

Pharmacodynamics

Pharmacodynamics

- Pharmacology: drug, dynamics: action/activity
- “What the drug does to the body”
- It deals with the study of the biochemical and physiological effects of drugs and their mechanisms of action

Dosage

**Plasma
Concen.**

**Site of
Action**

Effects



Pharmacokinetics

Pharmacodynamics

Site of action

- Where the drug acts
- Two drug may show same effect but their site of action may differ:
 - Pilocarpine and morphine

Mechanism of drug action

- Interacting with a discrete target biomolecules:
 - Enzymes
 - Ion channels
 - Transporters
 - Receptors
- Physical or chemical property:
 - Bulk laxatives (ispaghula)—physical mass
 - Paraamino benzoic acid—absorption of UV rays
 - Activated charcoal—adsorptive property
 - Mannitol—osmotic activity

Types of Drug action

- It is the initial combination of the drug with its receptor resulting in a conformational change in the latter (agonists), or prevention of conformational change through exclusion of the agonist (antagonists).
- Stimulation, depression, irritation, replacement, cytotoxic action

Types of Drug action

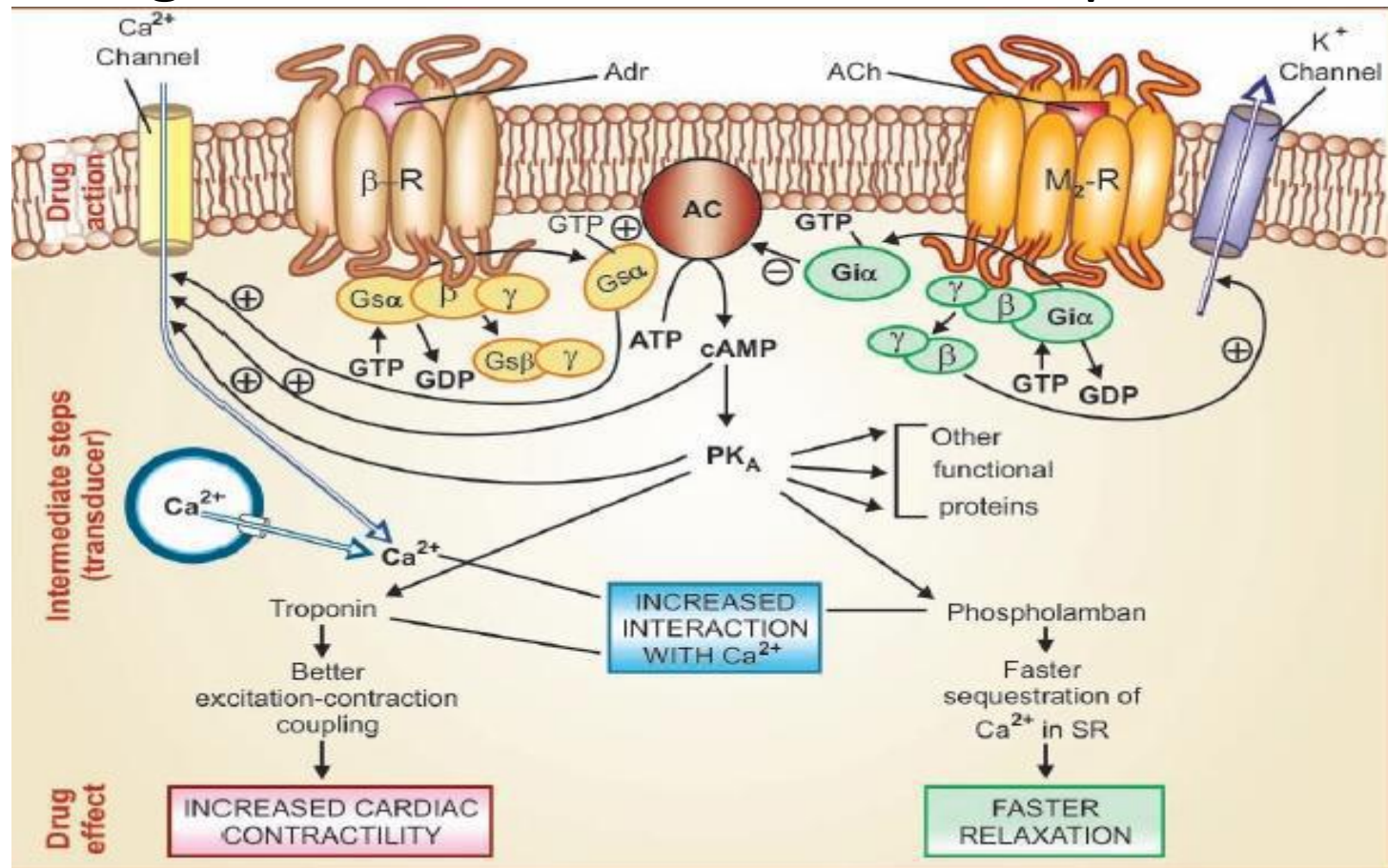
- Stimulation
 - Increasing the activity of some specific organs or system. For example; adrenaline stimulates the heart resulting in an increase in heart rate and force of contraction.
- Depression
 - Decreasing the activity of some specific organs or system. For example, alcohol, barbiturates, general anaesthetics, etc. depress the CNS.
- Cytotoxic action
 - Selective toxic for the infecting organism/cancer cells. For example; antibiotics/anticancer drugs

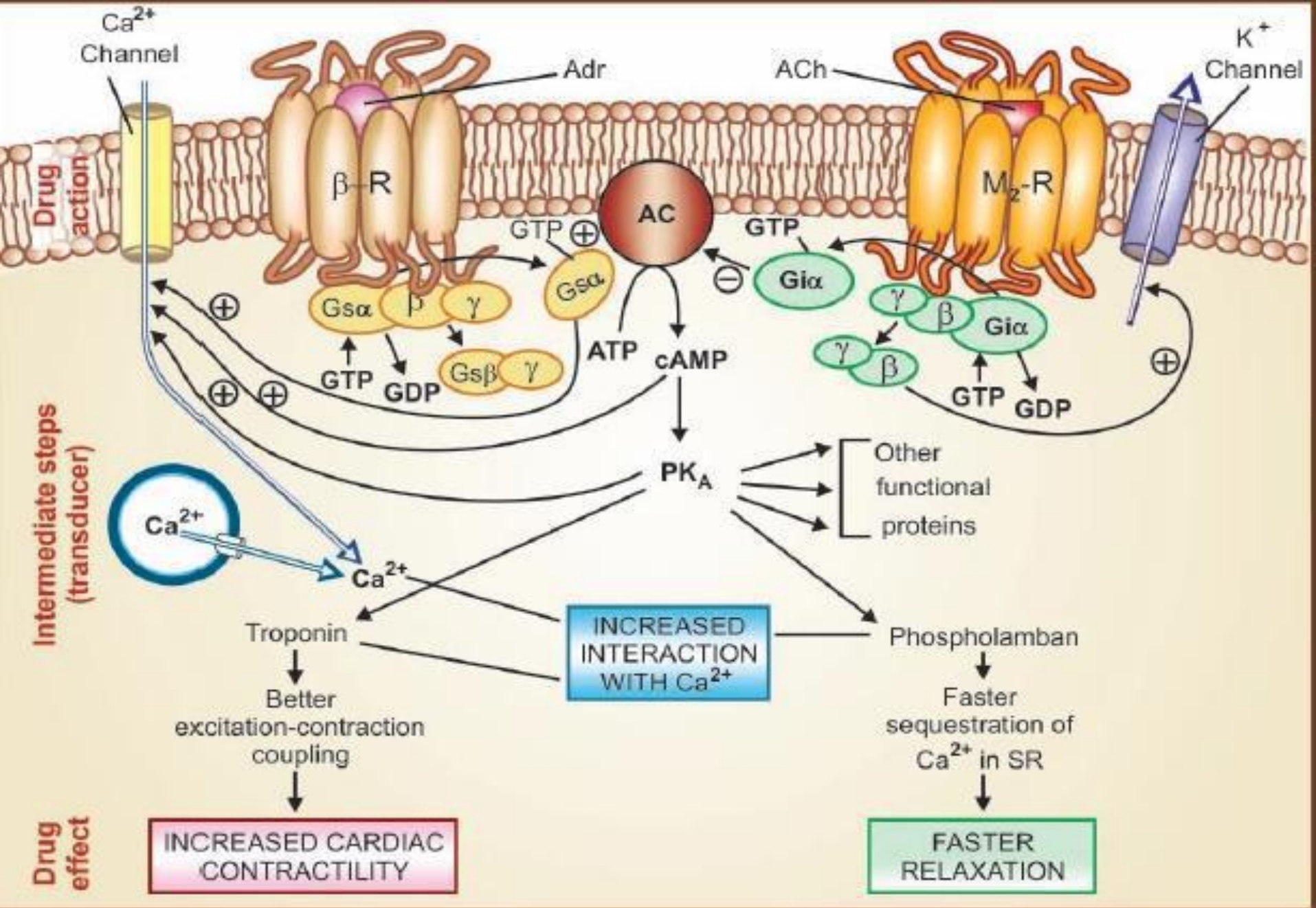
Types of Drug action

- Irritation
 - Topical uses on the skin and adjacent tissues
 - Skin relieves deep seated pain, it is called counterirritant, e.g. eucalyptus oil, methyl salicylate, etc.
 - Useful in sprains, joint pain and myalgia
 - Exert their action by:
 - Reflexly increasing local circulation in deeper structures
 - Blocking impulse conduction in the spinal cord
- Replacement
 - When there is a deficiency of endogenous substances, they can be replaced by drugs
 - for example
 - insulin in diabetes mellitus
 - Thyroxine in cretinism and myxedema

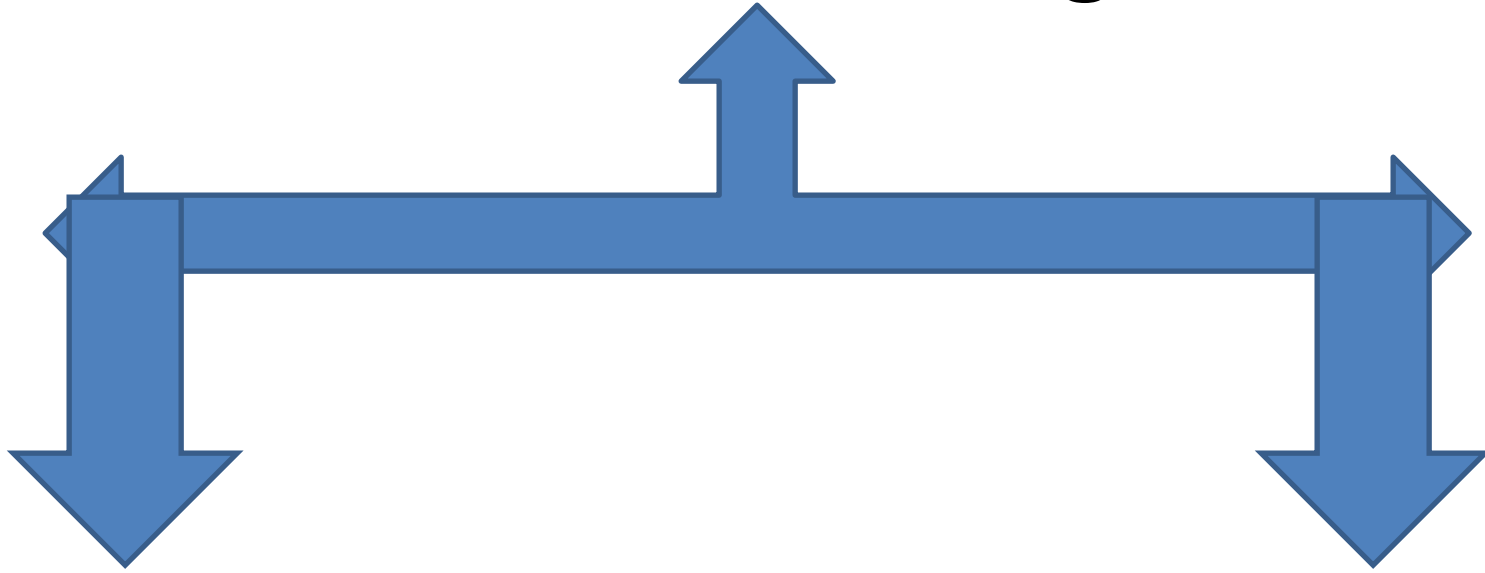
Drug effect

- It is the ultimate change in biological function brought about as a consequence of drug action, through a series of intermediate steps





Mechanism of drug action



Non-receptor mediated

Receptor mediated

Non-receptor mediated MOA

- **By physical action**
 - Osmosis
 - Exerting an osmotic effect
 - Example
 - 20% mannitol in cerebral edema and acute congestive glaucoma
 - Adsorption
 - Activated charcoal adsorbs toxins
 - Used for treatment of drug poisoning
 - Demulcent
 - Produce soothing effect
 - Cough syrup on pharyngitis by coating the inflamed mucosa
 - Radioactivity
 - Radioactive isotopes emit rays and destroy the tissue
 - E.g. I131 IN hyperthyroidism

Non-receptor mediated MOA

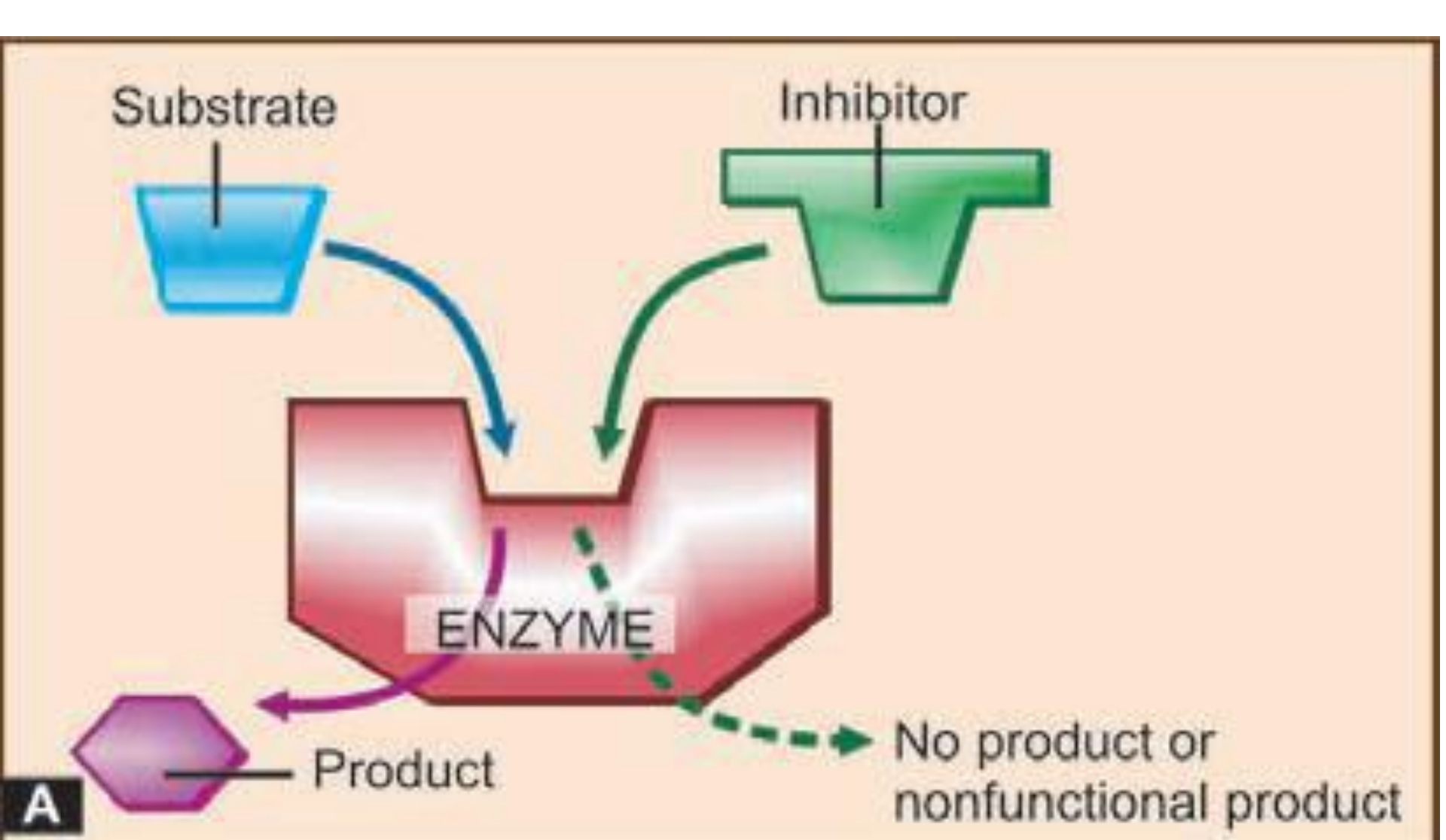
- By Chemical action
 - Antacids are weak bases-neutralize gastric acid-useful in peptic ulcer
 - Metal like iron, copper, mercury,etc, are eliminated from the body with the help of chelating agents.
 - Chelating agents traps metal & form water-soluble complexes
 - Rapidly excreted out from the body
 - Example, dimercaprol (BAL) is arsenic poisoning
 - Deferrioxamine in iron poisoning
 - D-penicillamine in copper poisoning

MOA: interacting with enzymes

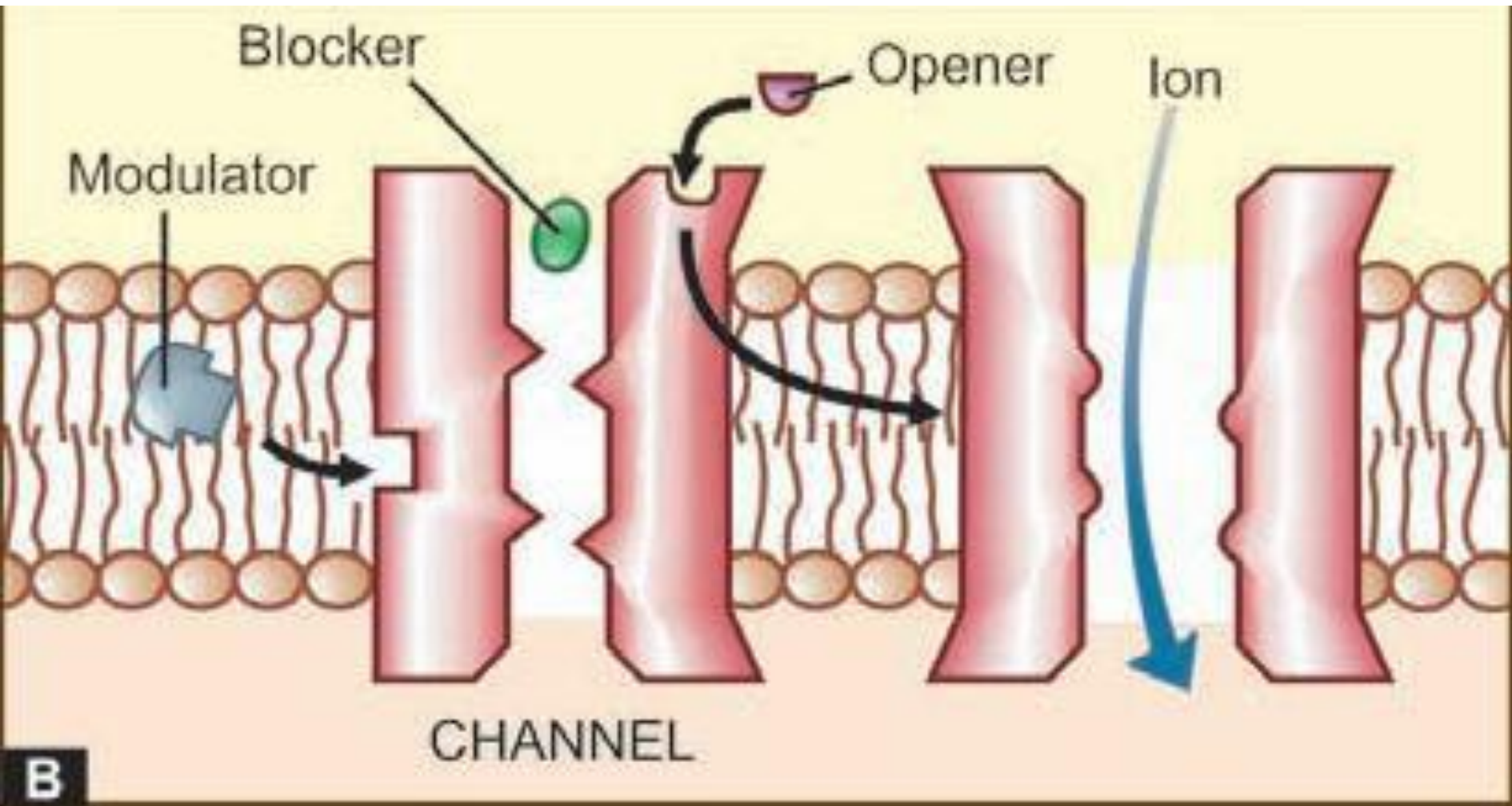
- Enzyme stimulation is relevant to some natural metabolites only, e.g. pyridoxine acts as a cofactor and increases decarboxylase activity.
- Several enzymes are stimulated through receptors and second messengers, e.g. adrenaline stimulates hepatic glycogen phosphorylase through β -receptors and cyclic AMP.

MOA: interacting with enzymes

- Enzyme induction:
 - Many drugs induce microsomal enzymes
- Enzyme inhibition:
 - Nonselective
 - Selective
 - **Competitive:**
 - Equilibrium: cholinesterase-physostigmine
 - Nonequilibrium : cholinesterase-organophosphate
 - **Noncompetitive: cyclooxygenase-aspirin**



MOA: interacting with ion channel



MOA: interacting with ion channel

- Quinidine blocks myocardial Na⁺ channels.
- Phenytoin modulates (prolongs the inactivated state of) voltage sensitive neuronal Na⁺ channel.
- Nicorandil opens ATP-sensitive K⁺ channels.

MOA: interacting with transporters

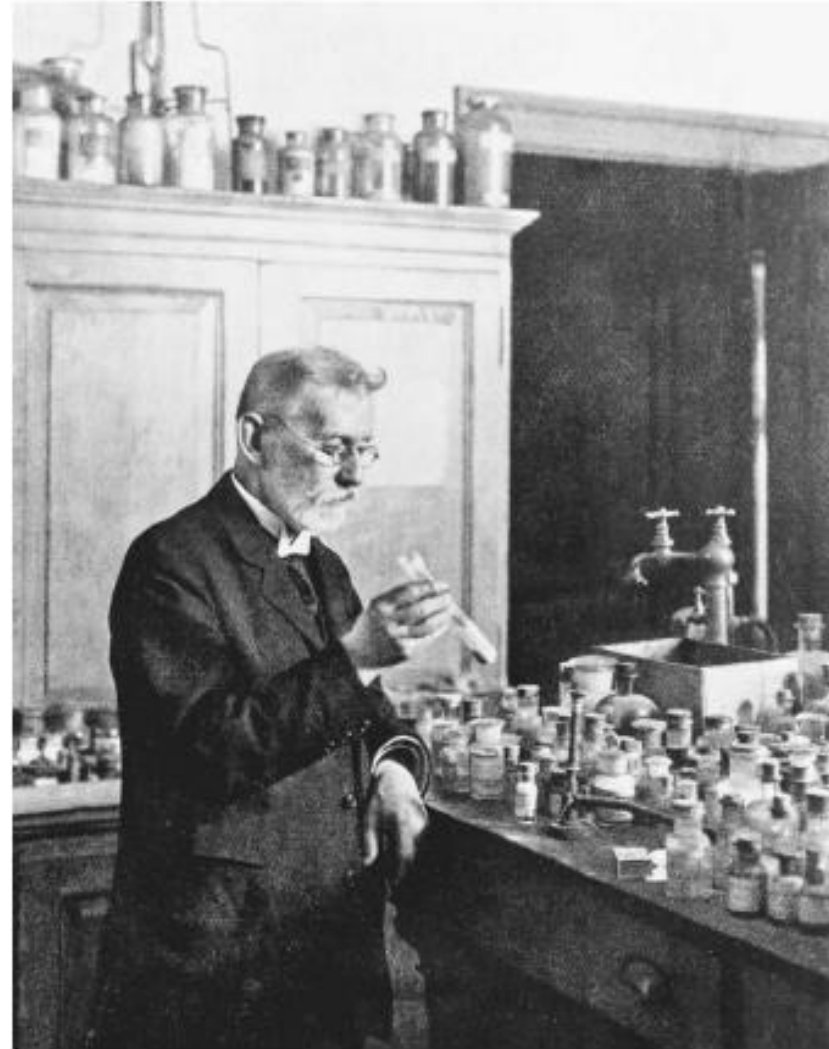
- Many drugs produce their action by directly interacting with the solute carrier class of transporter proteins
 - Fluoxetine inhibit neuronal reuptake of 5-HT by interacting with serotonin transporter
 - Furosemide inhibits the $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter in the ascending limb of loop of Henle.

MOA: through antibody production

- Vaccine produce their effect by stimulating the formation of antibodies
- For example;
 - Vaccine against tuberculosis (BCG)
 - Oral polio vaccine, etc.

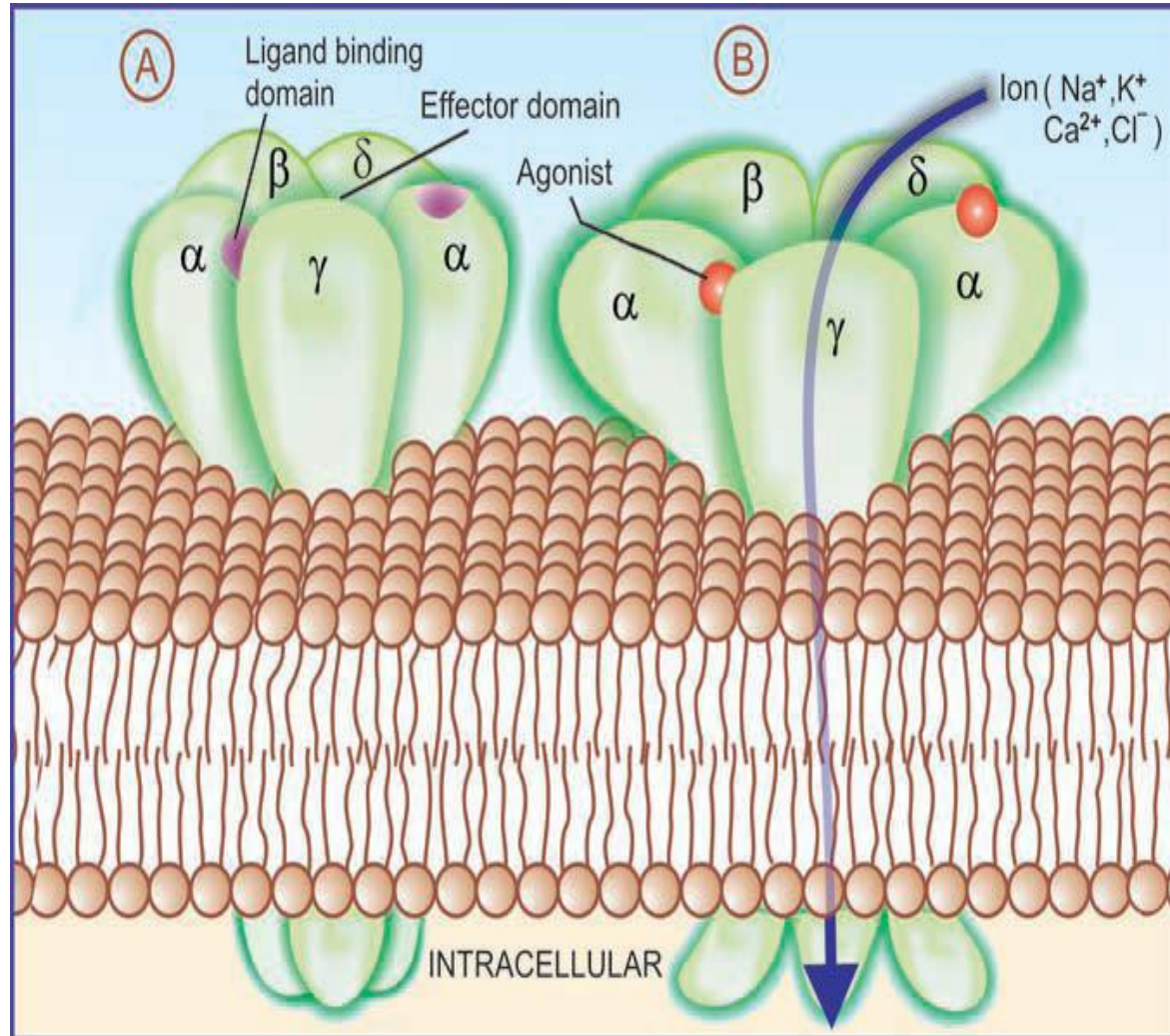
MOA: interacting with receptors

- Receptor: A macromolecule or binding site located on the surface, cytoplasm 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.

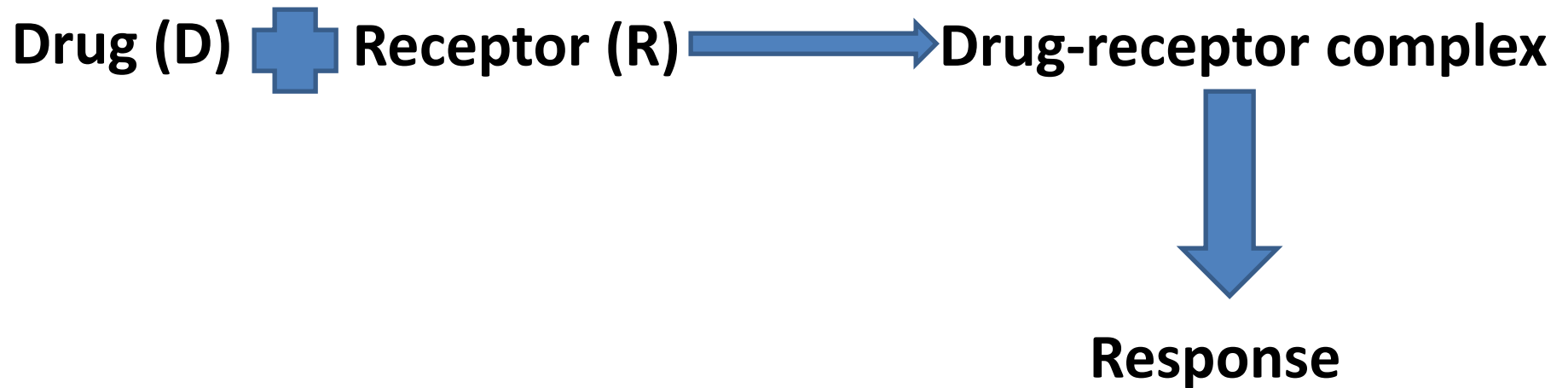


MOA: interacting with receptors

- The receptor molecule
 - Ligand binding domain
 - Effector domain which undergoes a functional conformational change.



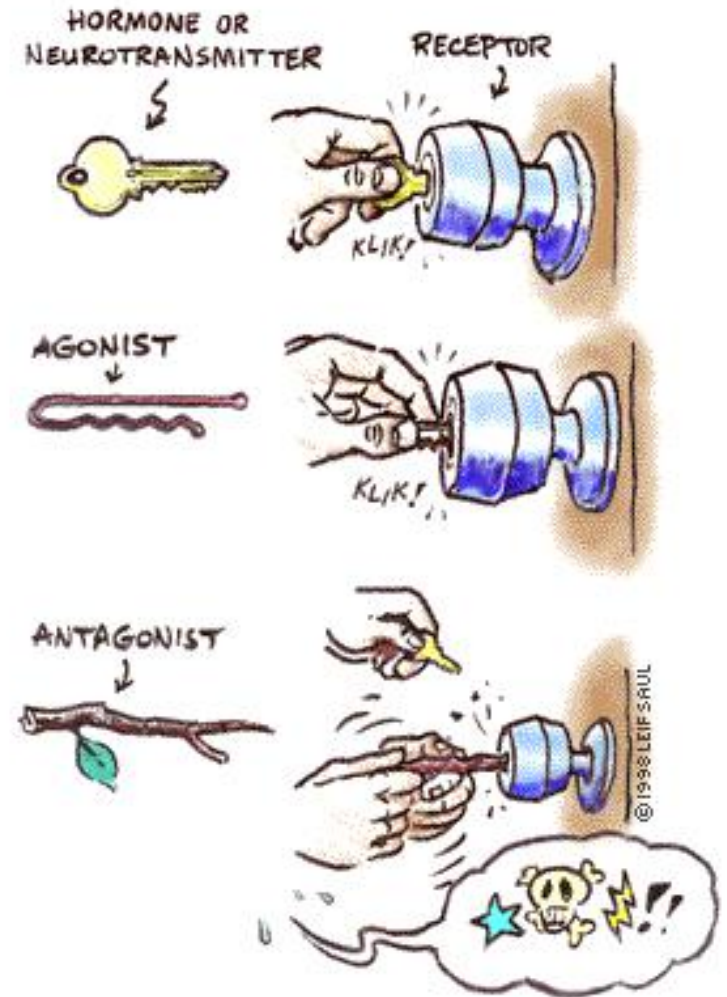
MOA: interacting with receptors



For example, adrenergic receptors (α and β), cholinergic receptors (muscarinic and nicotinic), opioid receptors, etc.

MoA: interacting with receptors

- Agonist
- Antagonist
- Inverse agonist
- Partial agonist



MoA: interacting with receptors

- Agonist:
 - Drugs that bind to physiological receptors and mimic the regulatory effects of the endogenous signaling compounds
 - Agonist has high affinity + high intrinsic activity (e.g. morphine and adrenaline)
- Antagonist:
 - Drugs that block or reduce the action of an agonist
 - No stimulatory action of their own that still may produce useful effects
 - Competitive antagonist has high affinity without intrinsic activity
 - Example, Naloxone and atropine
 - Produces receptor blockade

MoA: interacting with receptors

- Inverse agonists:
 - Has full affinity towards the receptor but produces effect opposite to that an agonist
 - Example, benzodiazepines produce antianxiety and anticonvulsant effects by interacting with benzodiazepines receptors, but **β -carboline**s act as inverse agonist at benzodiazepine receptors and produce anxiety and convulsions.
 - Affinity + intrinsic activity between 0 to -1 (example, **β -carboline**s)
- Partial agonists:
 - Drug that binds to the receptor but produces an effect less than that of an agonist
 - Inhibits the effect of agonist
 - Affinity + less intrinsic activity (e.g. buprenorphine and pindolol)

MoA: interacting with receptors

- Ligand(*Latin: ligare—to bind*)
- Any molecule which attaches selectively to particular receptors or sites. The term only indicates affinity or ability to bind without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.

MoA: interacting with receptors

- Affinity:
 - The ability to bind with the receptor
- Intrinsic activity:
 - The capacity to induce a functional change in the receptor

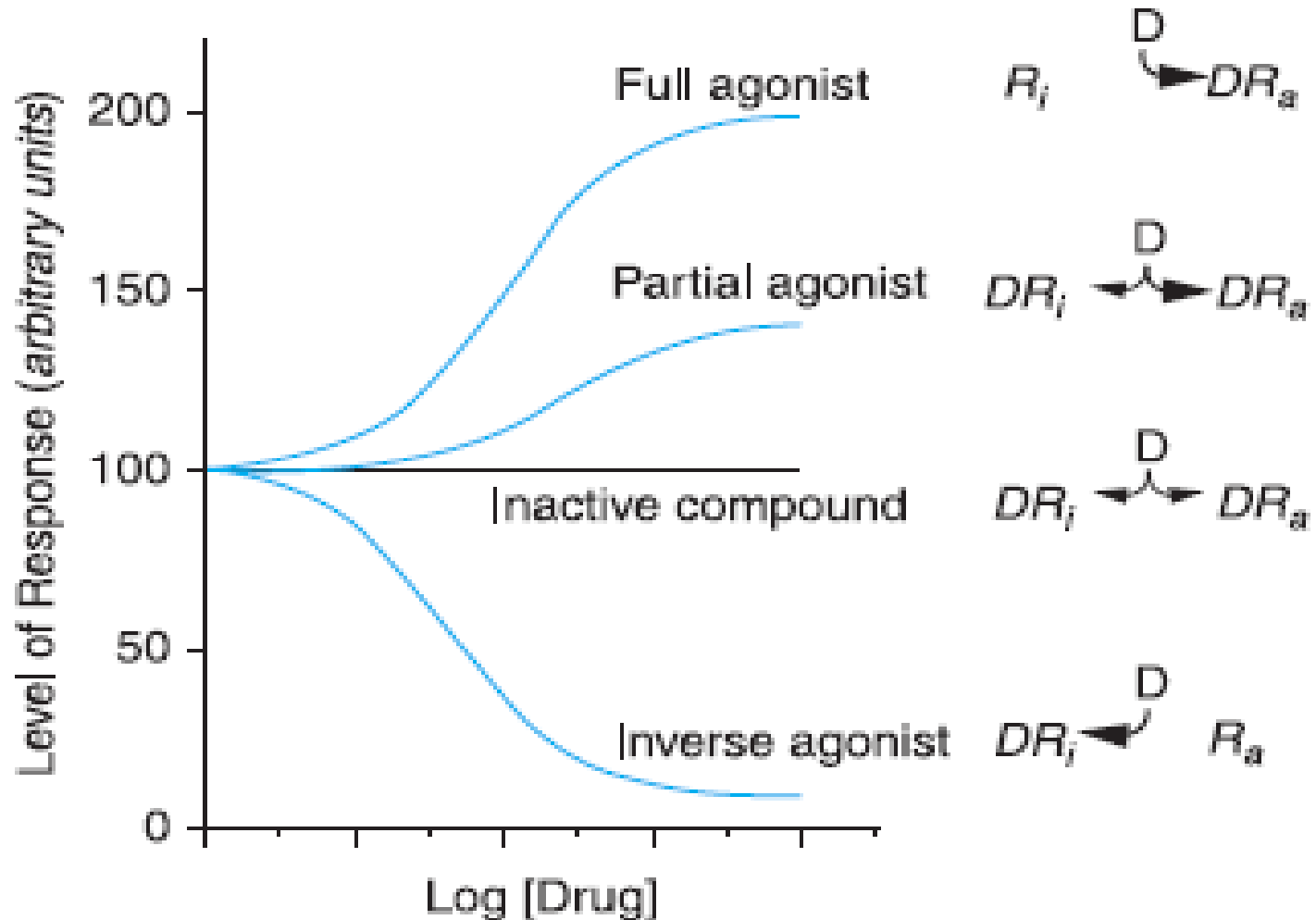
Drug specificity

- The range of actions produced by it.
- It is governed by:
 - Whether a drug acts on a single receptor/ target or on many targets, and
 - How widely the target is distributed in the body.
- High specificity: omeprazole
- Low specificity(broad specificity): amiodarone

Structure activity relationship

- Both the affinity of a drug and its intrinsic activity are determined by its chemical structure

Two state receptor model



Structural families of receptors

Structural families	Functional family	Example drugs
GPCR(G Protein-Coupled Receptors)	β adrenergic receptors Muscarinicreceptors Eicosanoidreceptors	Dobutamine, Propanolol Atropine Misoprostol, Monteleukast
Ion channel	Ligand-gated Voltage-gated	Nicotine, gabapentin Lidocaine, verapamil
Transmembrane enzymes	Receptor tyrosine kinase	Herceptin, imatinib
Transmembranenon-enzymes	Cytokine receptors	
Nuclear	Steroid receptors Thyroidhormone receptors	Estrogens, androgens TH
Intracellular enzymes	Soluble Guanylylcyclase	Nitrovasodilators

- GPCR
 - Metabotropic receptors
 - Over 800 GPCRs
 - Regulate impressive number of physiological functions
 - Targets for many drugs
 - Examples:
 - Muscarinic cholinergic

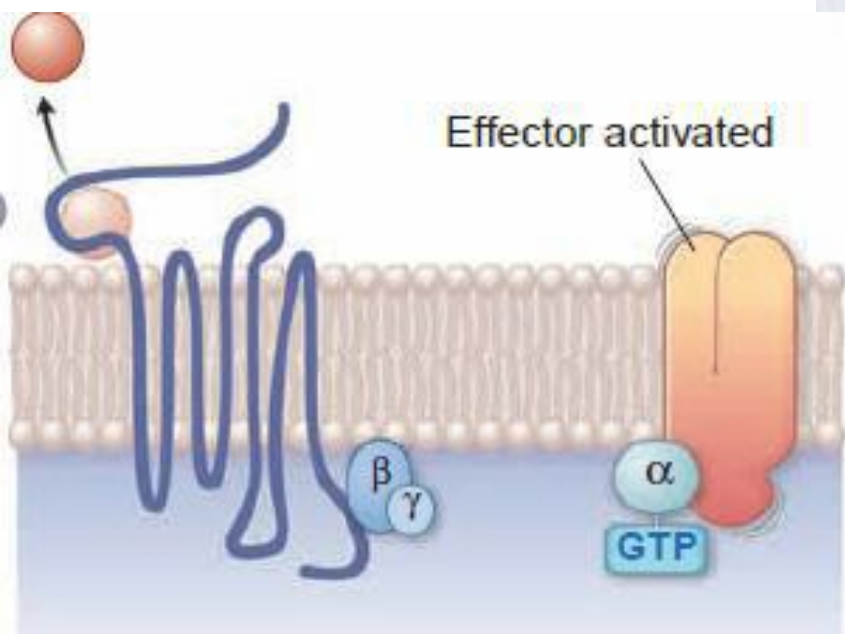
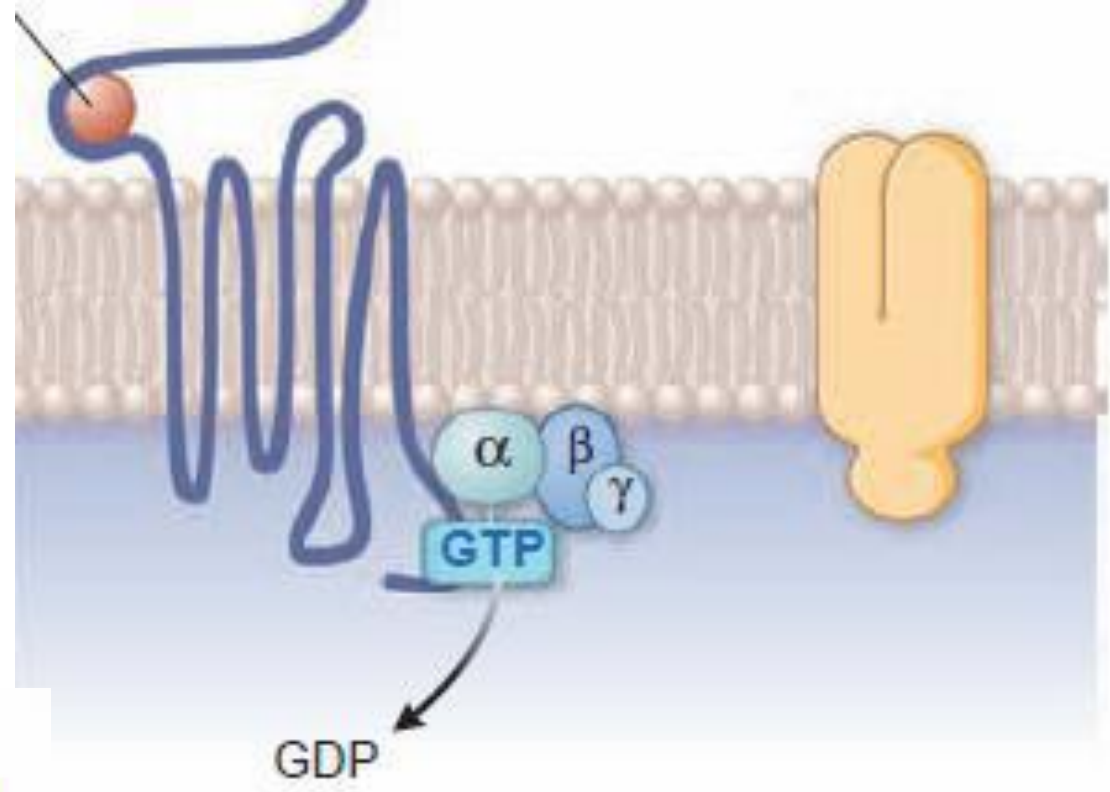
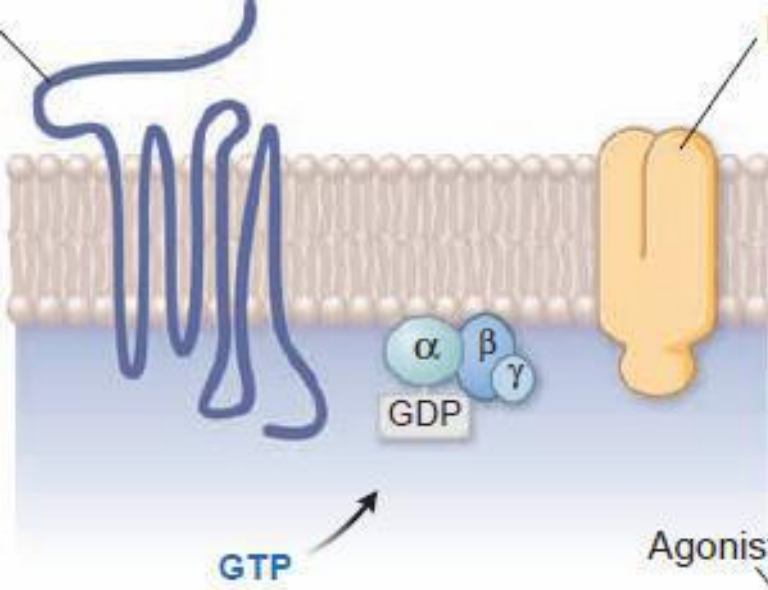


Fig: GPCR-drug interaction

G PROTEIN

ACTIONS

G-stimulatory (G_s)

Activates Ca^{2+} channels, activates adenylyl cyclase

G-inhibitory (G_i)

Activates K^+ channels, inhibits adenylyl cyclase

G_o

Inhibits Ca^{2+} channels

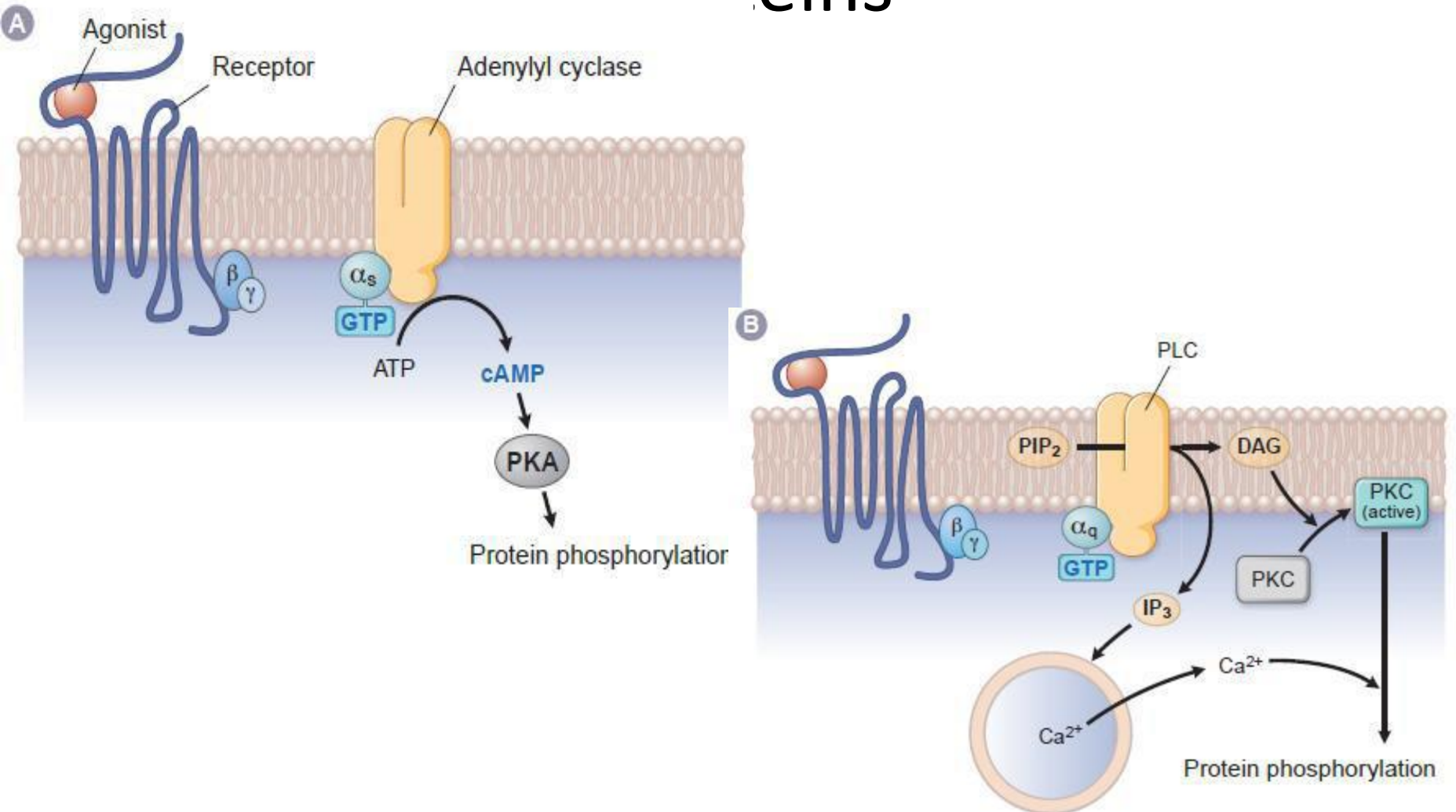
G_q

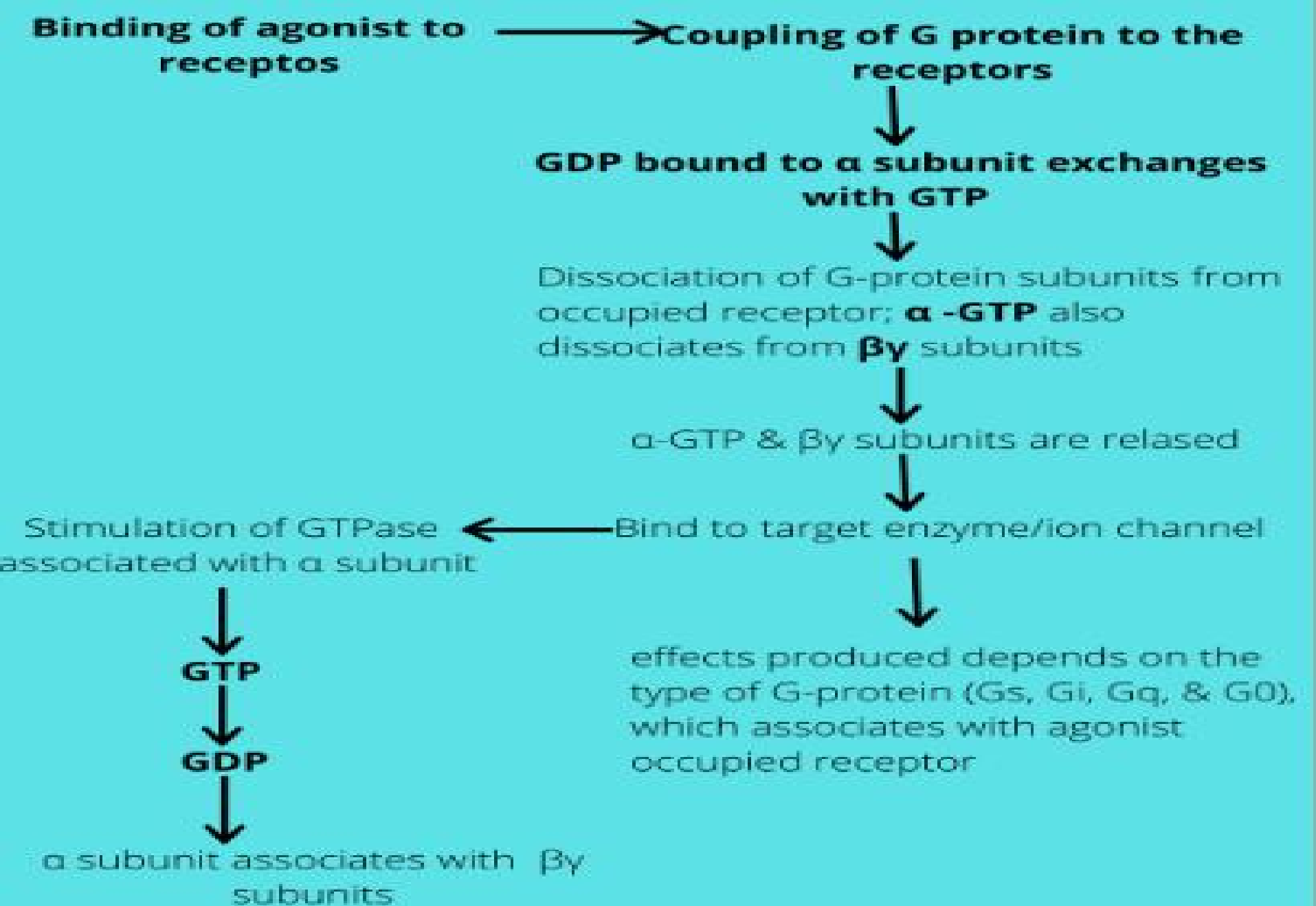
Activates phospholipase C

$G_{12/13}$

Diverse ion transporter interactions

Fig: activation of AC and PLC by G-proteins





- $G_s \rightarrow$ stimulates Adenylyl cyclase \rightarrow increase cAMP , e.g. β -adrenergic receptors
- $G_i \rightarrow$ inhibits Adenylyl cyclase \rightarrow decrease cAMP, e.g. α_2 -adrenergic receptors in smooth muscle
- $G_q \rightarrow$ stimulates Phospholipase C \rightarrow increase IP3 & DAG, e.g. muscarinic (M1) receptors
- $\beta \gamma \rightarrow$ stimulates or inhibits \rightarrow enzymes and ion channels, e.g. all GPCRs

- Ion channel regulation
- Guanylyl cyclase: cGMP

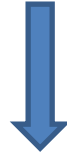
Ligand-gated Ion channel receptor

- Inotropic receptors
- 232 distinct ion channels
- Regulate the flow of Na^+ , K^+ , Ca^{2+} and Cl^- across the cell membrane to carry out important functions like neurotransmission, cardiac conduction, muscle contraction, secretion
- Important drug targets
- Onset of action of the drug is fastest

Binding of agonist to inotropic receptors



Opens the ion channels (Na⁺, K⁺, Ca²⁺, Cl⁻)



Flow of ions through channels



Hyperpolarization/depolarization



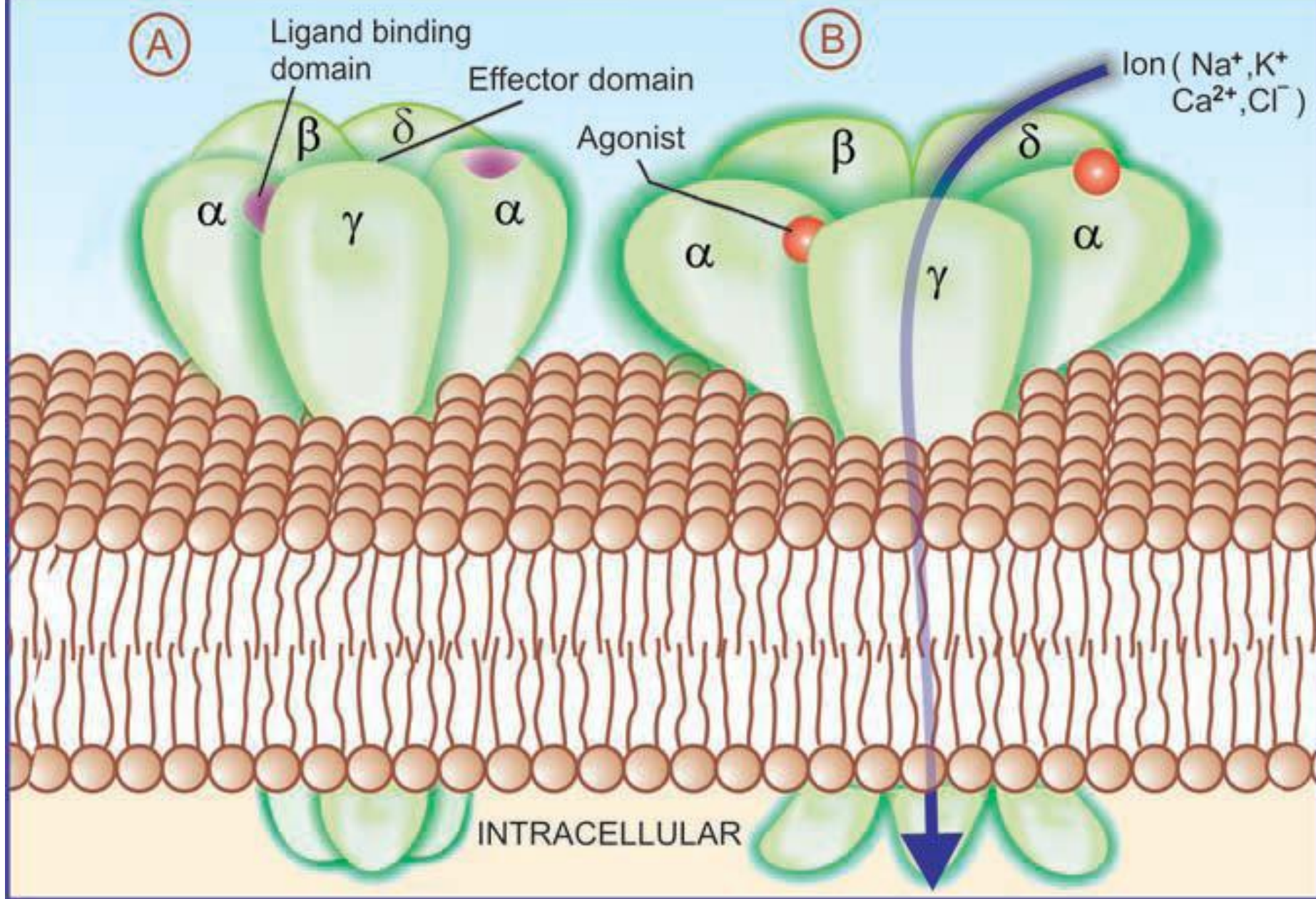
Tissue response

Ion channel receptor

- **Classification:**
 - Voltage-activated channels
 - Ligand-activated channels
 - Store-activated
 - Stretch-
 - Temperature-
- Nicotinic receptor, GABAA receptors, glutamate receptor, glycine receptor

Voltage-activated channels

- Voltage-activated Na⁺channel
 - Local anesthetic: lidocaine
 - Antiarrhythmic drugs
- Voltage-activated Ca²⁺channel
 - Calcium channel blockers: Nifedipine, diltiazem
- Voltage-activated K⁺ channel
 - Antiarrhythmic drugs



Transmembrane enzyme receptor

- Physiological membrane receptors with extracellular ligand binding domain and intrinsic enzymatic activity on the cytoplasmic surface of the cell
 - Insulin receptor
 - Epidermal growth factor receptor
 - Platelet derived growth factor
 - Vascular endothelial growth factor

Binding of agonist to extracellular domain of receptors



Dimerization of the receptor



Stimulates intrinsic kinase activity



Activates intracellular signalling pathways



Gene transcription



Tissue response

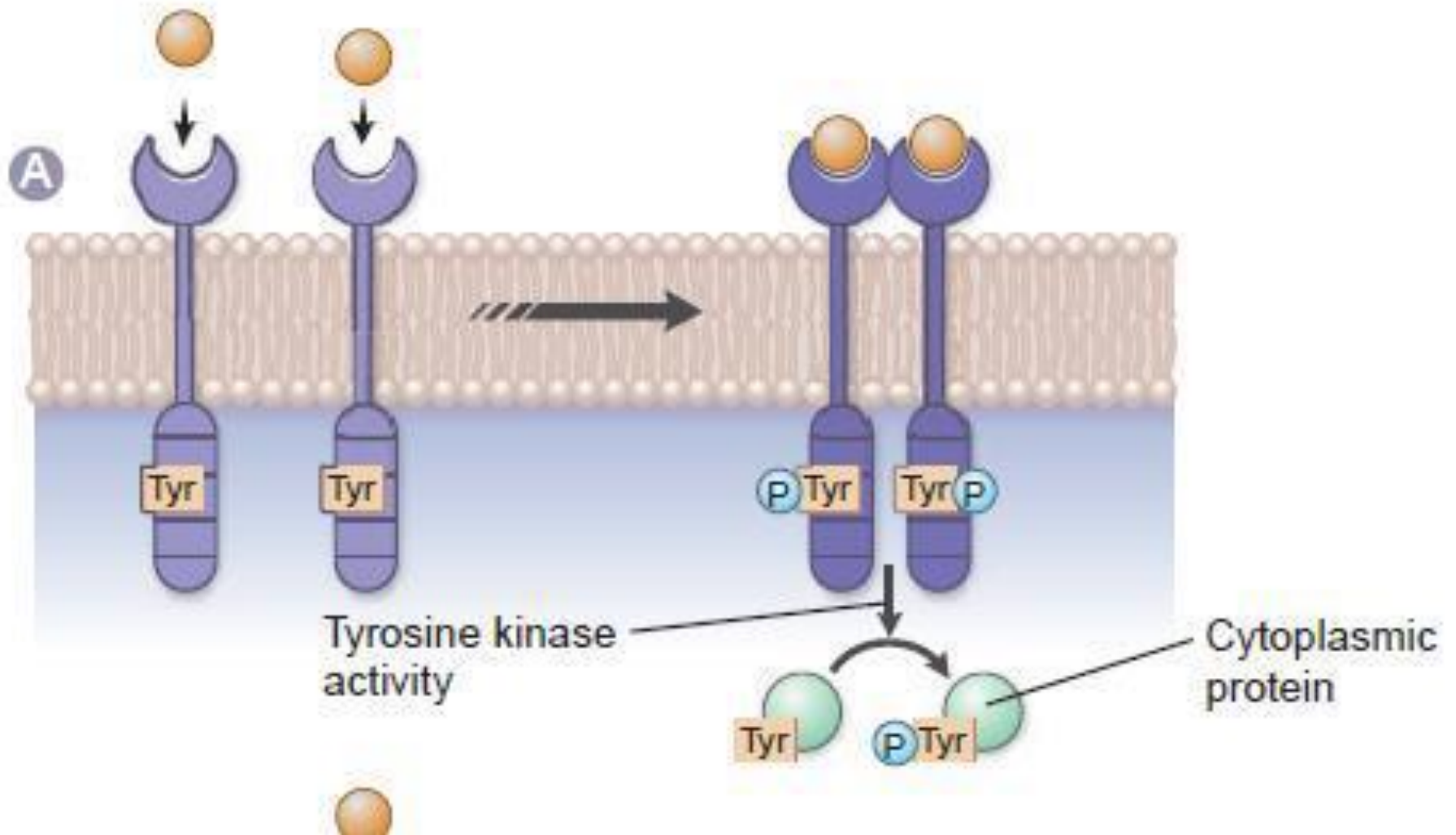


Fig: transmembrane receptor tyrosine kinase

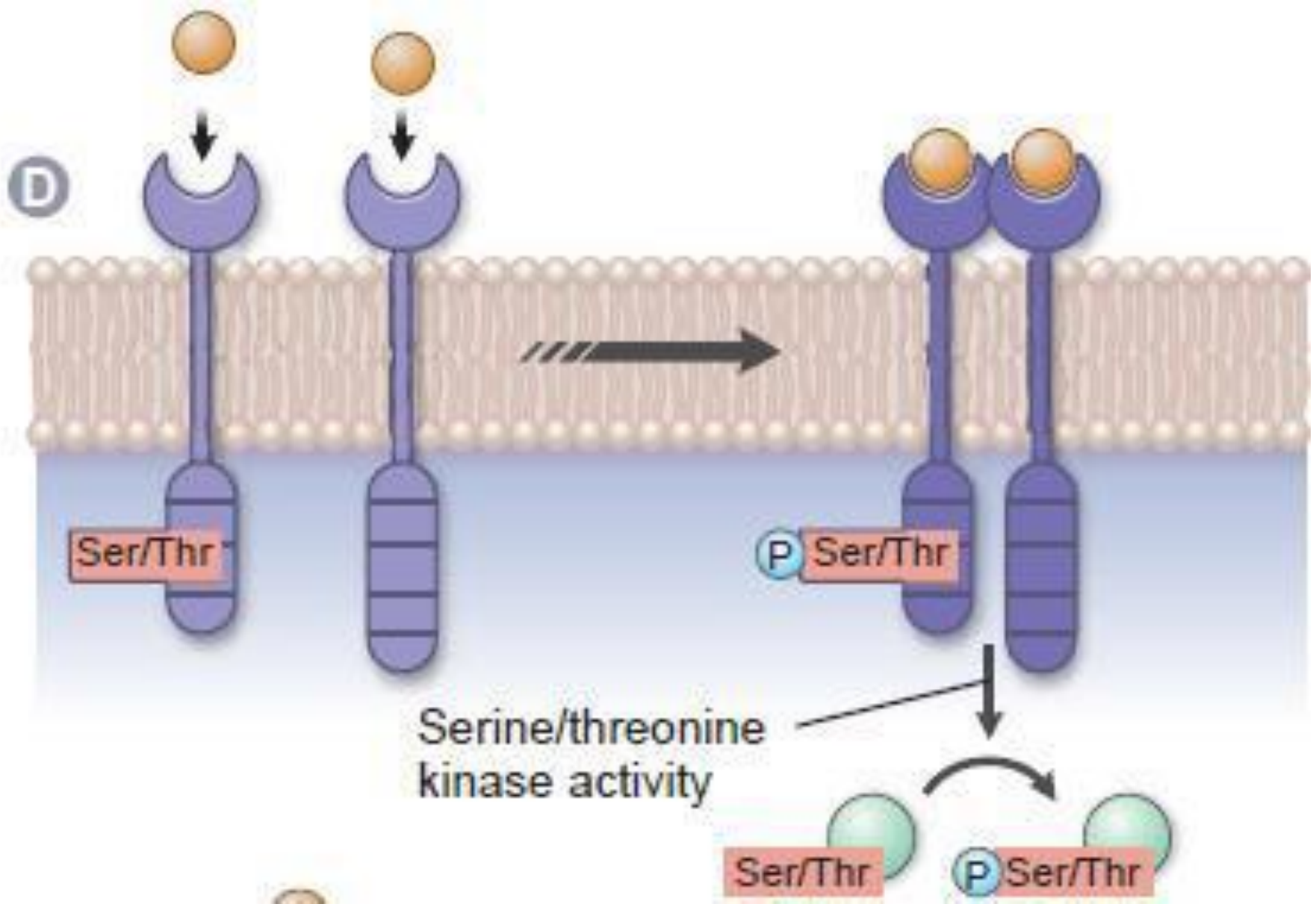


Fig: receptor serine/threonine kinase

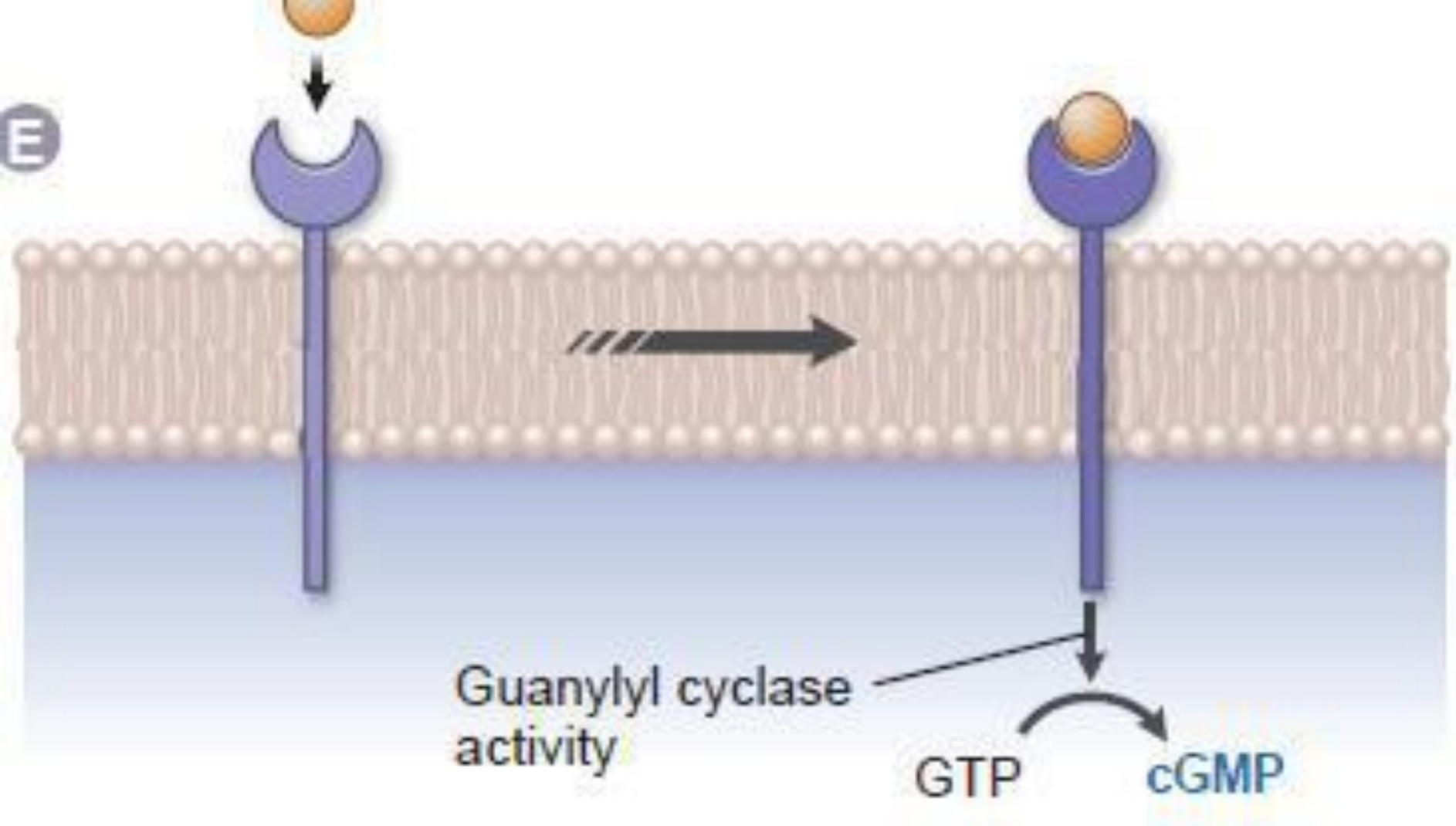
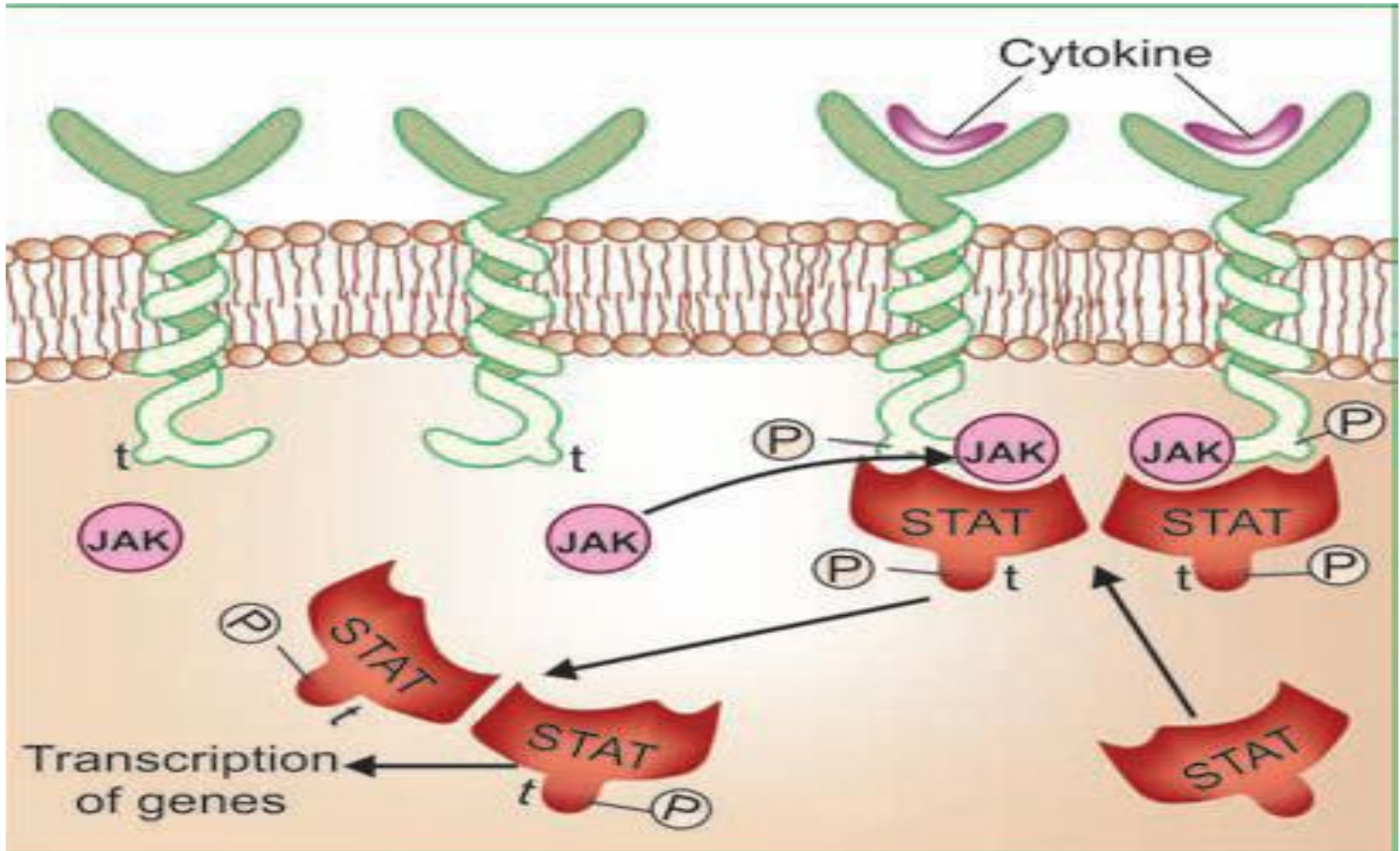


Fig: receptor guanylyl cyclases

Transmembrane non-enzymes

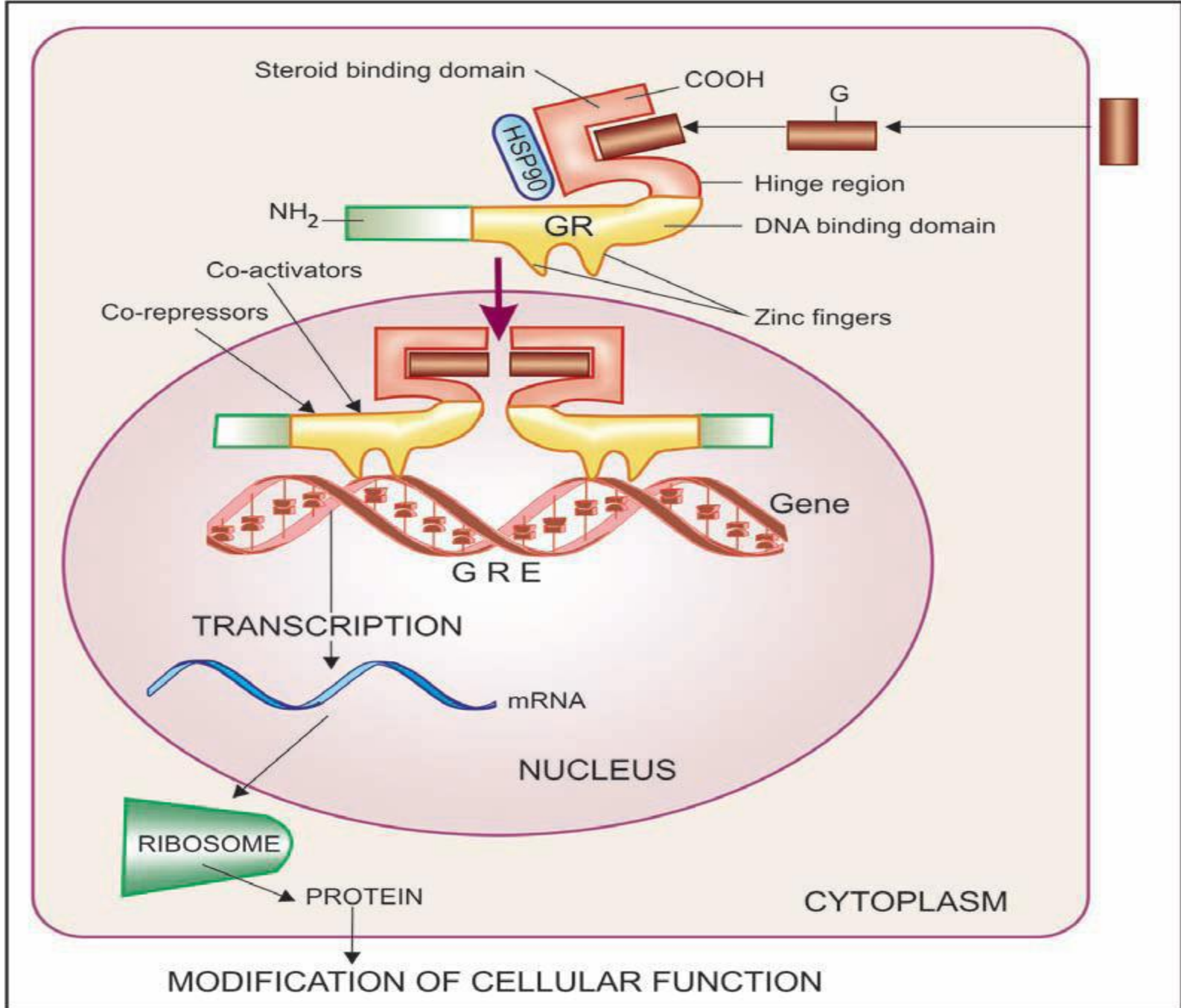
- No intrinsic enzymatic activity
- Signal to nucleus in direct manner
- JAK: janus kinase
- STAT: signal transducer and activator of transcription

JAK-STAT pathway



Nuclear receptors

- 48 receptors
- Regulates the expression of genes controlling numerous physiological processes such as reproduction, development and metabolism
- Examples:
 - Steroid hormone receptors
 - Retinoic acid receptor
 - Liver X receptor
 - Peroxisome proliferator activated receptors



- Ligand binding
- Dimerization:
 - Homodimer
 - Heterodimer
- Hormone response element
- Co-regulators
 - Co-activators: histone acetylase
 - Co-repressors: histone deacetylase

Intracellular enzymes

- Soluble guanylate cyclase
- Nitrovasodilators
- NO stimulate GC to produce cGMP which activate PKG in vascular smooth muscle and cause vasodilation

Regulation of receptors

- Supersensitivity:
 - Unmasking of receptors or
 - their proliferation (*up regulation*)
 - or accentuation of signal amplification by the transducer.

- Desensitization
 - Continued stimulation of cells with agonists generally results in a state
 - Also referred to as *adaptation, refractoriness, or down-regulation*
 - The effect to the same concentration of drug is diminished
 - Downregulation: decreased synthesis/increased degradation
 - Types: homologous and heterologous
 - Beta-2 receptors and salbutamol

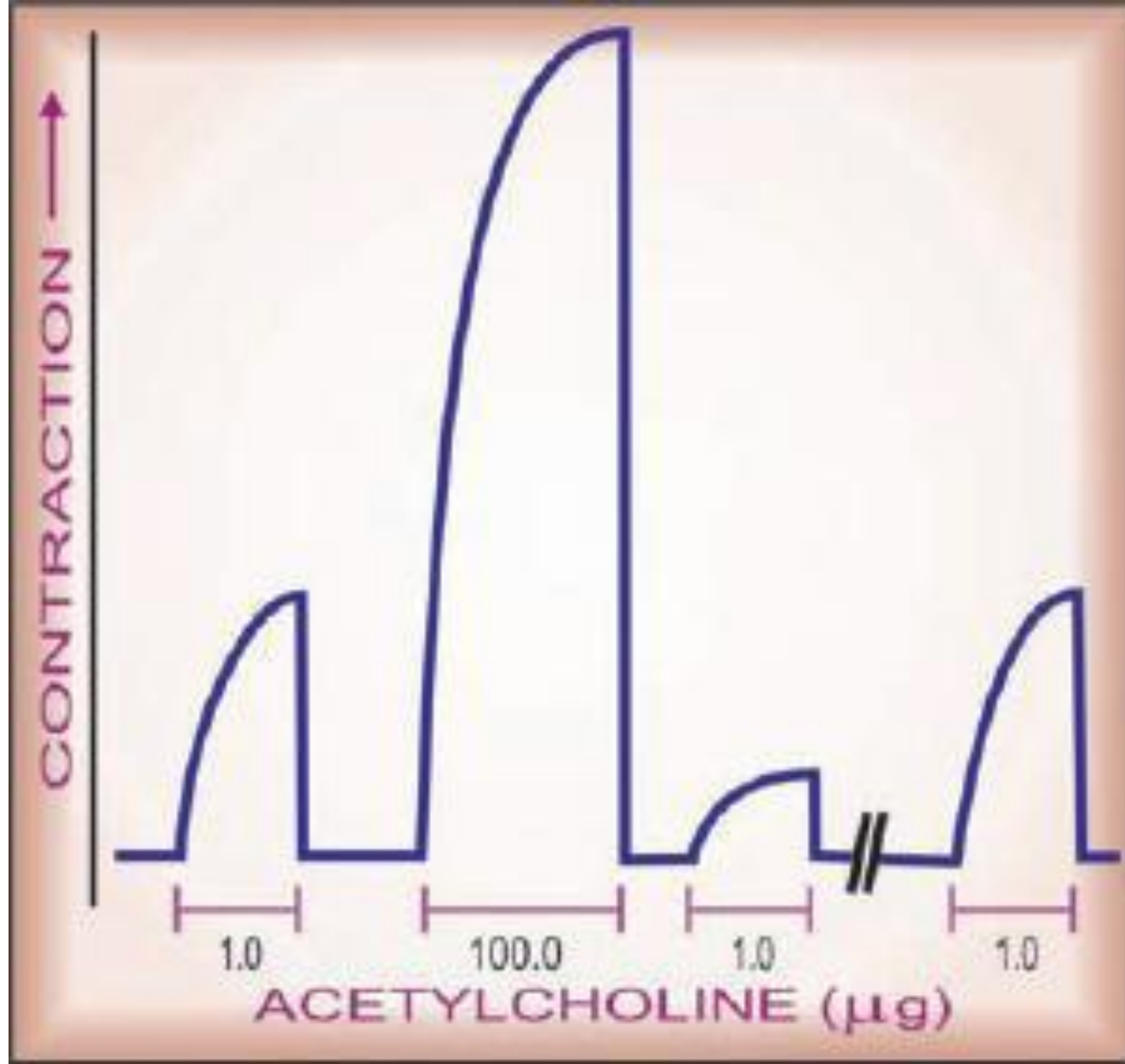
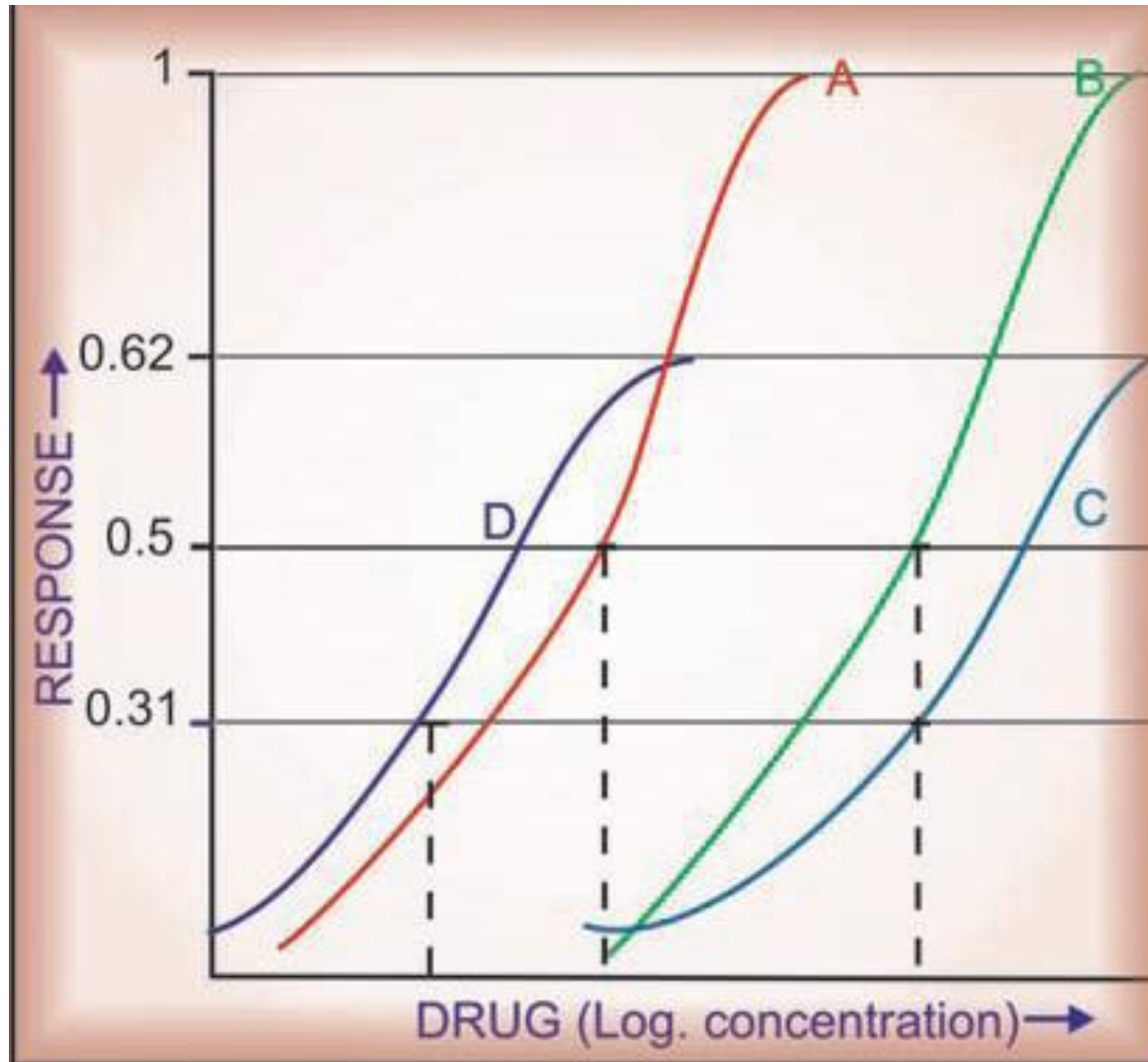


Fig: phenomenon of desensitization

Dose response curve



Dose response curve

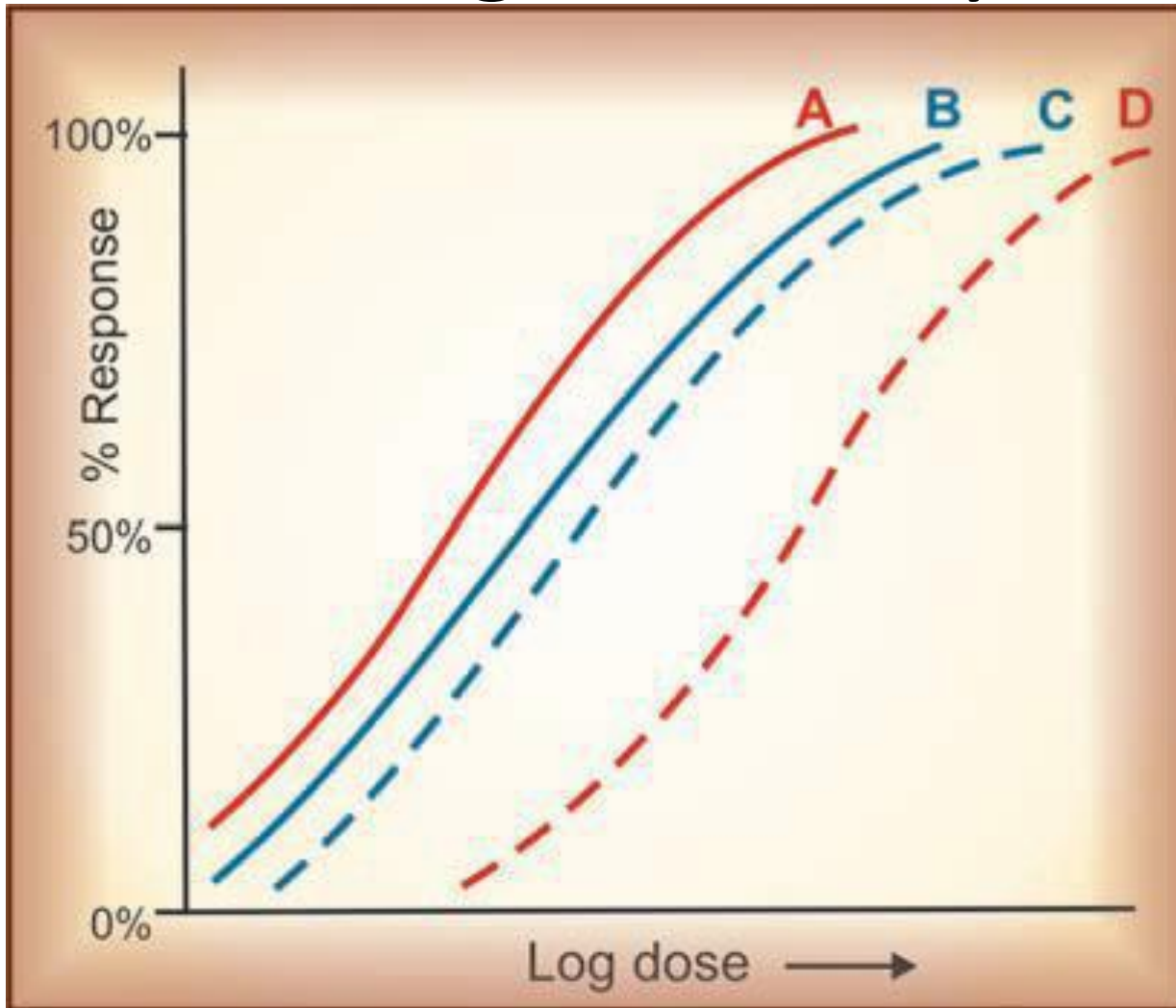
- Pharmacological effect of a drug depends on its concentration at the site of action, which in turn is determined by the dose of drug administered.

Types of Dose-response curve

- Graded dose-response
 - Plotted on a graph takes the form of a rectangular hyperbola, where log dose-response curve is sigmoid shaped
- Quantal dose-response curve
 - Certain pharmacological effects which cannot be quantified but can only be said to be present or absent (all or none)
 - E.g. a drug causing ovulation

- Potency :
 - The amount of drug needed to produce a certain response
 - Lower the dose required for a given response, the more potent is the drug
 - Example, analgesic dose of morphine is 10 mg and that of pethidine is 100 mg.
 - Therefore, Morphine is ten times more potent than pethidine as analgesic
- Efficacy:
 - The maximal response that can be elicited by the drug
 - Example, morphine is more efficacious than aspirin as an analgesic
- Therapeutic efficacy
 - Depends not only on the relative potency and efficacy of the drug, but on many pharmacokinetic and pathophysiological variables

Drug selectivity



- Therapeutic index (TI)
 - Safety margin
 - The gap between the therapeutic effect DRC and the adverse effect DRC

- Therapeutic window
 - The dose which produces minimal therapeutic effect and the dose which produces maximal acceptable adverse effect

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

OR

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

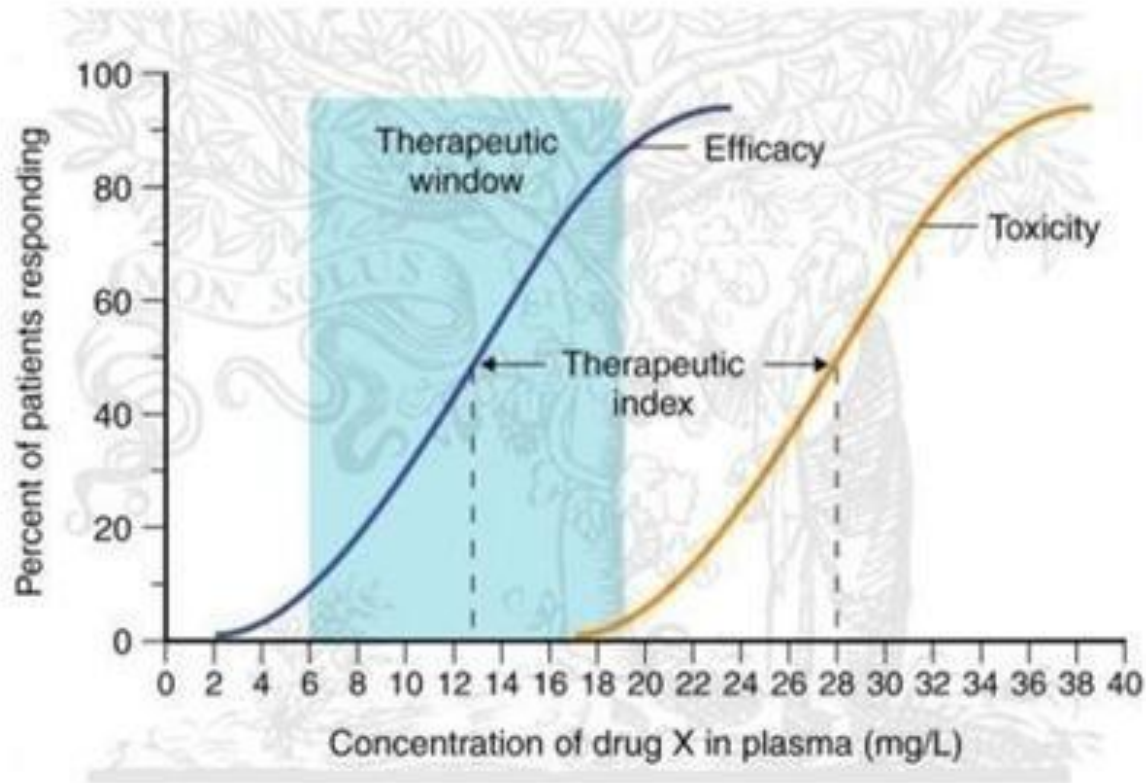
Therapeutic index (TI)

- An index of drug safety margin
- It is the ratio of median lethal dose to the median effective dose.
- LD50:
 - Dose of a drug, which is lethal for 50% of the population
- ED50:
 - Dose of a drug, which produces the desired effect in 50% of the population
- Higher the value of therapeutic index, safer is a drug, e.g. penicillin has a high TI

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

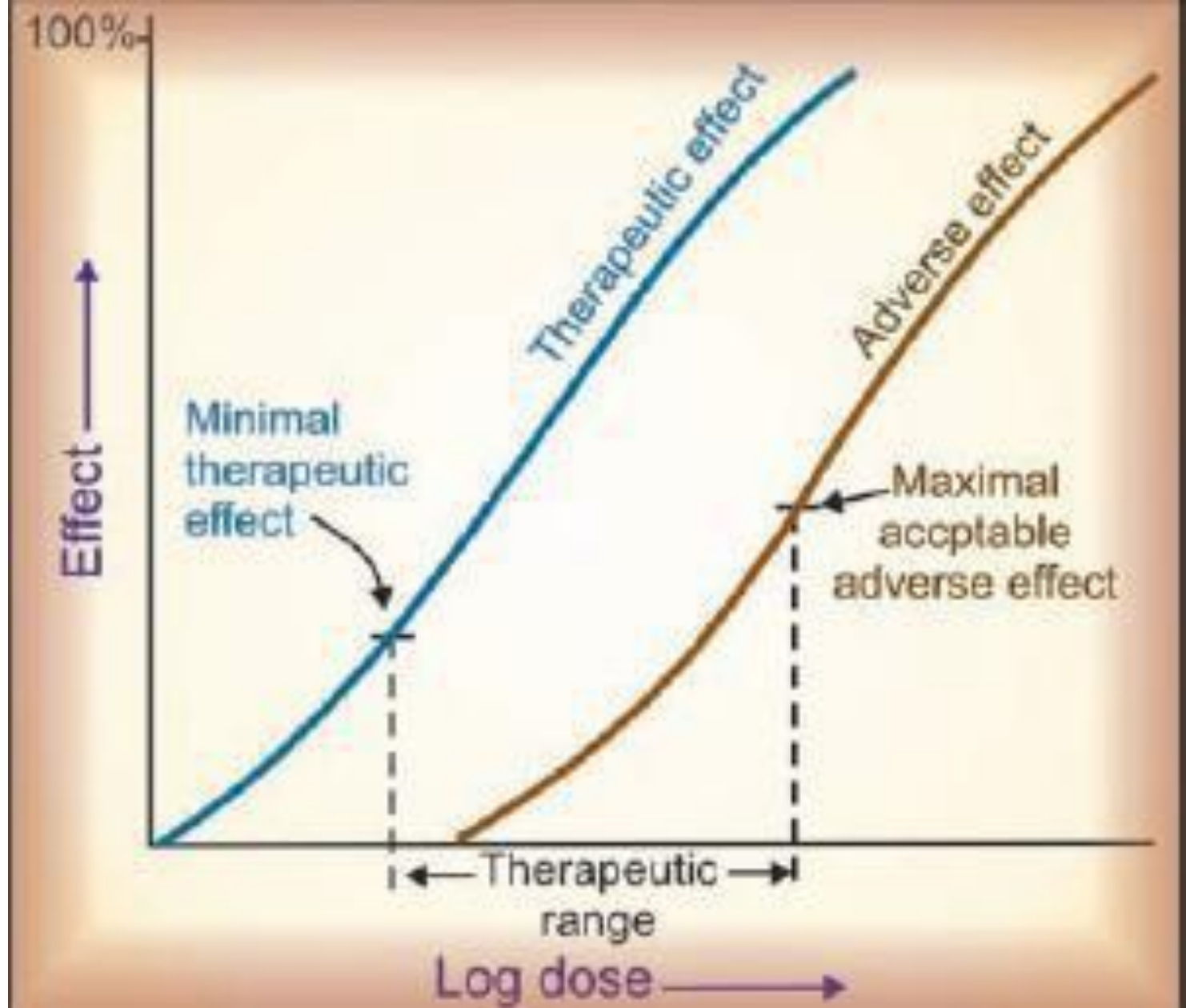
or $\frac{LD_{50}}{ED_{50}}$

Therapeutic Window vs Therapeutic Index



- Drugs with Narrow TI:
 - Require regular drug level monitoring to ensure effective treatment without unacceptable adverse effects
 - Examples:
 - Digoxin
 - Cyclosporine
 - Theophylline
 - Warfarin

- Therapeutic window
 - Range of dosage of drug that can be used effectively without unacceptable adverse effect
 - Ranges from minimum effective dose to minimum toxic dose
 - Below therapeutic window, the dose is ineffective to treat
 - Above the therapeutic window, toxicity appears frequently
 - Useful more than TI for clinical management purpose as a safety measure and dosage guide



Risk benefit ratio

- Conveys a judgement on the estimated harm (adverse effects, cost, inconvenience) vs expected advantages (relief of symptoms, cure, reduction of complications/mortality, improvement in quality of life)
- Drugs only prescribed when the benefits outweigh the risks

Combined effects of drugs

- Synergism
 - Additive
 - Supraadditive
- Antagonism
 - Physical
 - Chemical
 - Physiological
 - Receptor

Synergism

- When two or more drugs are administered simultaneously, their combined effect is greater than that elicited by either drug alone
- Example,
 - Sulphamethoxazole +trimethoprim; pyrimethamine +sulphadoxine

Supra-additive (potentiation)

- Enhancement of action of one drug by another drugs
- Effect of drugs $A+B >$ Effect of drug A+ Effect of drug B
- Example,
 - Levodopa+carbidopa; acetylcholine+physostigmine.
 - Carbidopa and physostigmine inhibits the breakdown of levodopa and acetylcholine, respectively, thus enhancing their effects

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 (enalapril+ hydrochlorothiazide)	Tackling two contributory factors
Tyramine + MAO inhibitors	Increasing releasable CA store

- Additive effect
 - Combined effect of two or more drugs is equal to the sum of their individual effect
 - Effect of drugs $A+B = \text{Effect of drug A} + \text{Effect of drug B}$
 - Example,
 - Combination of ibuprofen and paracetamol as analgesic

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

Antagonism

- Effect of one drug is decreased or abolished in the presence of another drug
 - Physical antagonism
 - Opposing action of two drugs is due to their physical property
 - Example, adsorption of alkaloids by activated charcoal for alkaloid poisoning

Antagonism

- Chemical antagonism
 - Opposing action of two drugs is due their chemical property
 - Example,
 - Antacids are weak bases; that neutralize gastric acid and are useful for in peptic ulcer.
 - Tannins + alkaloids—insoluble alkaloidal tannate is formed

Antagonism

- Physiological/functional antagonism
 - Two drugs act at different receptor or by different mechanisms on the same physiological system and produce opposite effects
 - Example,
 - insulin and glucagone on blood sugar
 - Histamine and adrenaline on bronchial muscles and BP
 - Hydrochlorothiazide and triamterene on urinary K.excretion.

Receptor antagonism

- Binds to the same receptor as agonist and inhibits its effects
- May be competitive or non-competitive.

Competitive antagonism

- Equilibrium type:
 - Both agonist and the antagonist bind reversibly to the same site on the receptor
 - Overcome (reversible) by increasing the concentration of the agonist
- Non-equilibrium
 - Antagonist binds to the same site on the receptor as agonist but binding is irreversible
 - Antagonist forms strong covalent bond with receptor
 - Example, phenoxybenzamine is an irreversible antagonist of adrenaline at alpha receptor

Non-competitive antagonism

- Antagonist binds to a different site on the receptor and prevents the agonist from interacting with receptor
- In this type, the antagonistic effect cannot be overcome by increasing the concentration of the agonist
- Example, diazepam and bicuculline

Receptor antagonism

Competitive (equilibrium type)

1. Antagonist binds with the same receptor as the agonist
2. Antagonist resembles chemically with the agonist
3. Parallel rightward shift of agonist DRC
4. The same maximal response can be attained by increasing dose of agonist (surmountable antagonism)
5. Intensity of response depends on the concentration of both agonist and antagonist
6. Examples: ACh—Atropine
Morphine—Naloxone

Noncompetitive

- Binds to another site of receptor
Does not resemble
Flattening of agonist DRC
Maximal response is suppressed (unsurmountable antagonism)

Maximal response depends only on the concentration of antagonist
Diazepam—Bicuculline