PHARMACODYNAMICS

INTRODUCTION

- Pharmacodynamics:
  - It starts with describing what the drugs do & body response to it.
  - Definition: Study of biochemical & physiological effects of drug and their mechanism of action at **organ level** as well as **cellular level**

DRUG ACTION BY PHY-CHEMICAL PROPERTIES

Color	– Tincture
Physical mass	– Ispaghula,
Physical form	– Dimethicone (antifoaming)
Smell	- Volatile Oils
Taste	- Bitters
Osmotic action	– Mannitol, Magsulf
Adsorption	– Activated Charcoal
Soothing-demulcent	– Soothing agents like calamine
Oxidizing property	– Pot. Permanganate

PRINCIPLES OF DRUG ACTION

- The basic types of drug action can be broadly classed as:
- Stimulation
- Depression
- Irritation
- Replacement

STIMULATION

- Selective enhancement of the level of activity of specialized cells.
- Adrenaline stimulates heart.
- Pilocarpine stimulates salivary glands.

DEPRESSION

Selective depression activity of special cells.

- Barbiturates depress CNS

IRRITATION

- A nonselective, noxious effect and particularly applied to less specialized cells (epithelium, connective tissue).
- Strong irritation results in inflammation, corrosion, necrosis & morphological damage.

REPLACEMENT

Use of natural metabolites, hormones or their congeners in deficiency states.

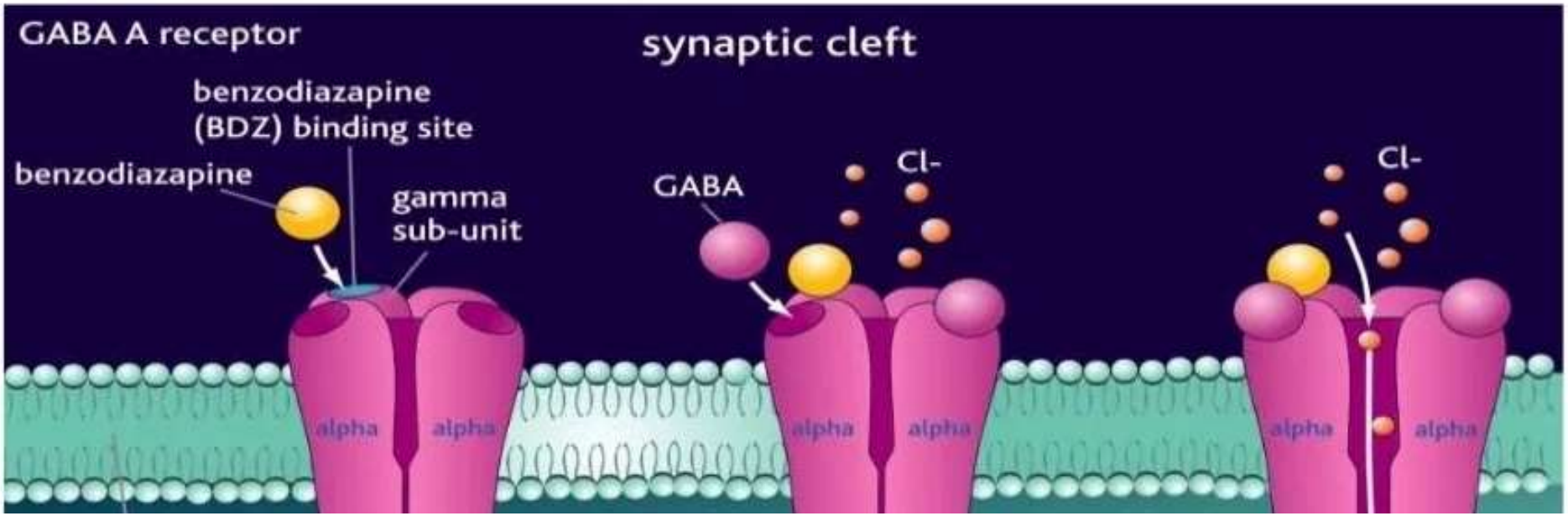
- Levodopa in parkinson

CYTOTOXIC ACTION

- Selective cytotoxic action on invading parasites or cancer cells, attenuating them without significantly affecting the host cells.
- Utilized for cure/palliation of infections and neoplasms.

Ex.- penicillin, chloroquine, zidovudine, cyclophosphamide, etc.

MECHANISM OF DRUG ACTION



MECHANISM OF DRUG ACTION

Only a handful of drugs act by virtue of their simple physical or chemical property; examples are:

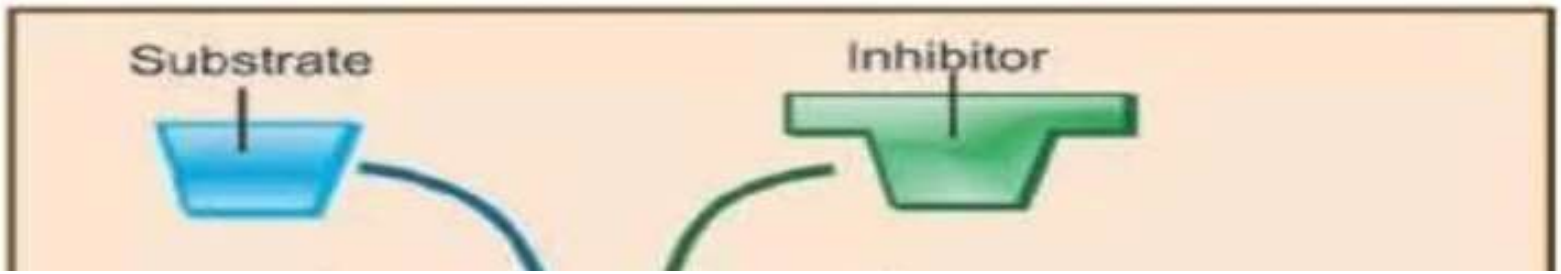
- Bulk laxatives (ispaghula)—physical mass
- Paraamino benzoic acid—absorption of UV rays
- Activated charcoal—adsorptive property
- Mannitol, mag. sulfate—osmotic activity
- ^{131}I and other radioisotopes—radioactivity
- Antacids—neutralization of gastric HCl

- Majority of drugs produce their effects by interacting with a discrete target biomolecule, which usually is a protein. Such mechanism confers selectivity of action to the drug.

- Functional proteins that are targets of drug action can be grouped into four major categories:
  - Enzymes,
  - Ion channels,
  - Transporters and

ENZYMES

- Almost all biological reactions are carried out under catalytic influence of enzymes;
- Drugs can either increase or decrease the rate of enzymatically mediated reactions.



ENZYME INHIBITION

- Selective inhibition of a particular enzyme is a common mode of drug action.
- Such inhibition is either competitive or noncompetitive.

Enzyme	Endogenous substrate	Competitive inhibitor
• Cholinesterase	Acetylcholine	Physostigmine, Neostigmine
• Monoamine-oxidase A (MAO-A)	Catecholamines	Moclobemide
• Dopa decarboxylase	Levodopa	Carbidopa, Benserazide

ION CHANNELS

- *Ligand gated channels* (e.g. nicotinic receptor)
- G-proteins are termed *G-protein regulated channels* (e.g.cardiac β1 adrenergic receptor activated Ca2+ channel).

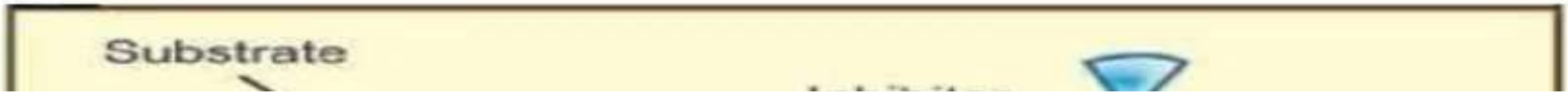
...CONTD.

- Drugs can also act on *voltage operated* and *stretch sensitive channels* by directly binding to the channel and affecting ion movement through it, e.g. local anaesthetics which obstruct voltage sensitive Na+ channels.

Certain drugs modulate opening and closing of the channels, e.g.:

TRANSPORTERS

- Several substrates are translocated across membranes by binding to specific transporters which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the conc. gradient using metabolic energy.



RECEPTORS

Drugs usually do not bind directly with enzymes, channels, transporters or structural proteins, but act through specific macromolecules – RECEPTORS

Definition: It is defined as a macromolecule or binding site located on cell surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other function, e.g. Muscarinic (M type) and Nicotinic (N type) receptors of Cholinergic system

DRUG – RECEPTOR INTERACTION

- **Agonist:** An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.
- **Inverse agonist:** An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.
- **Antagonist:** An agent which prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.

- **Agonists:** have both affinity and maximal intrinsic activity (IA = 1), e.g. adrenaline, histamine, morphine.

- **Competitive antagonists:** have affinity but no intrinsic activity (IA = 0), e.g. propranolol, atropine, chlorpheniramine, naloxone.

- **Partial agonists:** have affinity and submaximal intrinsic activity (IA between 0 and 1), e.g. dichloroisoproterenol (on β adrenergic receptor), pentazocine (on μ opioid receptor).

- **Inverse agonists:** have affinity but intrinsic activity with a minus sign (IA between 0 and –1),e.g. DMCM (on

Drug – Receptor occupation theory – Clark`s equation (1937)

- Drugs are small molecular ligands (pace of cellular function can be altered)
- Drug (D) and receptor (R) interaction governed by "law of mass action"
- Effect (E) Is the direct function of the Drug-Receptor complex

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \longrightarrow \mathbf{E} \text{ (direct function of DR complex}$$

...CONTD.

- Affinity: Ability to bind with a Receptor
- Intrinsic activity (IA): Capacity to induce functional change in the receptor
- Competitive antagonists: have Affinity but no IA
- Therefore, a theoretical quantity (S) – denoting strength was interposed

RECEPTOR SUBTYPES

Evaluation of receptors and subtypes – lead to discovery of various newer target molecules

Example Acetylcholine - Muscarinic and Nicotinic

- M1, M2, M3 etc.
- NM and NN
- α (alpha) and β (beta) ….

Criteria of Classification:

- Pharmacological criteria – potencies of selective agonist and antagonists – Muscarinic, nicotinic, alpha and beta

ACTION – EFFECTS !

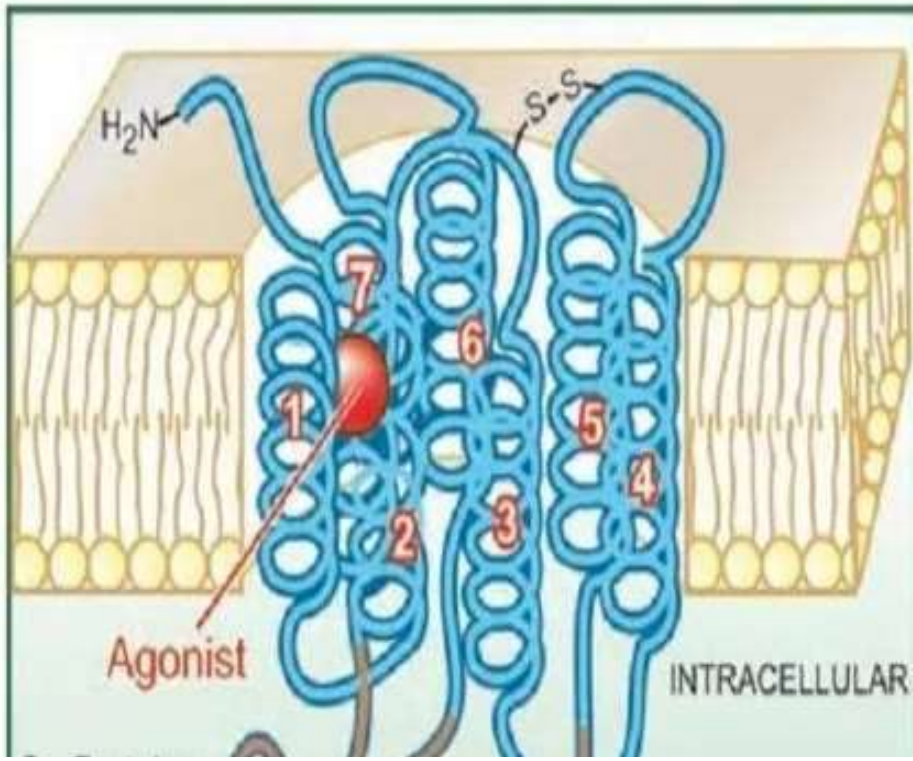
- **Receptors :** Two essential functions:
  - Recognition of specific ligand molecule
  - Transduction of signal into response
  - **Two Domains:**
    - Ligand binding domain (coupling proteins)
    - Effectors Domain – undergoes functional conformational change
- **"Action":** Initial combination of the drug with its receptors resulting in a conformational change (agonist) in the later, or prevention of conformational change (antagonist)

TRANSDUCER MECHANISM

- Most transmembrane signaling is accomplished by a small number of different molecular mechanisms (transducer mechanisms)
- Large number of receptors share these handful of transducer mechanisms to generate an integrated and amplified response
- Mainly 4 (four) major categories:
  1. **G-protein coupled receptors (GPCR)**
  2. **Receptors with intrinsic ion channel**

G PROTEIN COUPLED RECEPTOR

- Large family of cell membrane receptors linked to the effector enzymes or channel or carrier proteins through one or more GTP activated proteins (G- proteins).
- The molecule has 7 α-helical membrane spanning hydrophobic amino acid segments – 3 extra and 3 intracellular loops.
- Agonist binding - on extracellular face and cytosolic segment binds coupling G-protein



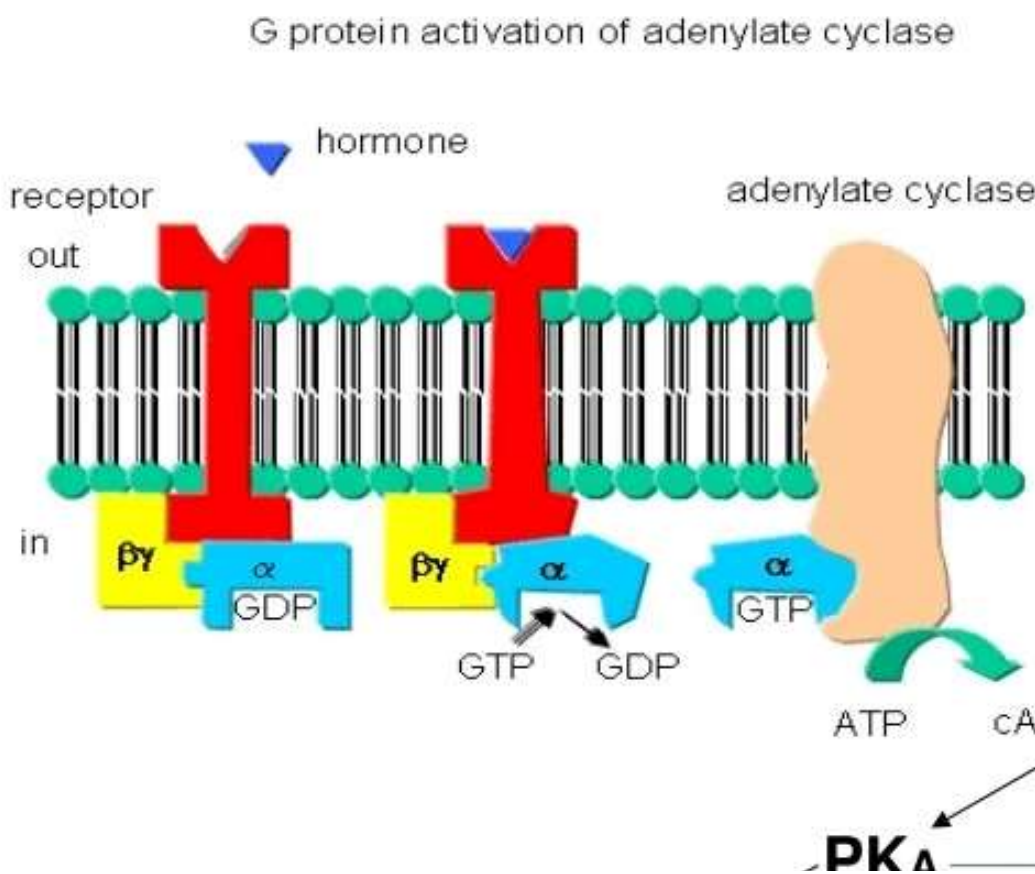
...CONTD.

- G-proteins float on the membrane with exposed domain in cytosol.
- Heteromeric in composition with alpha, beta and gamma subunits
- Inactive state – GDP is bound to exposed domain
- Activation by receptor GTP displaces GDP
- The α subunit carrying GTP dissociates from the other 2 – activates or inhibits "effectors"
- βγ subunits are also there for smooth activity

GPCR – 3 MAJOR PATHWAYS

1. Adenylyl cyclase: cAMP pathway
2. Phospholipase C: IP3-DAG pathway
3. Channel regulation

1. Adenylyl cyclase: cAMP pathway

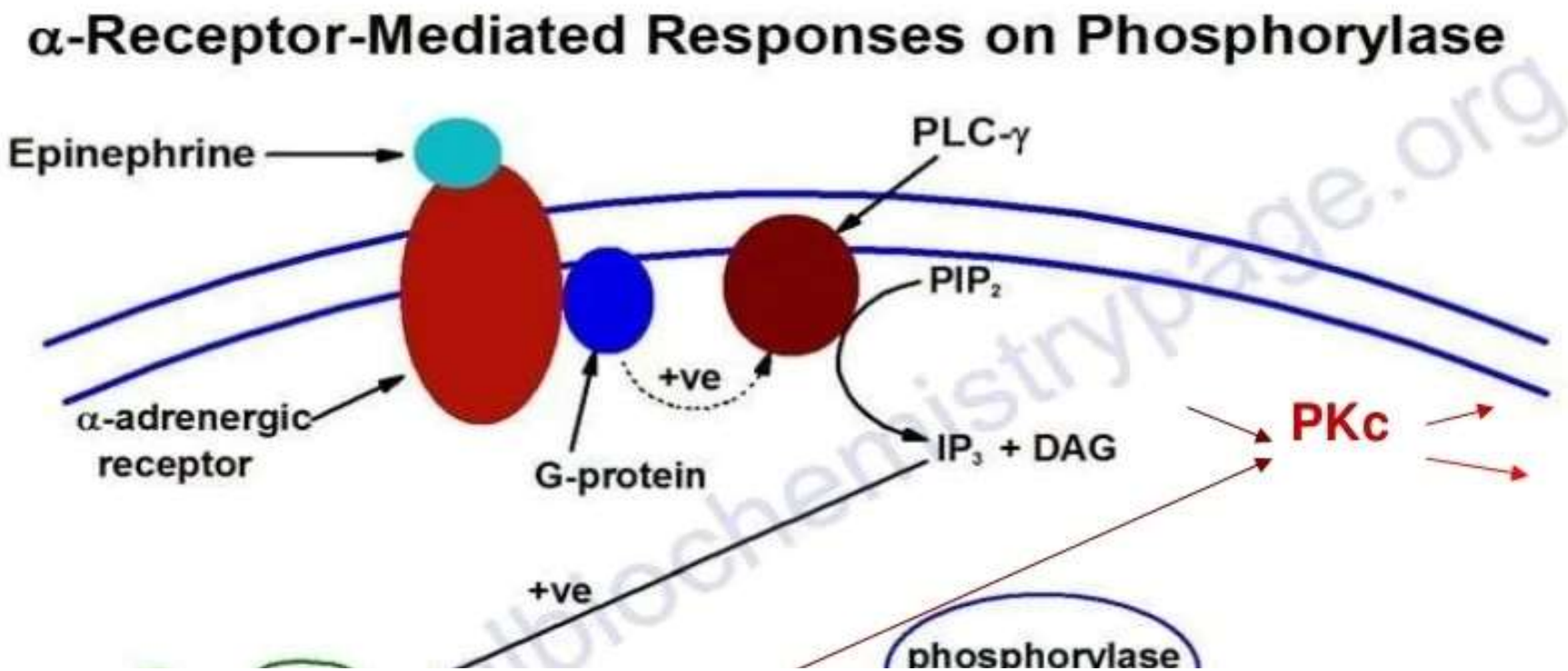


PKA alters the functions of many Enzymes, ion channels, transporters and structural proteins

Adenylyl Cyclase: cAMP pathway

- Main Results:
  - Increased contractility of heart/impulse generation
  - Relaxation of smooth muscles
  - Lipolysis & Glycogenolysis
  - Inhibition of Secretions
  - Modulation of junctional transmission
  - Hormone synthesis
  - Opens specific type of Ca++ channel – Cyclic nucleotide gated channel (CNG) - - -heart, brain and kidney

2. Phospholipase C (PLC):

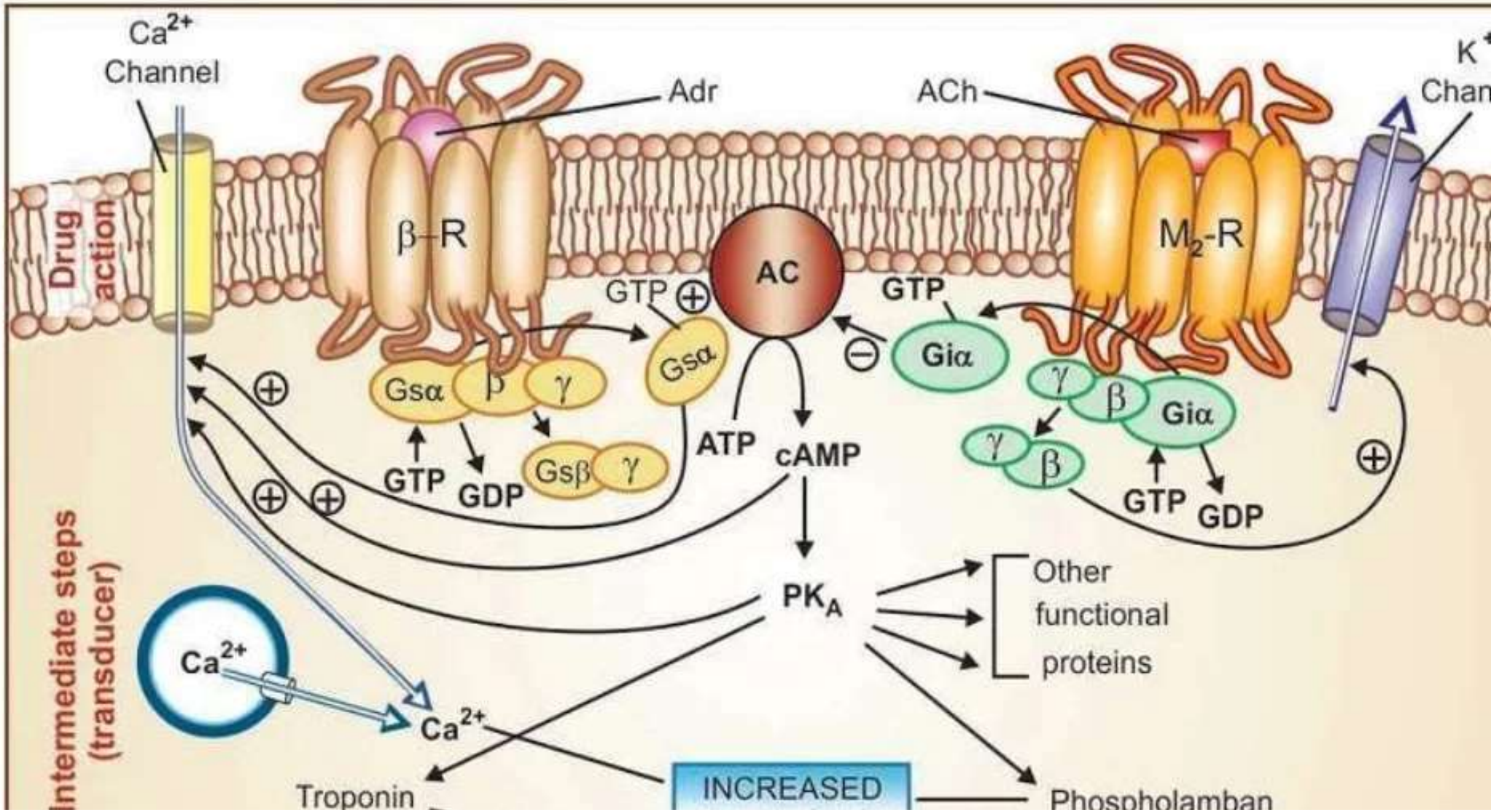


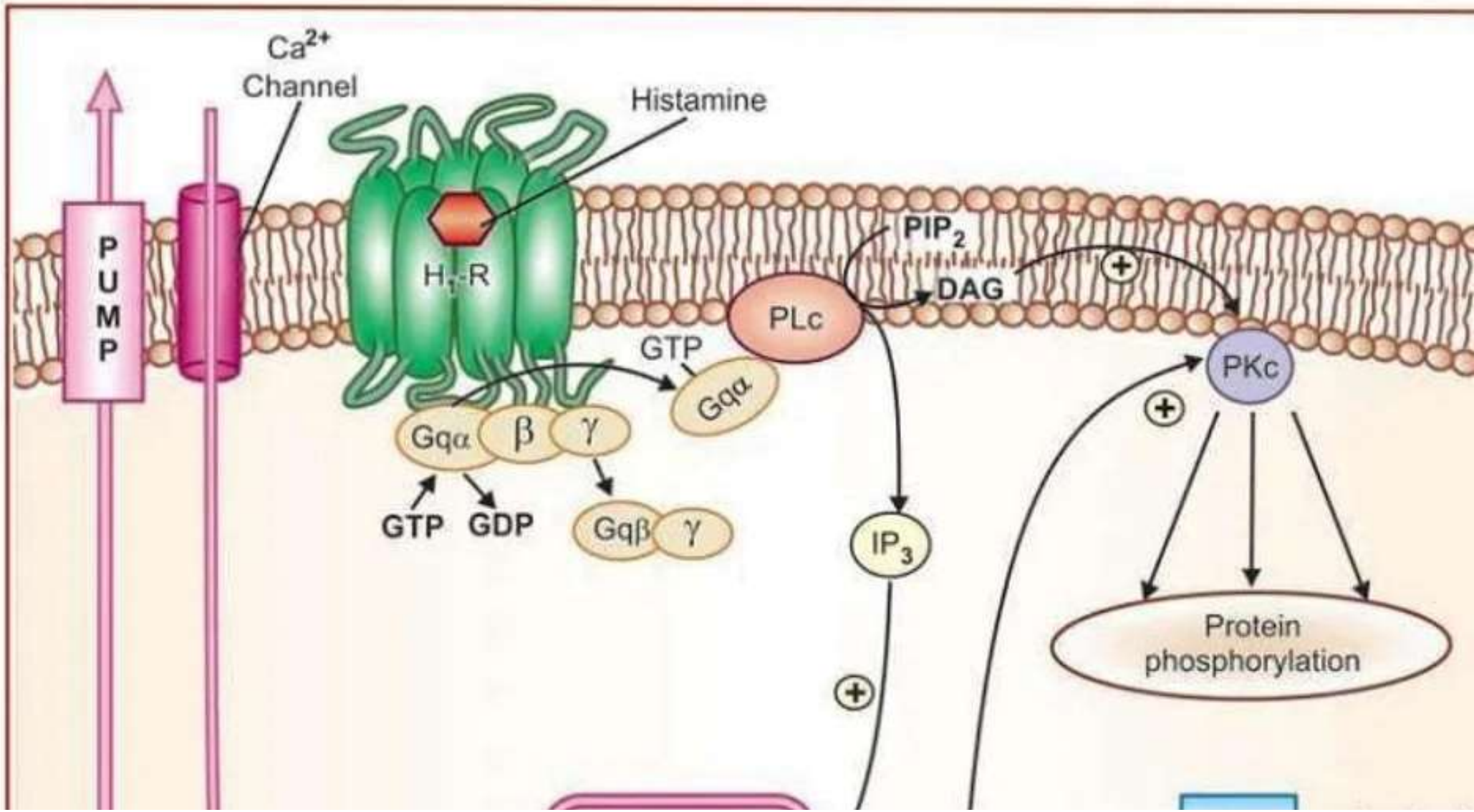
IP_3-DAG pathway

- Main Results:
  - Mediates /modulates contraction
  - Secretion/transmitter release
  - Neuronal excitability
  - Intracellular movements
  - Eicosanoid synthesis

3. Channel regulation

- Activated G-proteins can open or close ion channels
  – Ca++, Na+ or K+ etc.
- These effects may be without intervention of any of above mentioned 2nd messengers – cAMP or IP/DAG
- Bring about depolarization, hyperpolrization or Ca ++ changes etc.
  - Gs : Adenylyl cyclase activation, Ca2+ channel opening (myocardium and skeletal muscles)
-
  - Gi : Adenylyl cyclase inhibition, K+ channel opening
  - Go : Ca2+ channel inhibition(open K+ channel in heart and muscle


Ca2+ Channel
Adr
ACh
K+ Chan
Drug action
β–R
AC
M2-R
GTP
Gsα
Giα
Gsα β γ
GTP GDP
Gsβ γ
ATP
cAMP
γ β Giα
γ β
GTP GDP
PKA
Other functional proteins
Ca2+
Ca2+
Troponin
INCREASED
Phospholamban
Intermediate steps (transducer)

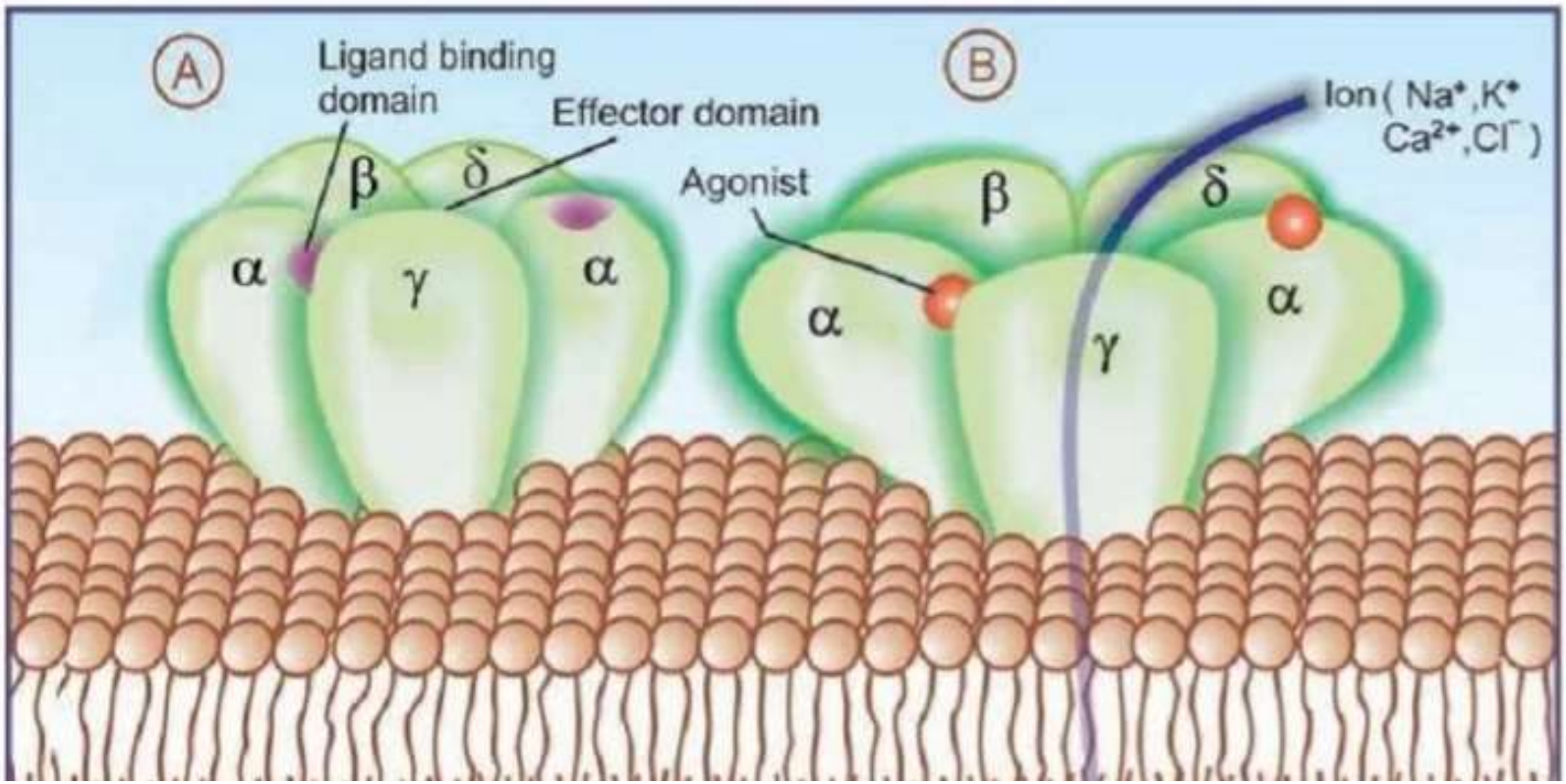

Ca2+
Channel
Histamine
PUMP
H1-R
PIP2
DAG
PLc
GTP
Gqα
PKc
Gqα
β
γ
GTP
GDP
Gqβ
γ
IP3
Protein
phosphorylation

G-PROTEINS AND EFFECTORS

- Large number can be distinguished by their α-subunits

G protein	Effectors pathway	Substrates
Gs	Adenylyl cyclase ↑ - PK_A	Beta-receptors, H_2 D_1
Gi	Adenylyl cyclase ↓ - PK_A	Muscarinic M_2 D_2, alpha-2

ION CHANNEL RECEPTOR



ION CHANNEL RECEPTOR

- These cell surface receptors, also called ligand gated ion channels, enclose ion selective channels (for Na^+, K^+, Ca^{2+} or Cl^-) within their molecules.
- Agonist binding opens the channel and causes depolarization/hyperpolarization/ changes in cytosolic ionic composition, depending on the ion that flows through.
- The nicotinic cholinergic, GABA-A, Glycine (inhibitory AA), excitatory AA glutamate (kainate, NMDA and

TRANSMEMBRANE ENZYME - LINKED RECEPTORS

- Utilized primarily by peptide hormones.
- Made up of a large extracellular ligand binding domain connected through a single transmembrane helical peptide chain to an intracellular subunit having enzymatic property.

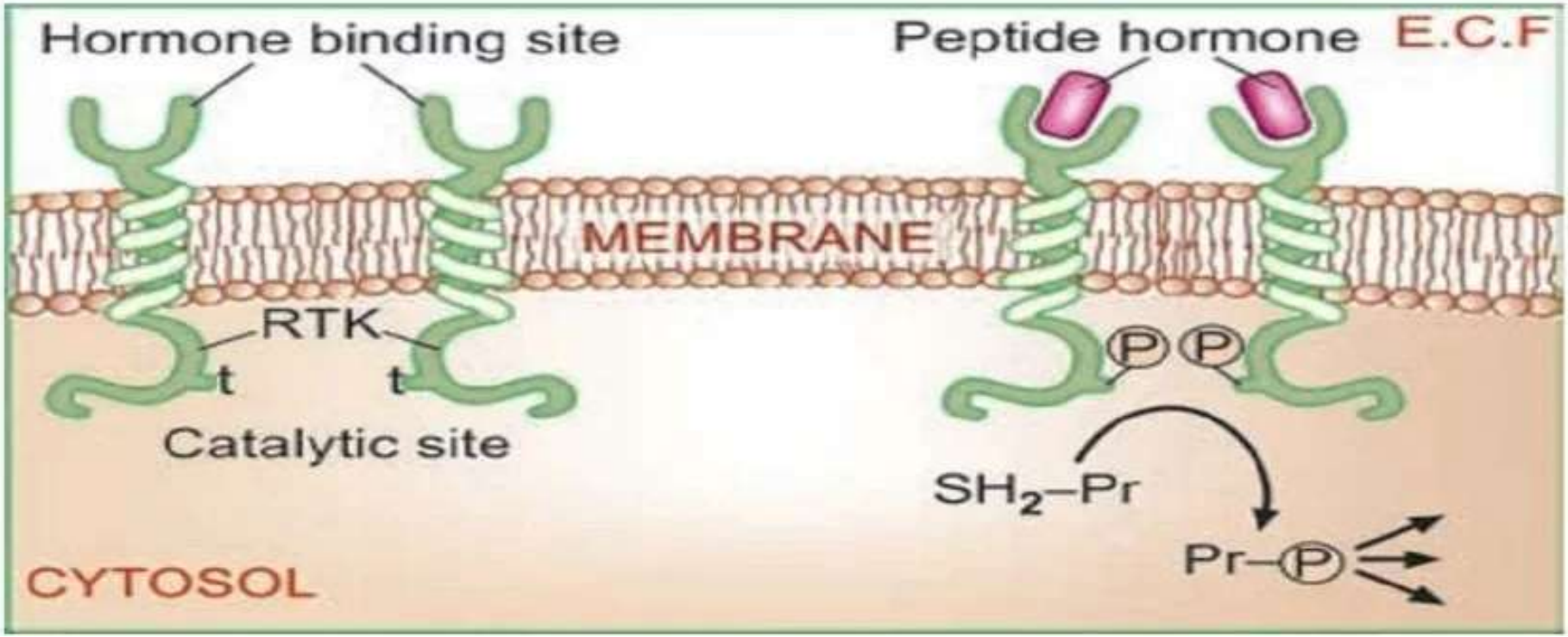
Enzyme Linked Receptors

Two types of receptors:

1. Intrinsic enzyme linked receptors
   - Protein kinase or guanyl cyclase domain

1. JAK-STAT-kinase binding receptor

TRANSMEMBRANE ENZYME - LINKED RECEPTORS



TRANSMEMBRANE ENZYME - LINKED RECEPTORS

- Extracellular hormone-binding domain and a cytoplasmic enzyme domain (mainly protein tyrosine kinase or serine or threonine kinase)
- Upon binding the receptor converts from its inactive monomeric state to an active dimeric state
- t-Pr-K gets activated – tyrosine residues phosphorylates on each other

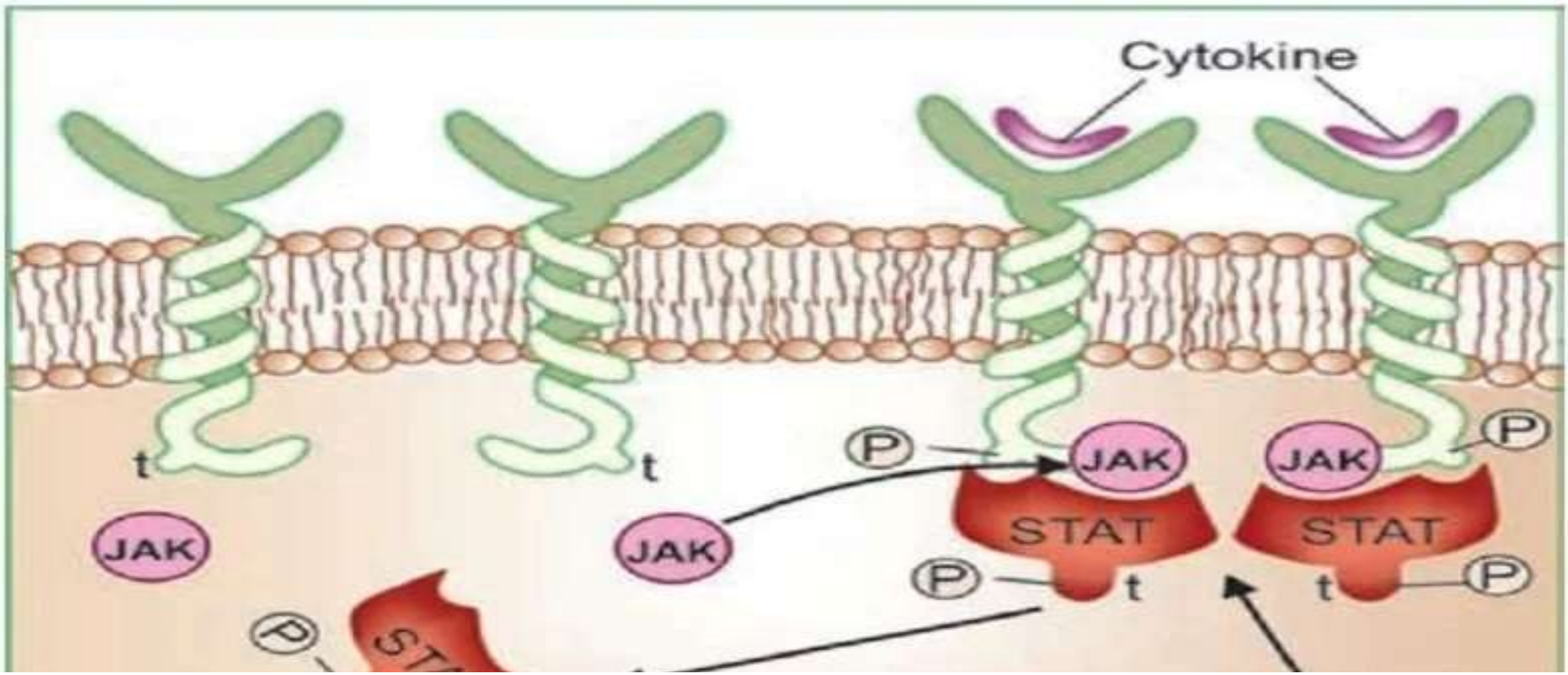
TRANSMEMBRANE JAK-STAT BINDING RECEPTORS

- Agonist induced dimerization alters the intracellular domain conformation to increase its affinity for a cytosolic tyrosine protein kinase JAK (Janus Kinase).

- On binding, JAK gets activated and phosphorylates tyrosine residues on the receptor, which now bind another free moving protein STAT (signal transducer and activator of transcription).

- This is also phosphorylated by JAK. Pairs of phosphorylated STAT dimerize and translocate to the nucleus to regulate gene transcription resulting in a biological response.

TRANSMEMBRANE JAK-STAT BINDING RECEPTORS

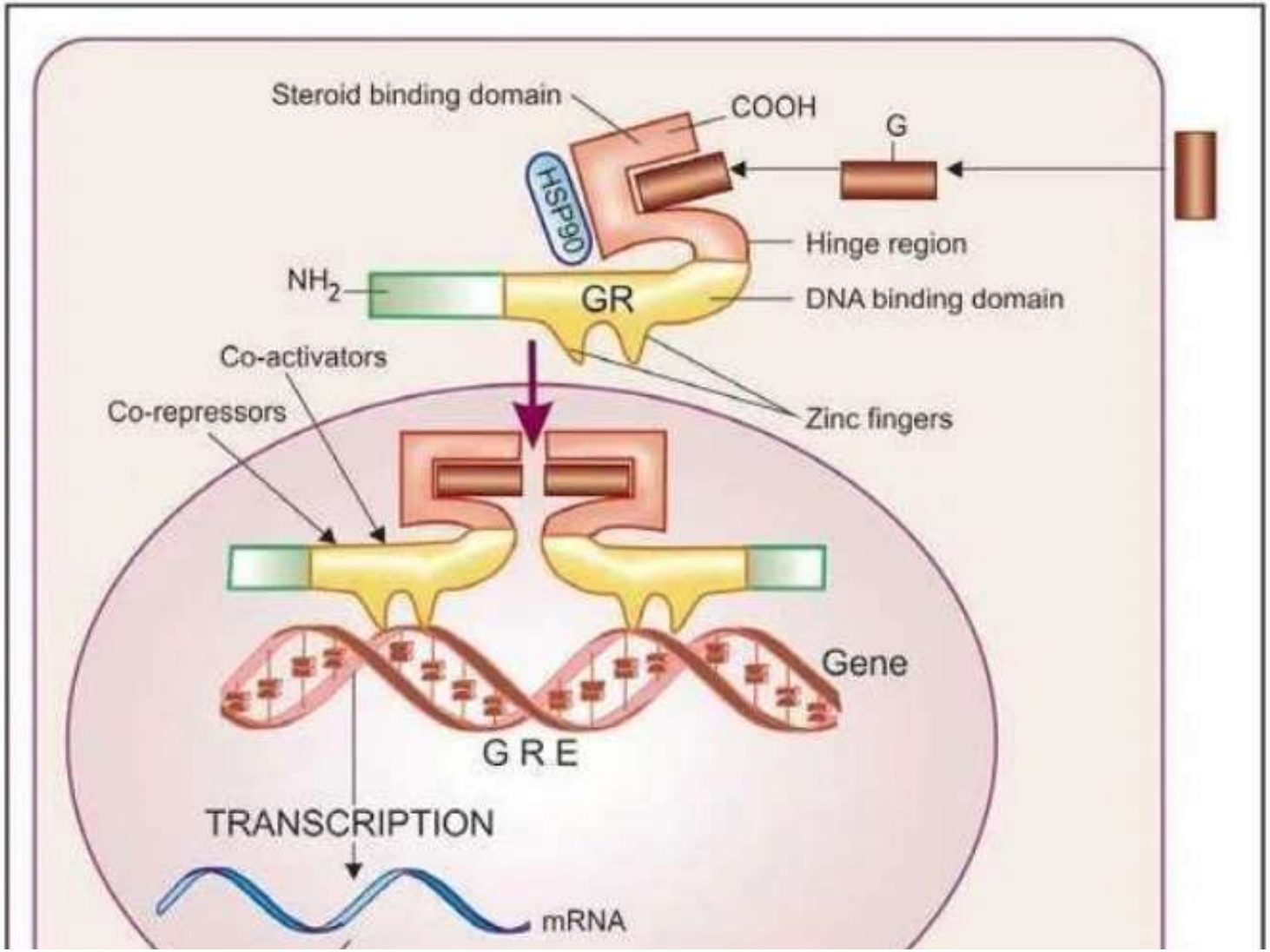


RECEPTORS REGULATING GENE EXPRESSION

Transcription factors, Nuclear receptors

- These are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messengers that penetrate the cell.

- The liganded receptor diamer moves to the nucleus and binds other co-activator/co-repressor proteins which have a modulatory influence on its capacity to alter gene function.


Steroid binding domain
COOH
G
HSP90
Hinge region
NH2
GR
DNA binding domain
Co-activators
Co-repressors
Zinc fingers
Gene
G R E
TRANSCRIPTION
mRNA

RECEPTOR REGULATION

- Up regulation of receptors:
  - In topically active systems, prolonged deprivation of agonist (by denervation or antagonist) results in supersensitivity of the receptor as well as to effector system to the agonist. Sudden discontinuation of Propranolol, Clonidine etc.
  - **3 mechanisms:**

Contd....

- Continued exposure to an agonist or intense receptor stimulation causes desensitization or refractoriness: receptor become less sensitive to the agonist
- Examples – beta adrenergic agonist & levodopa Causes:
    1. Masking or internalization of the receptors

Desensitization

- Sometimes response to all agonists which act through different receptors but produce the same overt effect is decreased by exposure to anyone of these agonists – heterologous desensitization

- Homologous – when limited to the agonist which is repeatedly activated – In GPCRs (PKA or PKC) Kinases may also phosphorylate the GPCRs

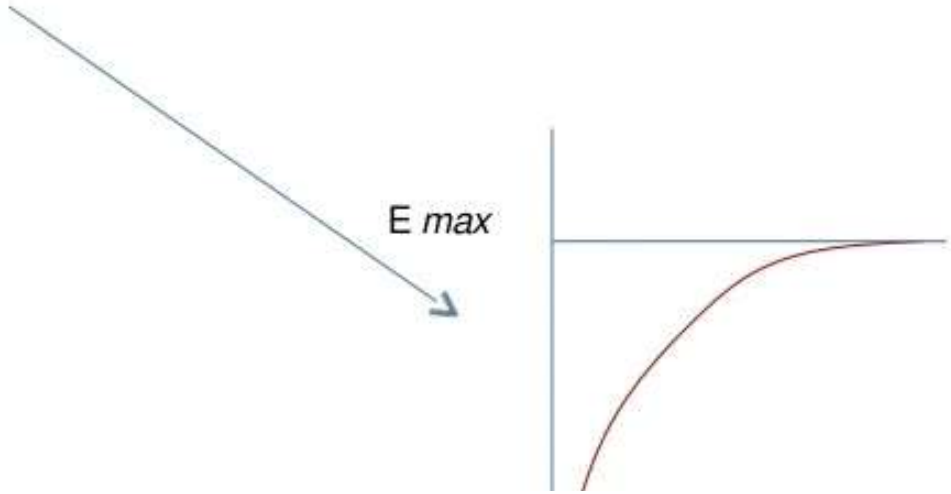
Non-receptor mediated drug action (clinically relevant examples)

- Physical and chemical means - Antacids, chelating agents and cholestyramine etc.
- Alkylating agents: binding with nucleic acid and render cytotoxic activity – Mechlorethamine, cyclophosphamide etc.
- Antimetabolites: purine and pyrimidine

Dose - Response Relationship

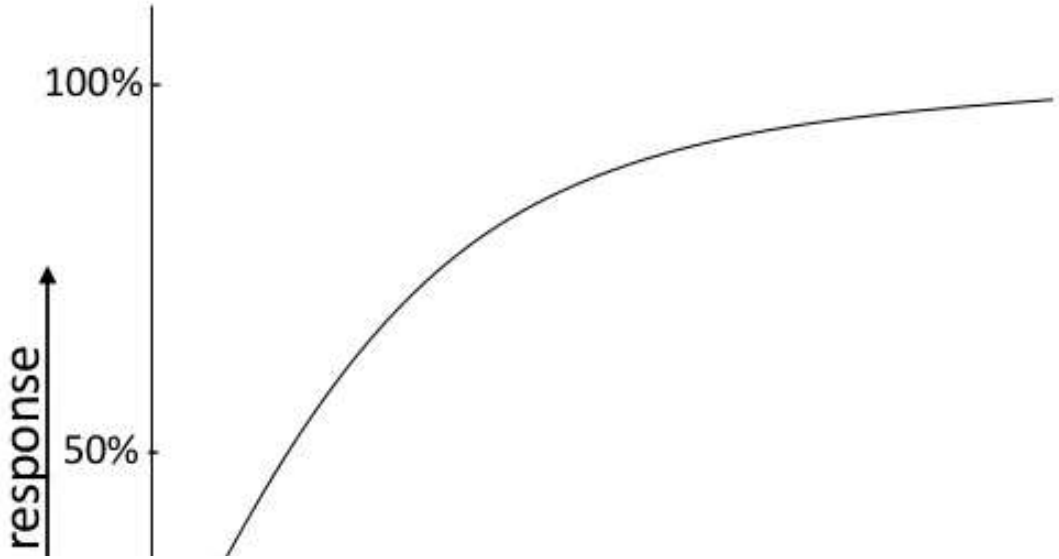
- Drug administered – 2 components of dose- response
  - Dose-plasma concentration
  - Plasma concentration (dose)-response relationship
- E is expressed as

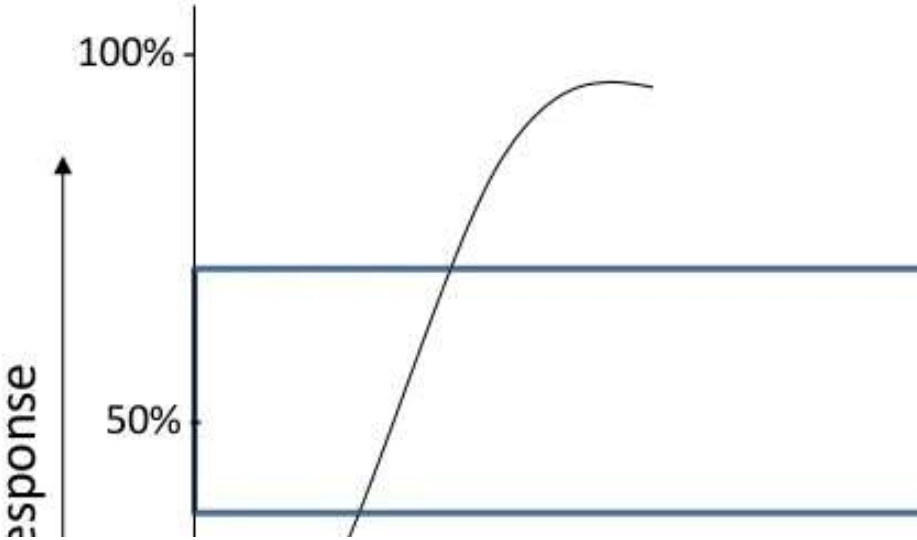
$$\frac{E_{max} X\ [D]}{Kd + [D]}$$



Dose-Response Curve

$$E = \frac{E_{max} X\ [D]}{Kd + [D]}$$





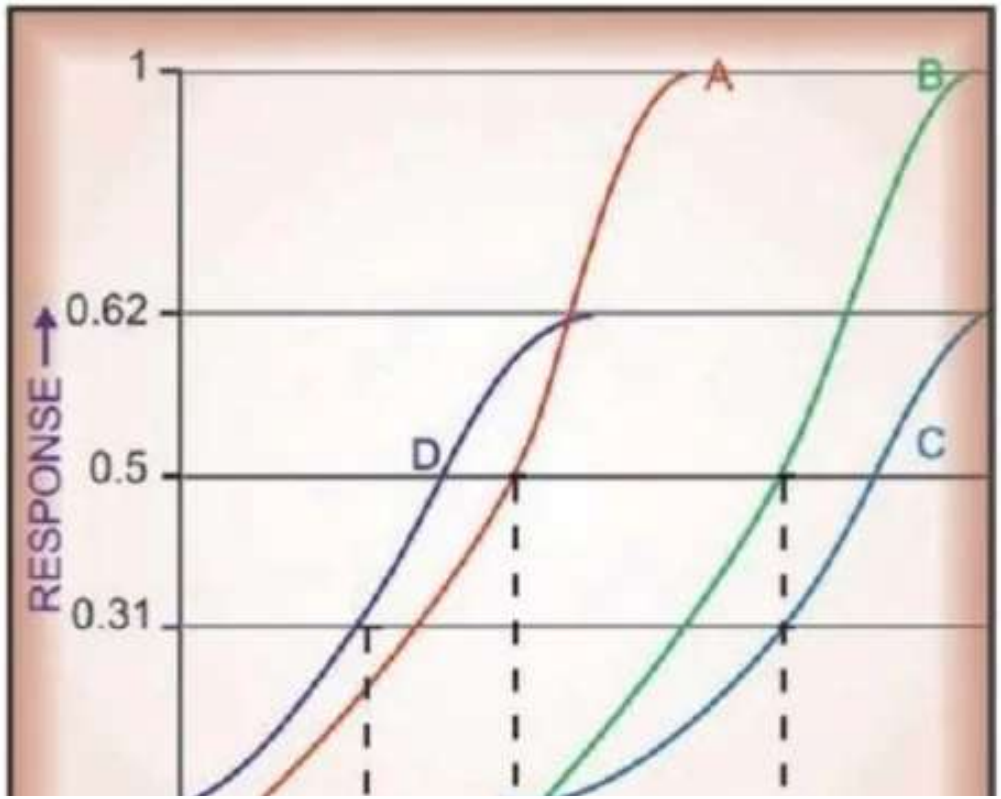
Dose-Response Curve

- Advantages:
  - Stimuli can be graded by Fractional change in stimulus intensity
  - A wide range of drug doses can easily be displayed on a graph
  - Potency and efficacy can be compared
  - Comparison of study of agonists and antagonists

DRUG POTENCY & EFFICACY

- Drug potency which refers to the amount of drug needed to produce a certain response.
- Drug efficacy and refers to the maximal response that can be elicited by the drug.

DRUG POTENCY & EFFICACY



Potency and efficacy - Examples

- Aspirin is less potent as well as less efficacious than Morphine
- Pethidine is less potent analgesic than Morphine but eually efficacious
- Diazepam is more potent but less efficacious than phenobarbitone
- Furosemide is less potent but more efficacious than metozolone
- Potency and efficacy are indicators only in different clinical

THERAPEUTIC INDEX

$$\text{Therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}}$$

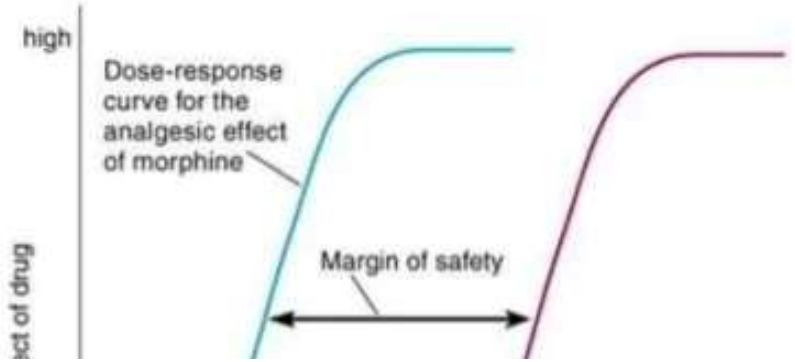
$$\text{or } \frac{LD_{50}}{ED_{50}}$$

Median effective dose (ED_{50}): The dose which

Therapeutic index (TI)

- It is defined as the gap between minimal therapeutic effect DRC and maximal acceptable adverse effect DRC (also called margin of safety)

► Dose-Response Curves for the Analgesic and Depressant Effects of Morphin



COMBINED EFFECT OF DRUGS

- Synergism
- When the action of one drug is facilitated or increased by the other, they are said to be synergistic.

ADDITIVE SYNERGISM

- The effect of the two drugs is in the same direction and simply adds up:
- Effect of drugs A + B = effect of drug A + effect of drug B.

Additive drug combinations	
Aspirin + paracetamol	as analgesic/ antipyretic
Nitrous oxide + halothane	as general anaesthetic
Amlodipine + atenolol	as antihypertensive
Glibenclamide + metformin	as hypoglycaemic
Ephedrine + theophylline	as bronchodilator

SUPRAADDITIVE SYNERGISM

- The effect of combination is greater than the individual effects of the components:
- effect of drug A + B > effect of drug A + effect of drug B
- This is always the case when one component given alone produces no effect, but enhances the effect of the other (potentiation).

Supraadditive drug combinations

Drug pair	*Basis of potentiation*
Acetylcholine + physostigmine	Inhibition of break down
Levodopa + carbidopa/ benserazide	Inhibition of peripheral metabolism
Adrenaline + cocaine/ desipramine	Inhibition of neuronal uptake
Sulfamethoxazole + trimethoprim	Sequential blockade
Antihypertensives	Tackling two contributory

ANTAGONISM

- When one drug decreases or abolishes the action of another, they are said to be antagonistic:
- effect of drugs A + B < effect of drug A + effect of drug B

PHYSICAL ANTAGONISM

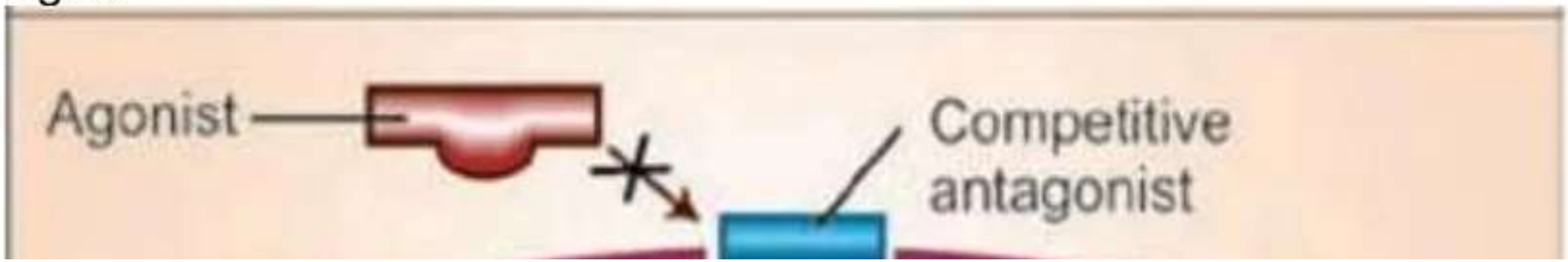
- Based on the physical property of the drugs,
  - e.g. charcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisonings.

CHEMICAL ANTAGONISM

- The two drugs react chemically and form an inactive product, e.g
- KMnO4 oxidizes alkaloids—used for gastric lavage in poisoning.
- Chelating agents (BAL, Cal. disod. edetate) complex toxic metals (As, Pb).

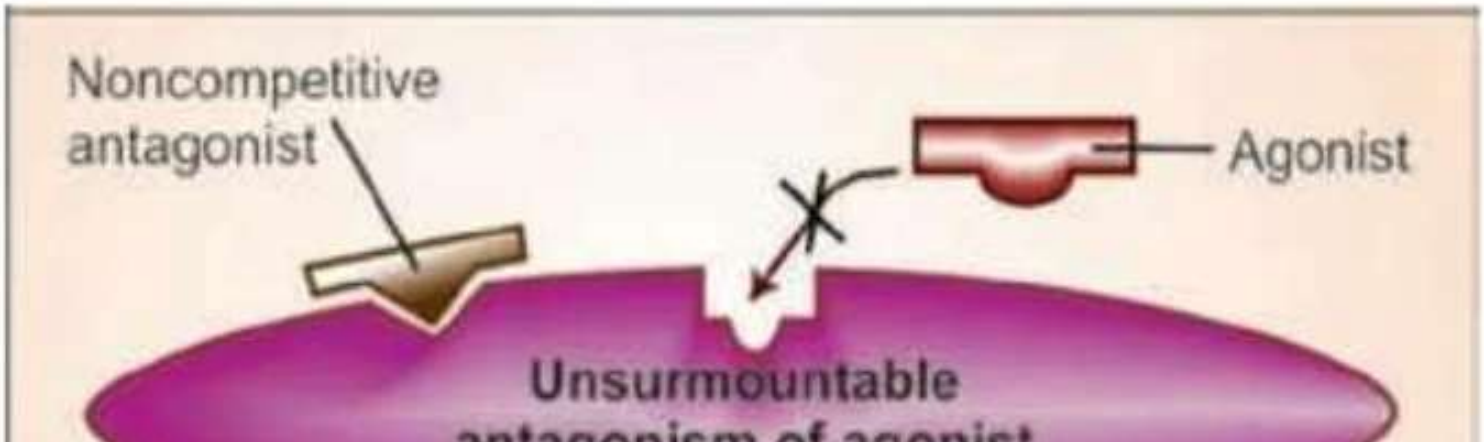
RECEPTOR ANTAGONISM

- Competitive antagonism (equilibrium type)
- The antagonist is chemically similar to the agonist, competes with it and binds to the same site to the exclusion of the agonist molecules.
- Because the antagonist has affinity but no intrinsic activity , no response is produced and the log DRC of the agonist is shifted to the right.



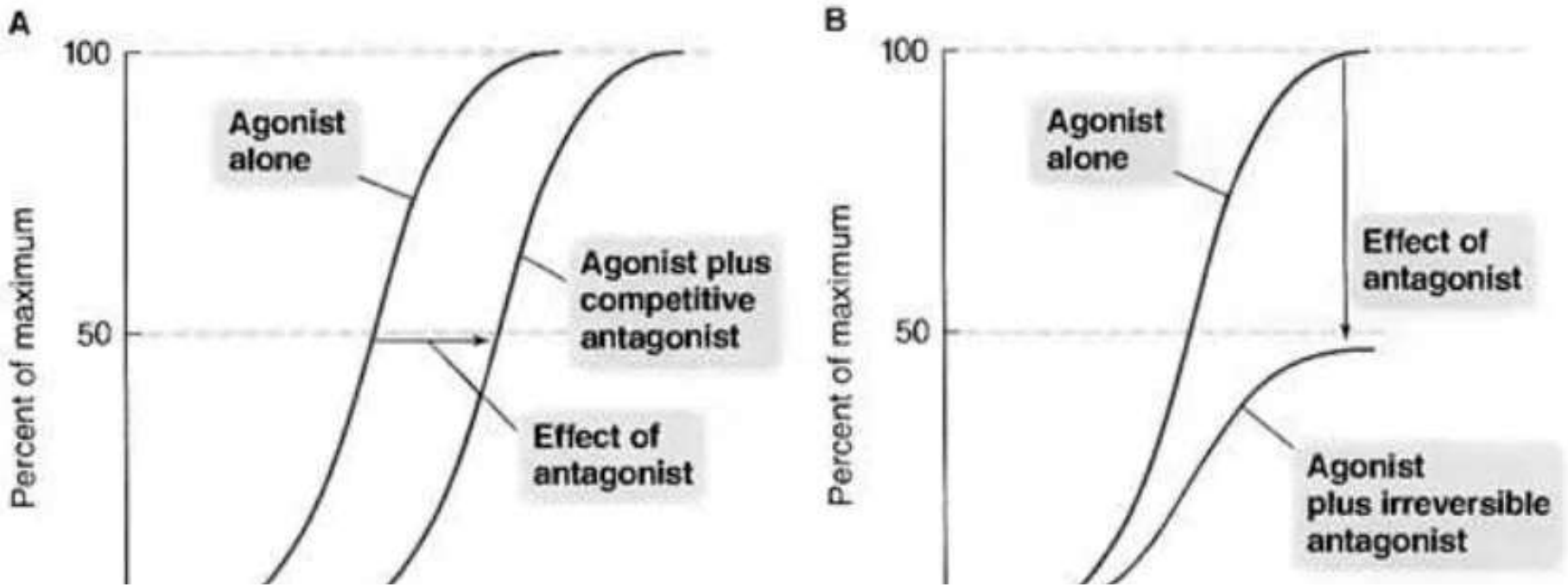
NONCOMPETITIVE ANTAGONISM

- **The antagonist is chemically unrelated to the agonist, binds to a different allosteric site altering the receptor in such a way that it is unable to combine with the agonist , or is unable to transduce the response.**

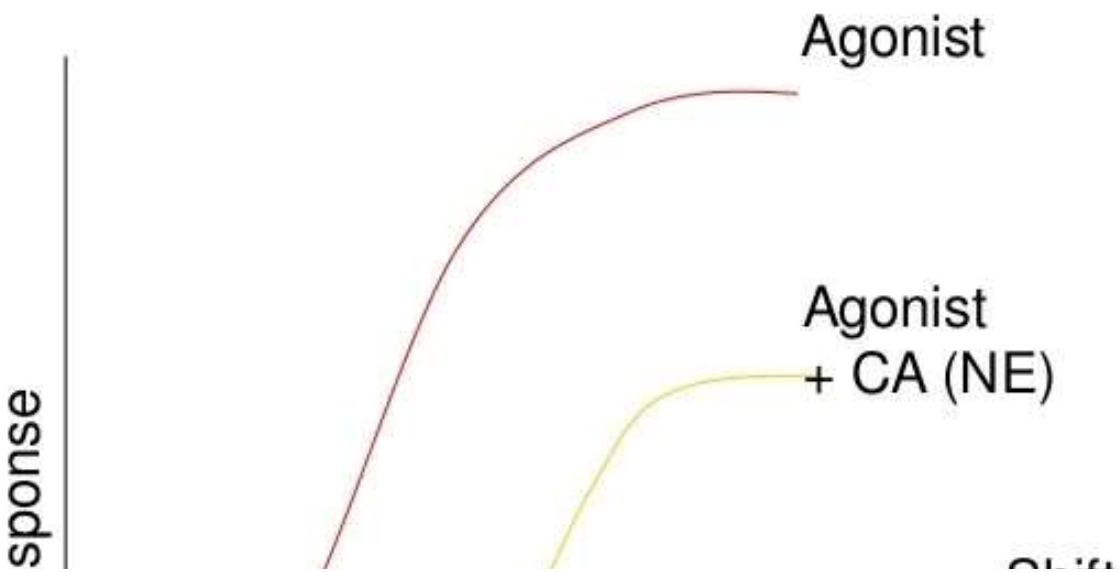


Competitive (equilibrium type)	Noncompetitive
1. Antagonist binds with the same receptor as the agonist	Binds to another site of receptor
2. Antagonist resembles chemically with the agonist	Does not resemble
3. Parallel rightward shift of agonist DRC	Flattening of agonist DRC
4. The same maximal response can be attained by increasing dose of agonist (surmountable antagonism)	Maximal response is suppressed (unsurmountable antagonism)
5. Intensity of response depends on the concentration of both agonist and antagonist	Maximal response depends only on the concentration of antagonist
6. Examples: ACh – Atropine	Diazepam – Bicuculline

Drug antagonism DRC



Drug antagonism DRC – Non-competitive antagonism



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