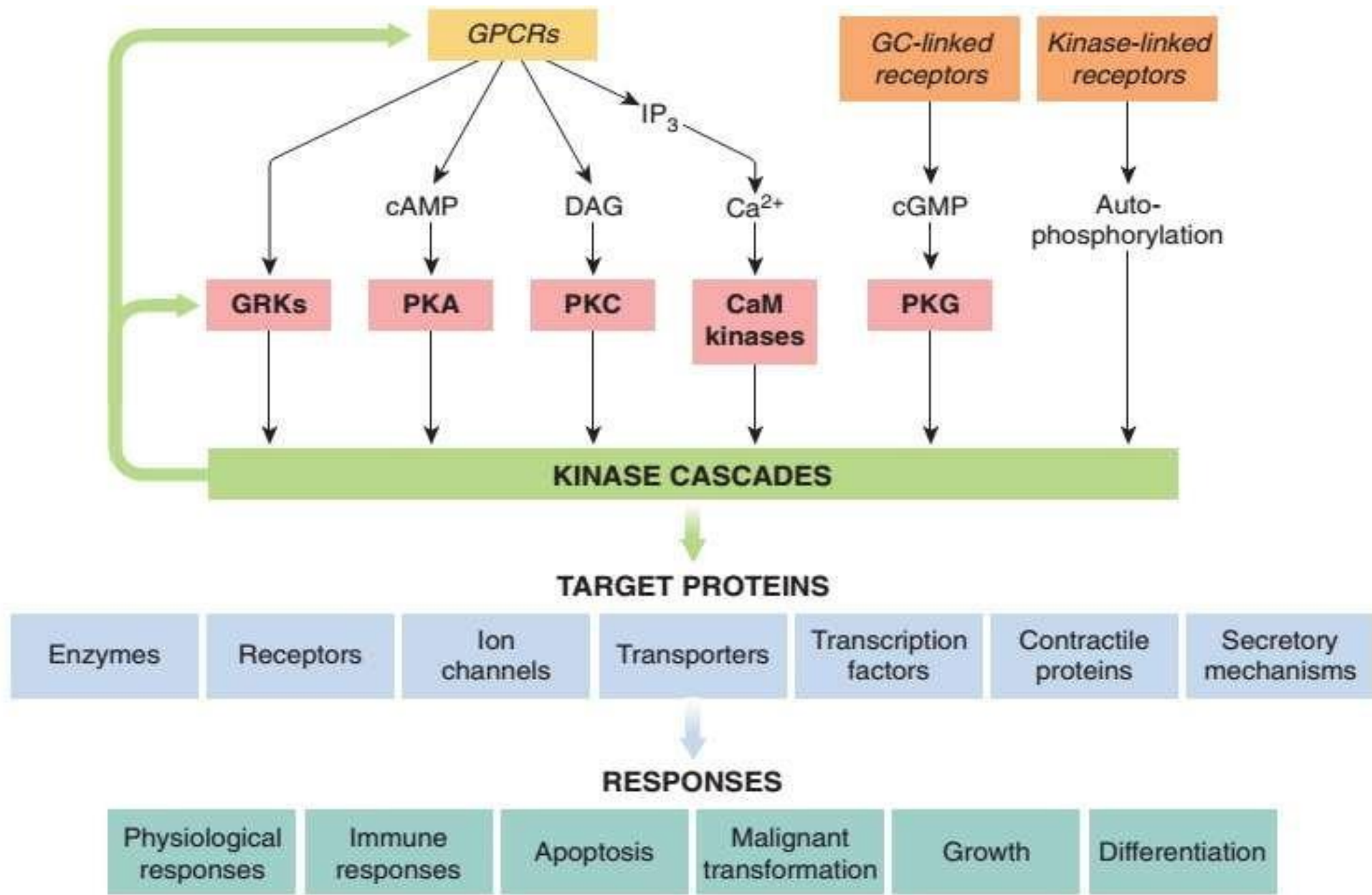
SIGNAL TRANSDUCTION

- Generally involves dimerization  autophosphorylation of tyrosine residues, act as acceptors for the SH2 domains of intracellular proteins
- Involved mainly in events controlling cell growth and differentiation, and act indirectly by regulating gene transcription
- Two important pathways are:
 - the Ras/Raf/ MAP kinase pathway - cell division, growth and differentiation.
 - the Jak/Stat pathway activated by many cytokines - controls the synthesis and release of many inflammatory mediators



(B)





TYPE 4 : NUCLEAR RECEPTORS

- Regulate gene transcription. ?Misnomer
- Timescale : Hours
- Location : Intracellular
- Effector : Gene transcription
- Coupling : Via DNA
- Examples : Steroid Hormones, Thyroid Hormones, Retinoic acid and Vitamin D receptors
- This family includes a great many (40%) orphan receptors

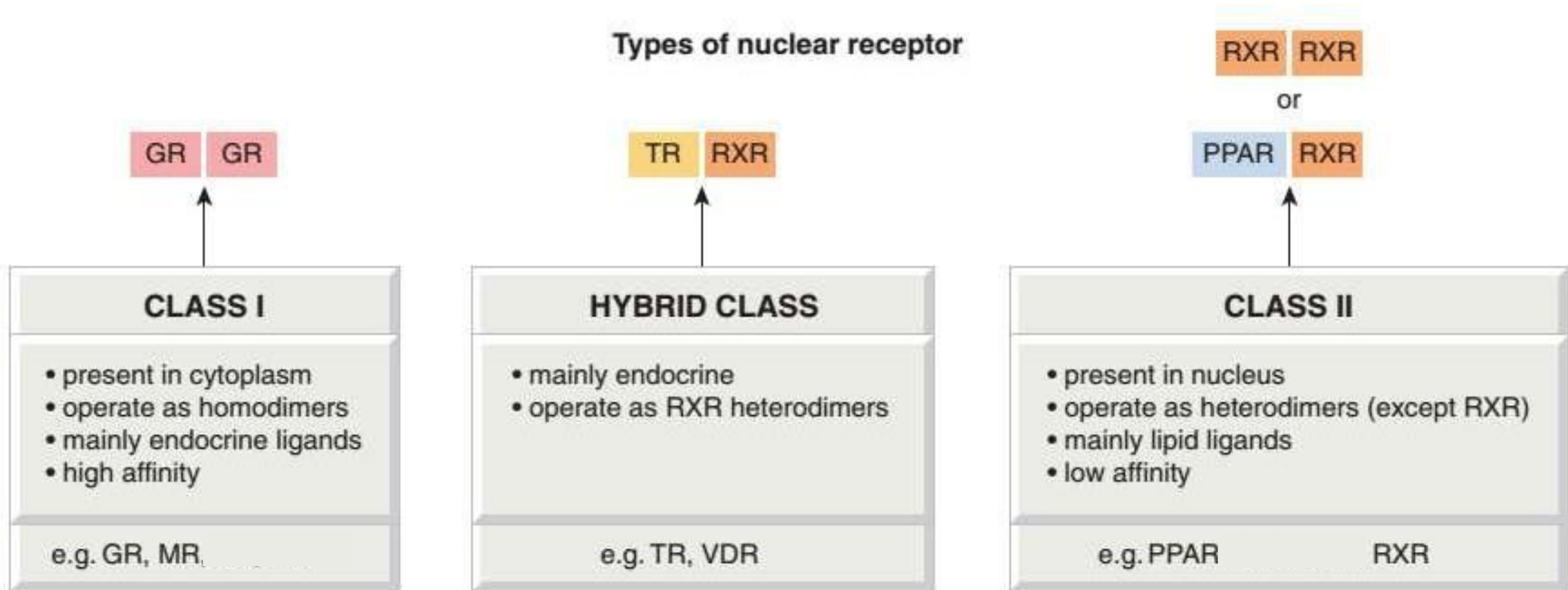
MOLECULAR STRUCTURE

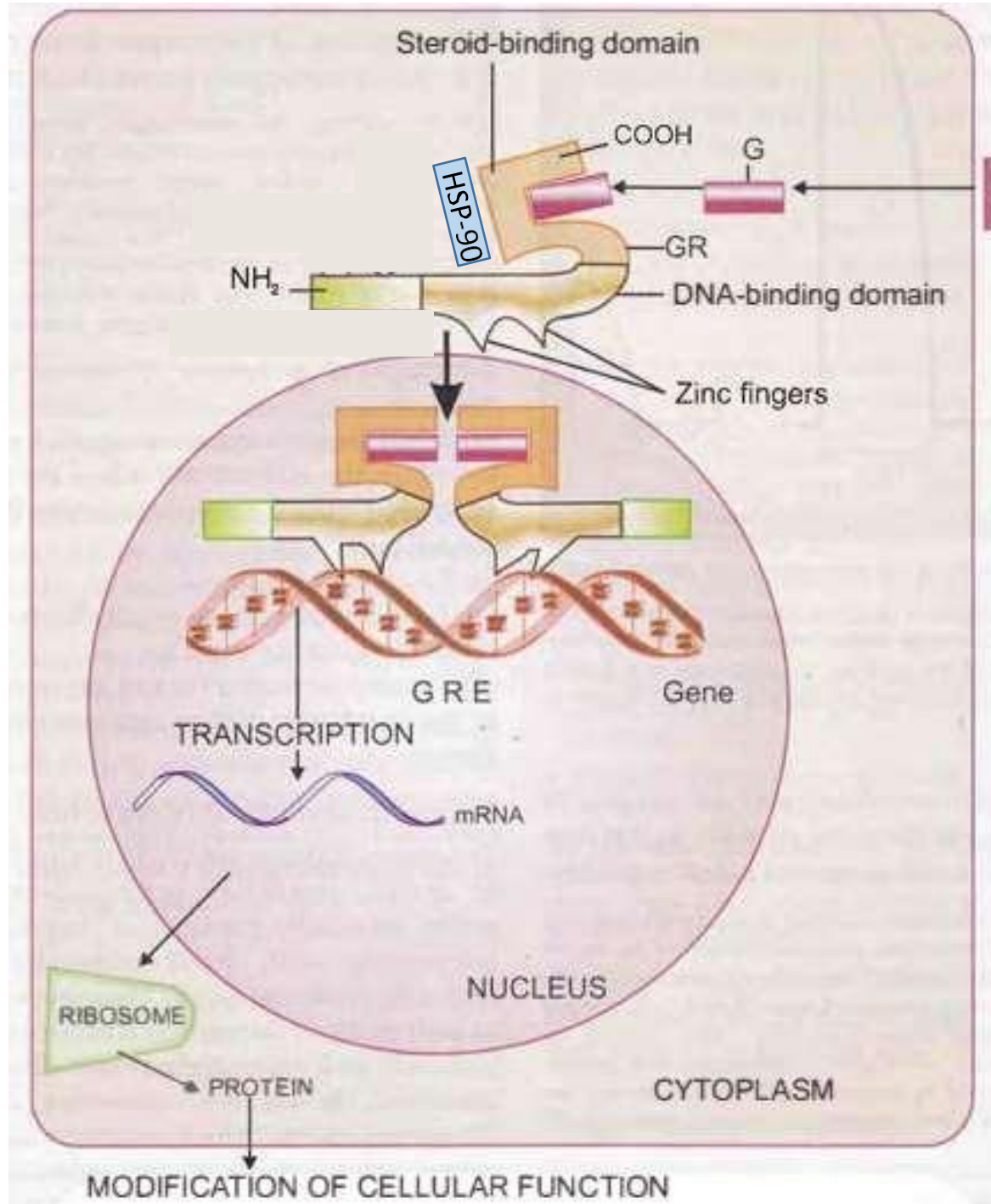


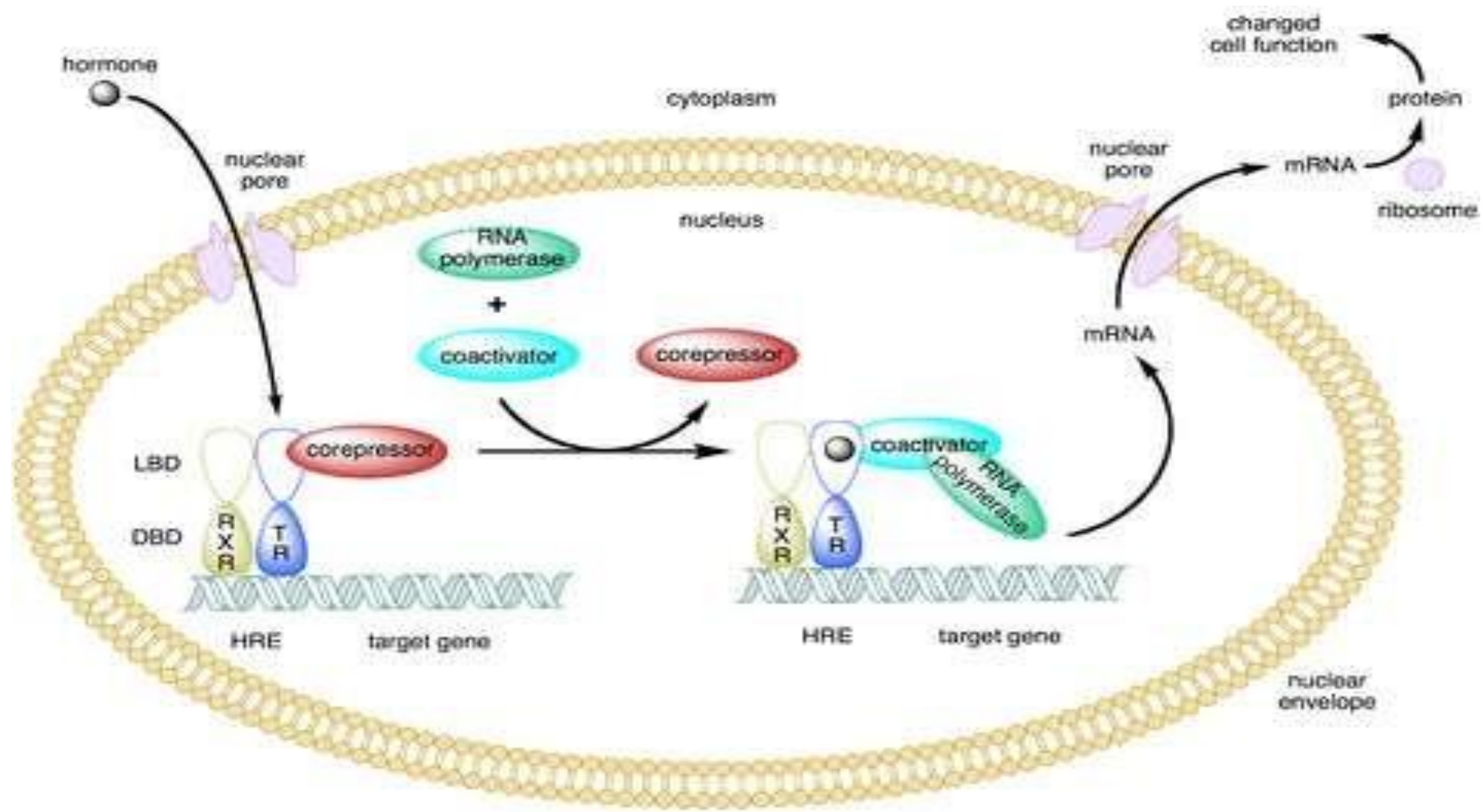
- The *N-terminal domain* harbours the *AF1* site that binds to other cell specific transcription factors and modifies the binding or activity of the receptor itself
- The *Core domain* consists of the structure responsible for DNA recognition and binding. They bind to the *hormone response elements* located in genes to regulate them
- *Hinge region* in the molecule allows it to dimerise with other NRs and also to exhibit DNA binding
- *C-terminal domain* contains the ligand binding module and is specific to each class of receptor

CLASSIFICATION OF NUCLEAR RECEPTORS

Types of nuclear receptor

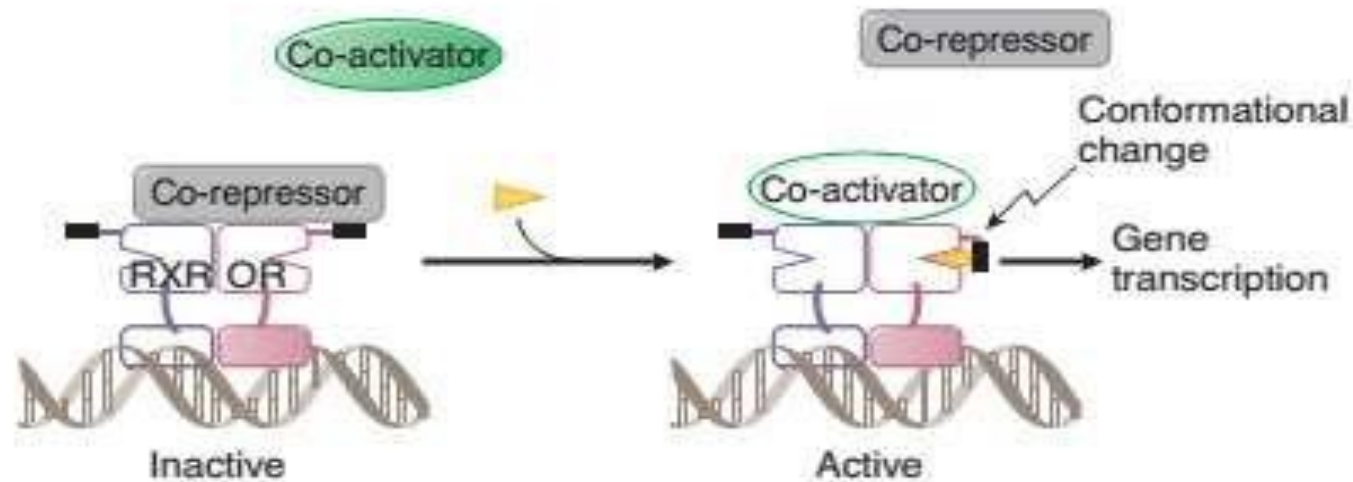






CONTROL OF GENE TRANSCRIPTION

- Hormone Response Elements : Short (4-5 bp) sequences of DNA to which the NRs bind to modify gene transcription, present symmetrically in pairs.
- Recruits *co-activators* or *co-repressors* to modify



- This receptor family responsible for the pharmacology of approximately 10% prescription drugs

SUMMARY

