

Principles & Mechanism of Drug Action

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INTRODUCTION

The chemical in a drug combines with or alters the molecules in body cells so that it changes the way the cells work.

Alter the pace of ongoing activity not impart new function

Types of drug action:

1. Stimulation
2. Depression
3. Irritation
4. Replacement
5. Cytotoxic action
6. Antimicrobial action
7. Modification of immune status



Stimulation:

- Selective enhancement of the level of activity of specialized cells
 - Eg: Adrenaline – heart, Pilocarpine- salivary glands
- Excessive stimulation: followed by depression
 - Eg: Picrotoxin : convulsions → coma & respiratory depression



Depression:

- Selective diminution of activity of specialized cells
- Eg: Barbiturates- CNS, Quinidine- heart
- Certain drugs stimulate one type of cells & depress the other.
Eg: Acetyl choline

↑ intestinal smooth muscle

↓ SA node in the heart

Morphine

↑ vagus
oculomotor nuclei
CTZ

↓ respiratory & cough centres



Irritation

- Non-selective often noxious effect – applied to less specialised cells (epithelium, connective tissue) eg. Bitters increase salivary and gastric secretion
- Counter irritants increase blood flow.
- Strong irritants cause corrosion ,necrosis



Irritant applied locally to the skin to relieve deep seated pain:
counterirritant

Stimulation of sensory nerve endings –skin



Afferent impulses relayed in cerebrospinal axis – efferent vasomotor fibers to internal organ



Increased circulation in skin- deep structures



Sensory impulses from skin Interfere with pain impulses from viscera & partial/complete exclusion



Vasodilation and blockade of pain impulses: relief of deep seated pain



Replacement

- Use of natural metabolites, hormones or their congeners in deficiency states.
- Ex- Levodopa in parkinsonism, Iron in anaemia, insulin in diabetes.



Cytotoxic action

- for invading bacteria parasite, cancer cells, without effecting the host cells
- Used for cure /palliation of infections and neoplasms

Eg

- Pencillins,
- chloroquin,
- zidovudine,
- cyclophosphamide.



Antimicrobial action:

- Prevention, arrest & eradication of infections
- Act specifically on causative organisms
- Eg: antibiotics

Modification of immune status:

- Enhancing or depressing the immune status
- Eg: Vaccines, sera, levamisole, corticosteroids



MECHANISM OF DRUG ACTION

- Drugs act by their physical or chemical property
- **Bulk laxatives** –physical mass
- **Dimethicone** – physical form opacity
- **PABA**- absorption of UV rays
- **Activated charcoal**- adsorptive property
- **Mannitol, MgSO₄** –osmotic activity
- **KMNO₄** –oxidising property
- **Antacids** –neutralisation of gastric activity



MECHANISM OF DRUG ACTION

MAJORITY OF DRUGS INTERACT WITH TARGET BIOMOLECULES:

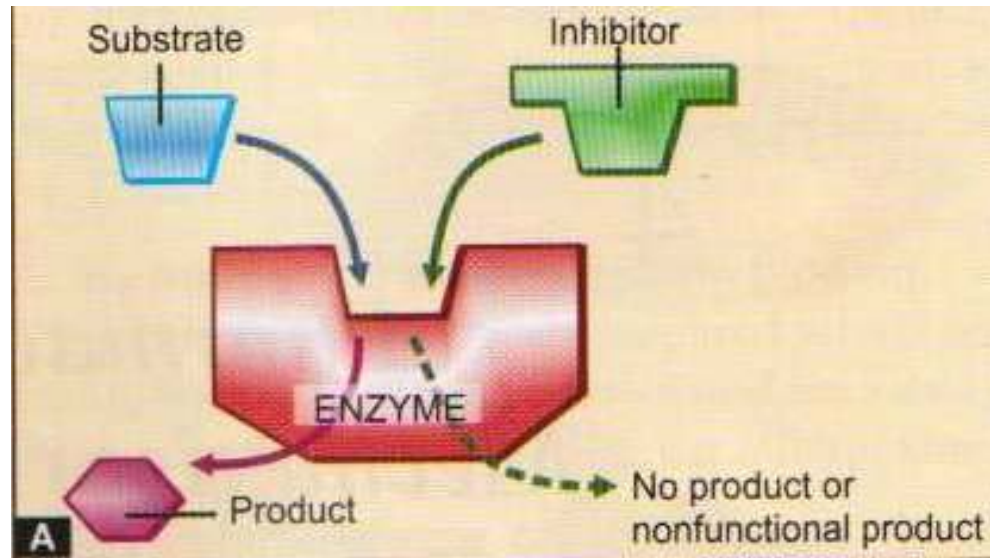
Usually a Protein

- **ENZYMES**
- **ION CHANNELS**
- **TRANSPORTERS**
- **RECEPTORS**



ENZYMES

- Important target : all biological reactions under enzyme action
- Enzyme stimulation/ enzyme inhibition



ENZYME STIMULATION

- Unusual with foreign substances
- Occurs with endogenous ones
- Adrenaline \longrightarrow adenylyl cyclase; pyridoxine as cofactor decarboxylase
- Stimulation affinity for substrate
- **Enzyme induction:** synthesis of more enzyme

\uparrow protein activity



ENZYME INHIBITION

NON SPECIFIC

- Denaturing proteins: altering tertiary structure
- Heavy metal salts
- Strong acids
- Phenol
- Alkalies
- Too damaging for systemic use

SPECIFIC

- I. Competitive/
equilibrium type
non- equilibrium type
- II. Non competitive
 - A. Reversible
 - B. Irreversible



ION CHANNELS

- Ion selective channels: transmembrane signaling & regulate intracellular ionic composition

Drugs

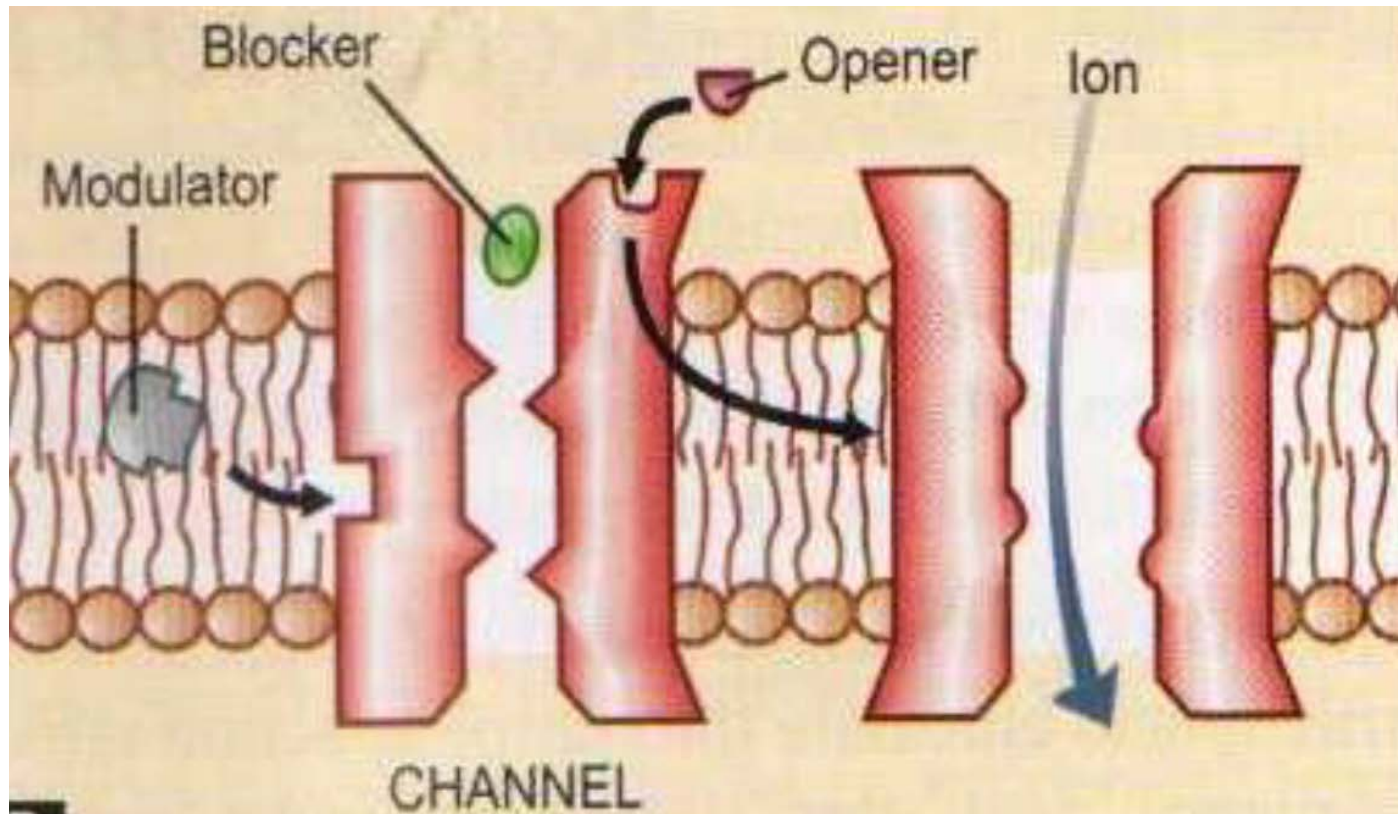
**Specific receptors:
ligand gated ion
channels/
G-protein coupled
receptors**

**Direct binding to
ion channel**

**Modulating
opening and
closing of the
channels**



ION CHANNELS



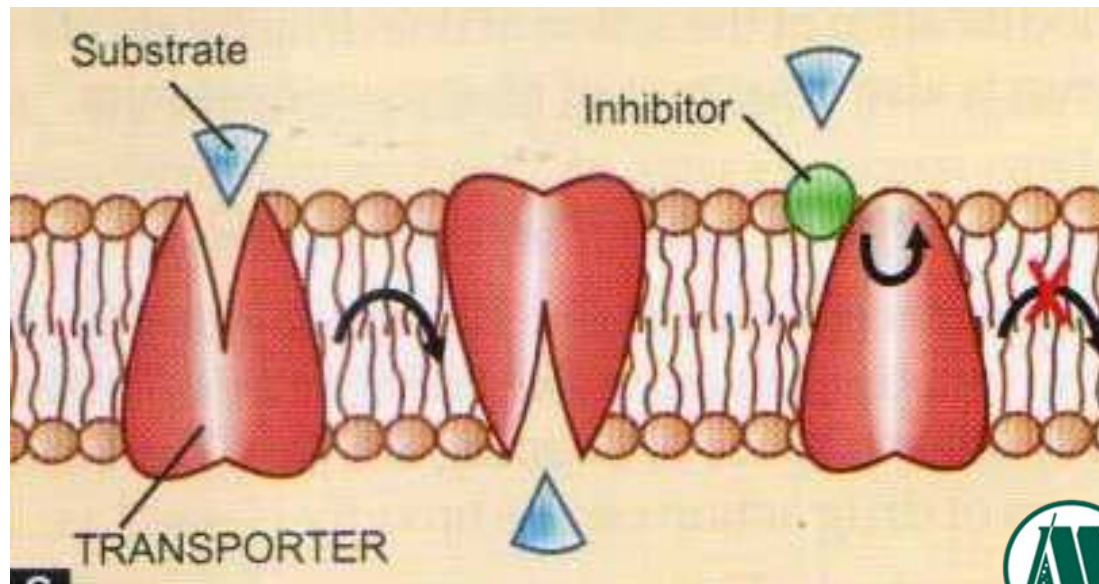
ION CHANNELS

Quinidine	Blocks	Myocardial Na ⁺ channels
Dofetilide Amiodarone	Block	Myocardial delayed rectifier K ⁺ channel
Nifedipine	Blocks	L-type voltage sensitive Ca ²⁺ channel
Nicorandil	Opens	ATP sensitive K ⁺ channels
Sulfonylureas	Inhibit	Pancreatic ATP sensitive K ⁺ channels
Amiloride	Inhibits	Renal epithelial Na ⁺ channel
Phenytoin	Modulates	voltage sensitive Na ⁺ channel
Ethosuximide	Inhibits	T-type Ca ²⁺ channels in thalamic neurones



TRANSPORTERS

- Substrates translocated across membranes by binding to specific transporters
- Facilitate diffusion: concentration gradient
- Pump against the concentration gradient using metabolic energy
- Drugs: direct interaction with the solute carrier(SLC) class of transporter proteins: inhibition



TRANSPORTERS

METABOLITE/ ION	TRANSPORTER	DRUG
Noradrenaline	Norepinephrine transporter-neurons	Desipramine Cocaine
Serotonin	Serotonin transporter-neurons	Selective Serotonin Reuptake Inhibitors
Dopamine	Dopamine transporter-neurons	Amphetamines
Noradrenaline Serotonin	Vesicular amine transporter	Reserpine
Acetyl choline	Choline uptake- neurons	Hemicholinium
GABA	GABA transporter GAT1	Tigabine
Organic acids: uric acid, penicillin	Organic anion transporter-renal tubules	Probenecid

Furosemide inhibits: $\text{Na}^+\text{K}^+ 2\text{Cl}^-$ cotransporter in ascending limb of LOH

Hydrochlorothiazide inhibits: Na^+Cl^- symporter in early distal tubule



RECEPTORS

DEFINITION:

- *'A macromolecule or binding site located on the 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'*



RECEPTORS

- The term agonist and antagonist is based on affinity and intrinsic activity.
- Affinity is tendency to occupy the receptor and intrinsic activity (efficacy) is the ability to initiate changes leading to effect.
- Agonist- drug having both affinity as well as intrinsic activity

Ex-Ach at muscarinic and nicotinic receptor

- Antagonist- drug having affinity but no intrinsic activity

Ex-atropine at muscarinic receptor

Partial agonist- drug having affinity but weak intrinsic activity

Ex- nalorphine at opioid receptor

- Inverse agonist- drug having both affinity as well as intrinsic activity but in a opposite direction to the agonist.

Ex- β -carboline at benzodiazepine receptor



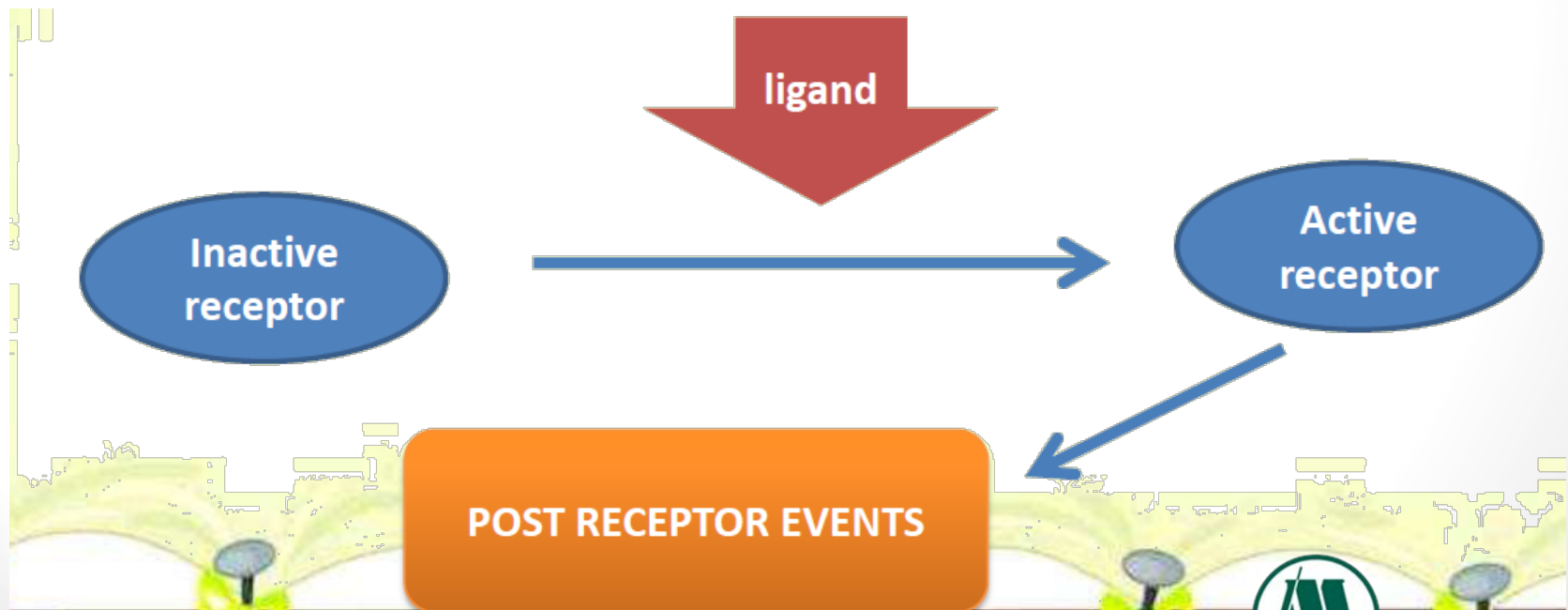
RECEPTORS

- The largest no. of drugs act through them-control effectors
- Cell membrane/ cytosol
- Endogenous substances & drugs
- Regulate cell function by altering:
 - **Enzyme activity**
 - **Permeability to ions**
 - **Conformational features**
 - **Genetic material**



RECEPTORS

- **Recognition molecule:** for specific ligands
- **Transmits the signal:** ligand to proteins in cell membrane & within the cell- amplify the original signal: *cascade effect*



RECEPTORS

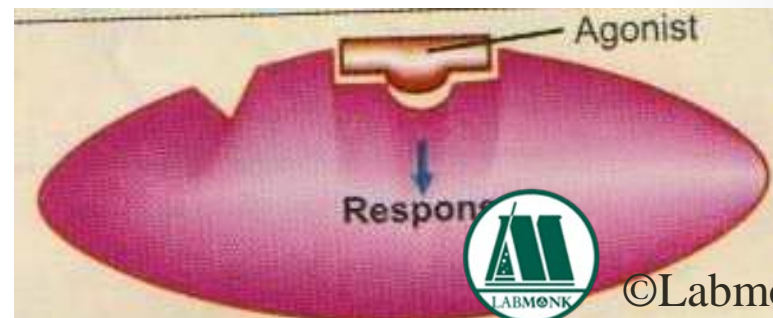
- **Selectivity:** binding of drugs to receptors depends on physico-chemical structure
- **Affinity:** strength of binding between the drug & receptor
- **Efficacy/ Intrinsic activity:** ability of a drug to elicit a pharmacological response after its interaction with the receptor



RECEPTORS

Agonist:

- Drug which initiates pharmacological action after binding to the receptor
- Similar to natural hormone/ transmitter
- High affinity & intrinsic activity
- Value rests on greater capacity to resist degradation & act for longer than endogenous ligands
- Bronchodilation : salbutamol >> adrenaline



RECEPTORS

- **Inverse agonist:**
 - An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist
 - β -carboline : BZD receptors in CNS stimulation, anxiety, increased muscle tone, convulsions



RECEPTORS

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
- Same affinity for the receptor & similar to agonist; poor intrinsic activity



RECEPTORS

Agonists and Antagonists

Agonists Drugs that occupy receptors and activate them.

Antagonists Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.



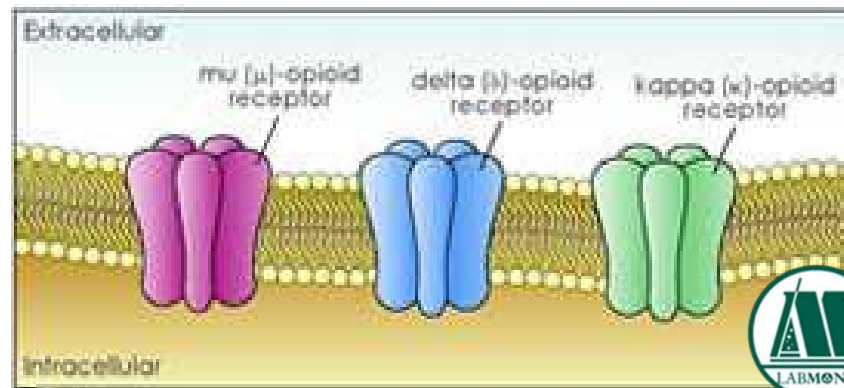
RECEPTORS

- **Partial agonists:**
 - An agent which activates the receptor to produce submaximal effect but antagonizes the action of a full agonist
 - Affinity equal to or less than agonists; less intrinsic activity



RECEPTORS

- Opioid drugs: agonists/partial agonists on some receptors, antagonists on other
- Pentazocine & nalbuphine agonists on κ - receptors; antagonist on μ
- β - blockers: pindolol& oxprenolol: partial agonist; propranolol: pure antagonist
- Exercise tachycardia maybe abolished by both types, but resting heart rate is lower with propranolol

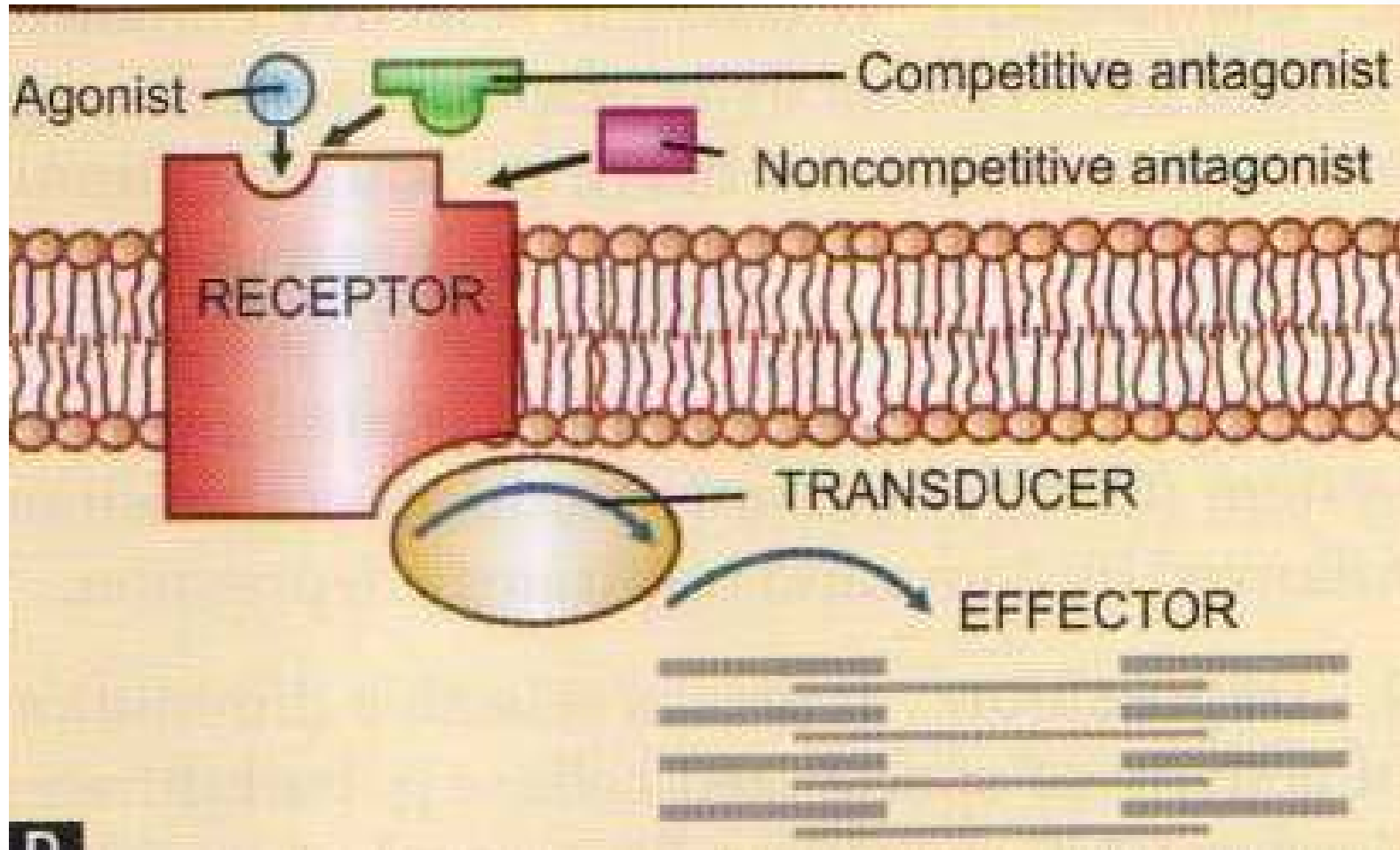


RECEPTORS

- **Ligands:**
- Any molecule which attaches selectively to particular receptors or sites
- Affinity/ binding without regard to functional change
- Agonists & competitive antagonists: ligands
- Multiple receptor types & subtypes: dopamine-2, histamine-3, acetyl choline & adrenaline-5



RECEPTORS



RECEPTOR REGULATION

Density & efficacy: regulated by-

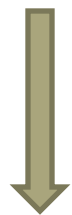
- Level of on-going activity
- Feedback from own signal output
- Other physiopathological influences



RECEPTOR REGULATION

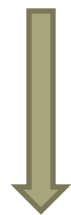
Down regulation

- Continued exposure to a drug/ agonist:
blunted response: *desensitisation/*
refractoriness/ tolerance



affinity to drug

&



no. of receptors

- Repeated admn. – adrenergic agonists in asthma —→ down regulate β -receptors



RECEPTOR REGULATION

Up regulation

- Depletion of noradrenaline/ treatment with adrenergic antagonists: supersensitivity of tissues to noradrenaline & ↑ in receptor no.
- • C/C admn. Of β -blocker: ↑ in adrenergic receptors
- • Sudden withdrawal of β -blockers in ischemic heart disease : susceptible to effects of circulating noadrenaline-arrhythmias



NATURE OF RECEPTORS

- Regulatory macromolecules: proteins/ nucleic acids
- Each receptor family: common structural motif & individual receptor differs in amino acid sequencing, length of loops etc.



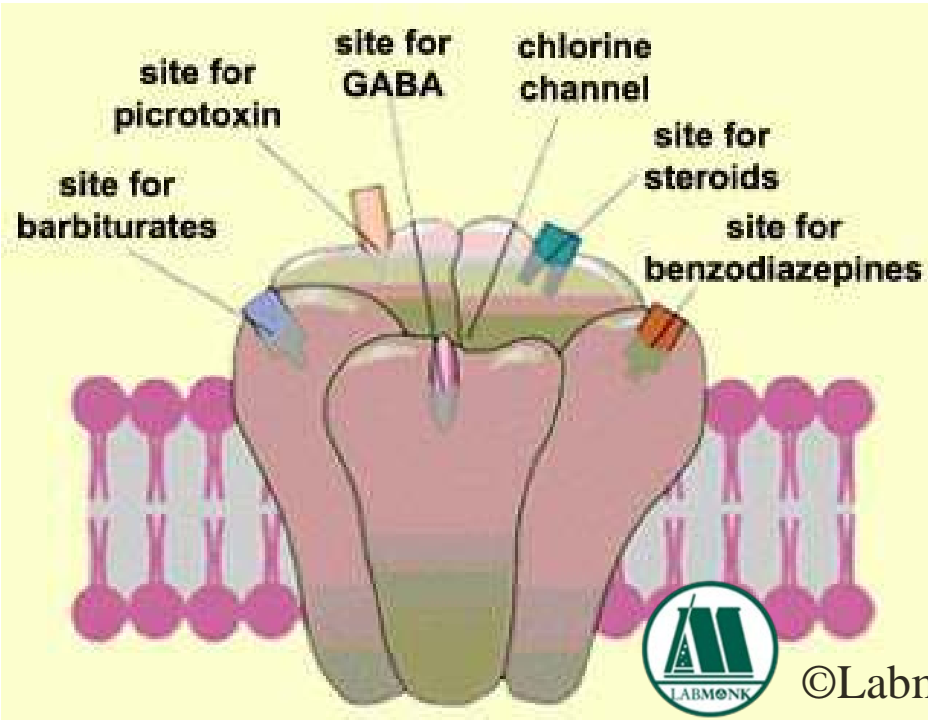
NATURE OF RECEPTORS

- **Physiological:** transmitters, autacoids, hormones.

Eg: *Cholinergic, adrenergic, histaminergic, leukotriene, steroid, insulin.*

- **Drug :** no known physiological ligands.

Eg: BZD, sulfonyl urea, cannabinoid receptors



CLASSIFICATION OF RECEPTORS

I. Pharmacological criteria:

- Relative potencies of agonists & antagonists
- Classical & oldest: direct clinical bearing
- Cholinergic, adrenergic & histaminergic receptors

II. Tissue distribution:

- Subtypes
- Cardiac β -receptor: β_1 & bronchial: β_2



CLASSIFICATION OF RECEPTORS

III. Ligand binding:

- Measurement of specific binding of high affinity radiolabelled ligand to cellular fragments in vitro & displacement by selective agonists/ antagonists
- 5-HT receptors distinguished

IV. Transducer pathway:

- Mechanism through which activation is linked to the response
- NM – G proteins; NN – Na⁺ influx
- β adrenergic cAMP
- α adrenergic IP₃- DAG pathway & cAMP
- GABAA : ligand gated Cl⁻ channel
- GABAB : K⁺ conductance through G- protein



CLASSIFICATION OF RECEPTORS

- **V. Molecular cloning:**
 - Receptor protein cloned: amino acid & 3D structure worked out
 - Subtypes: sequence homology
 - Doubtful functional significance



TRANSDUCER MECHANISMS

- Highly complex multistep process : amplification & integration of intra- and extracellular signals

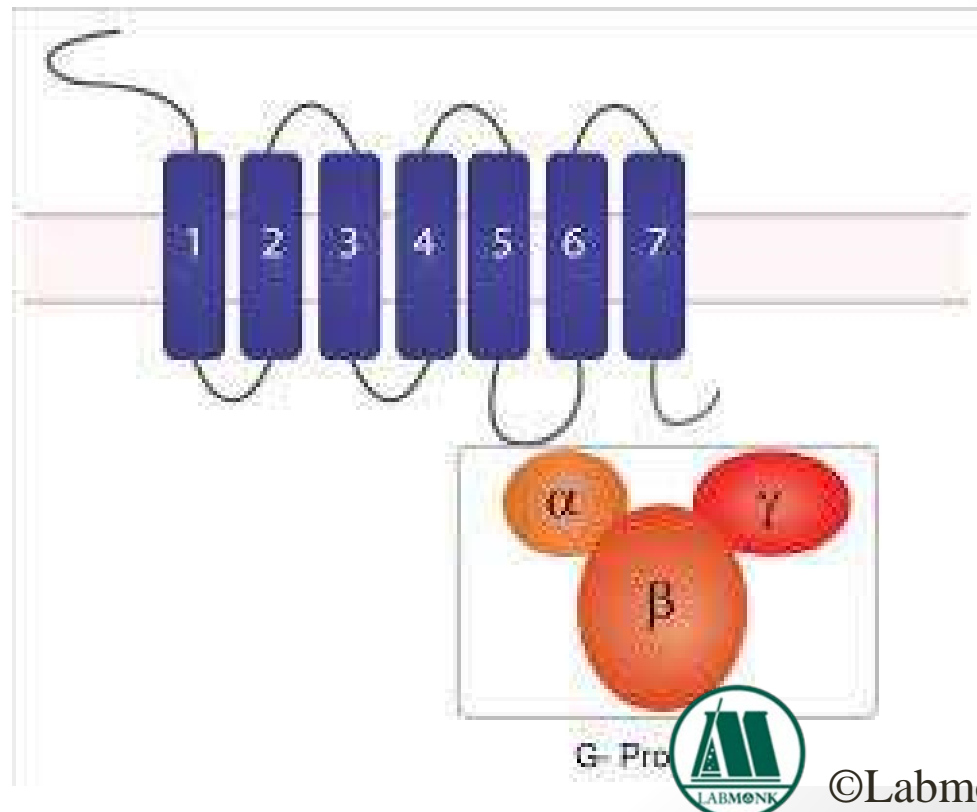
4 categories:

- G- protein coupled receptor: GPCR
- Receptors with intrinsic ion channel
- Kinase linked receptor
- Receptor regulating gene expression/
- Transcription factors



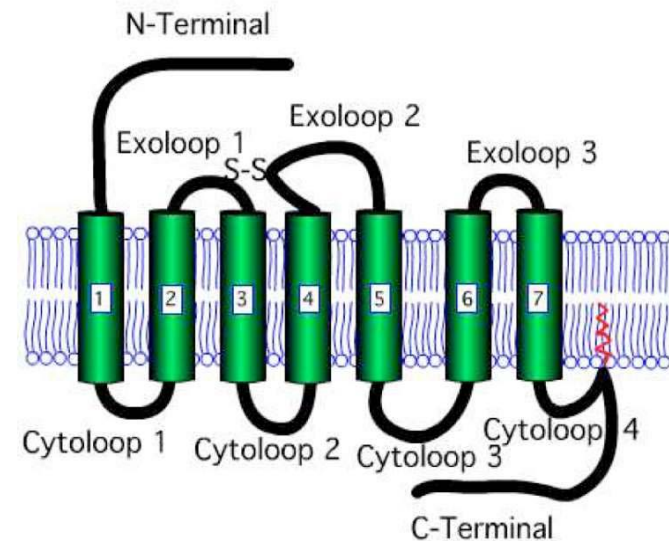
G- PROTEIN COUPLED RECEPTORS

- GTP-activated proteins/ G-proteins/ Guanine nucleotide binding proteins
- Coupled to certain receptors & regulate secondary messengers
- Gs/ Gi



G- PROTEIN COUPLED RECEPTORS

- 7 membrane spanning helical segments of hydrophobic amino acids
- Intervening segments: 3 loops on either side
- Amino terminus on extracellular side
- Carboxy terminus on cytosolic side
- Agonist binds: between helices on extracellular face
- Recognition site by cytosolic segments: Gprotein binding

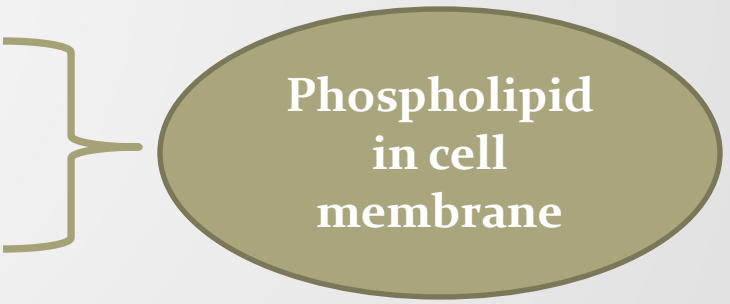


G- PROTEIN COUPLED RECEPTORS

2nd messengers:

- Intra cytoplasmic calcium ion concentration
- Camp

Inositol 1,3,5- triphosphate (IP₃)
&
Diacylglycerol (DAG)



Phospholipid
in cell
membrane

The diagram consists of a large, light-brown oval on the right containing the text 'Phospholipid in cell membrane'. A bracket on the left side of the oval points to the text 'Inositol 1,3,5- triphosphate (IP3) & Diacylglycerol (DAG)' on the left, indicating that these two molecules are products of the phospholipid.

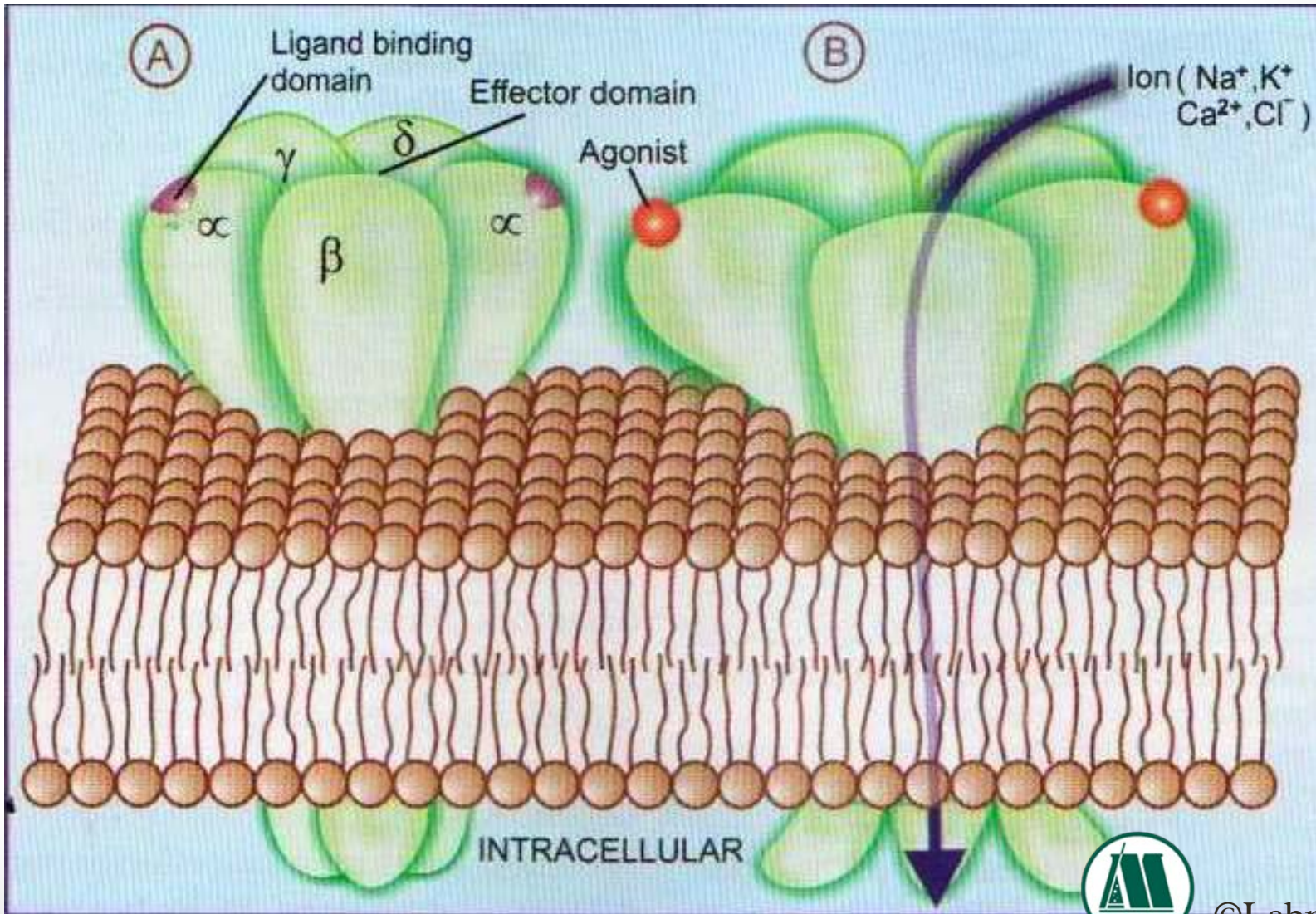


RECEPTORS WITH INTRINSIC ION CHANNEL

- Cell membrane spanning proteins: Agents bind with them open transmembrane channel Ion movement across membrane phospholipid bilayer
- Ion flow & voltage change: type of channel



RECEPTORS WITH INTRINSIC ION CHANNEL



RECEPTORS WITH INTRINSIC ION CHANNEL

- **Nicotinic Ach receptors:** Na^+
- **GABA receptor:** Cl^-
- **Tubocurarine & BZDs:** modify function of receptor channels
- **Onset & offset of response:** fastest- in milliseconds



KINASE LINKED RECEPTORS

2 types:

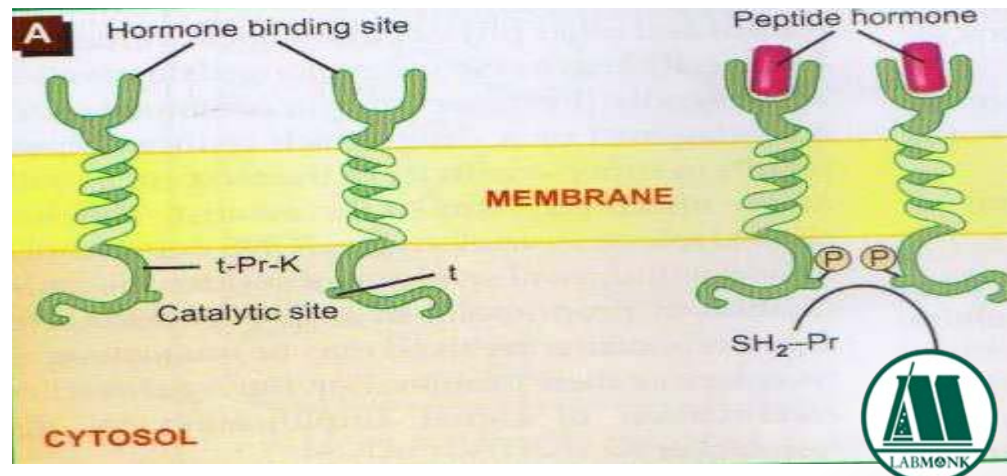
Intrinsic enzymatic activity

- Tyrosine kinases + hormone

self activation by autophosphorylation

Phosphorylates intracellular proteins on tyrosine residues

- Eg: Insulin, epidermal growth factor receptors

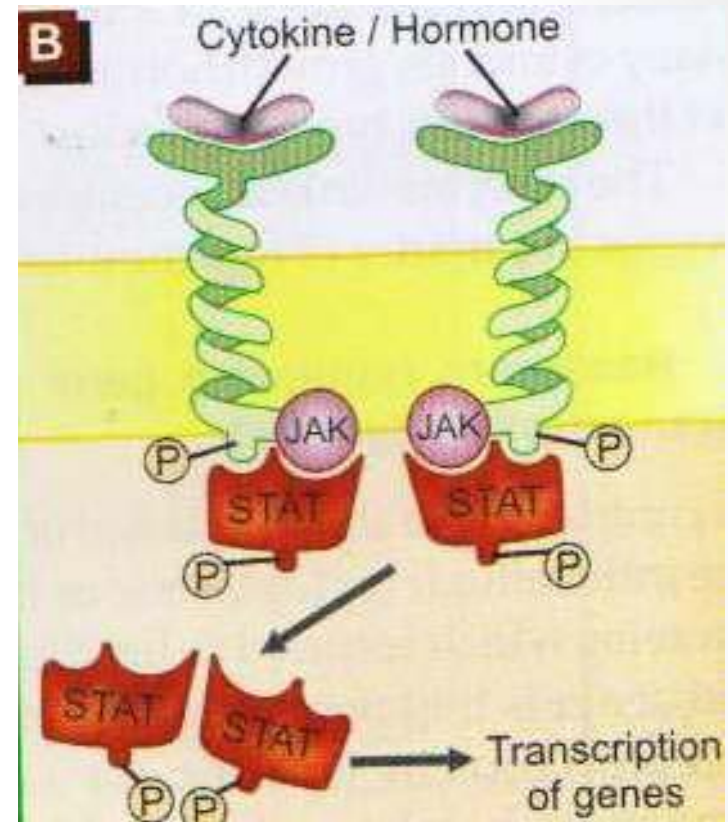
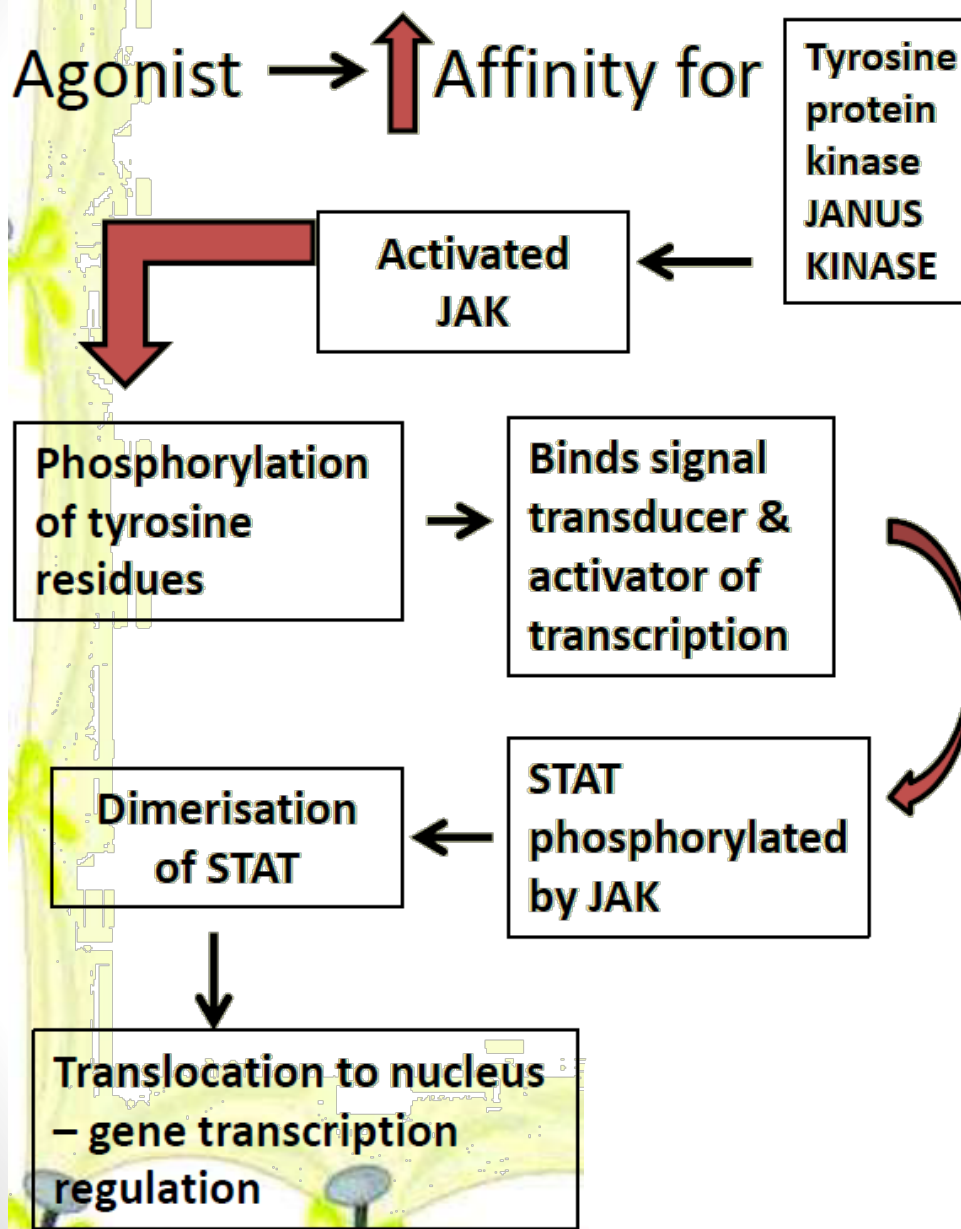


MECHANISM OF DRUG ACTION

- Others: action by means of other properties
- Chemically reactive agents
- Physically active agents
- Counterfeit biochemical constituents
- Protoplasmic poisons
- Formation of antibodies
- Placebo action
- Targeting specific genetic changes



JAK-STAT-Kinase binding receptors



CHEMICALLY REACTIVE AGENTS

- Interact with molecules/ ions or attack proteins/ macromolecules
- Lack specificity: except chelating agents
- Not affected by minor structural variations
- Covalent bonding/ strong ionic attachments
- Sodium hypochlorite \longrightarrow HOCl \longrightarrow chemical disruption of biologic matter
- Germicides & antineoplastic alkylating agents+ macromolecules

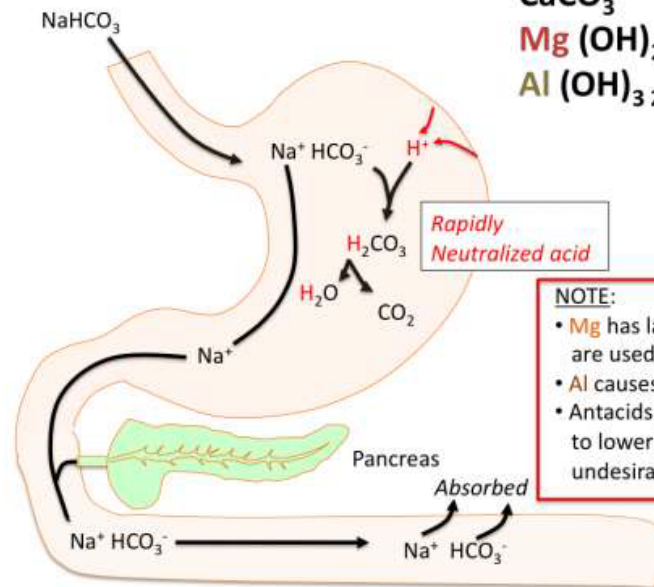


CHEMICALLY REACTIVE AGENTS

Neutralisation:

- Gastric antacids & metallic ion chelators + inorganic substances
- Anticoagulant action of heparin: neutralises the basic groups of clotting factors: prevents thrombin action

Na Bicarbonate



Other Antacids:

CaCO₃ (H⁺ binds w/ CO₃²⁻)

Mg (OH)₂ (H⁺ binds w/ OH⁻)

Al (OH)₃ (H⁺ binds w/ OH⁻)

NOTE:

- Mg has laxative effects (laxatives w/ Mg are used prior to endoscopy)
- Al causes constipation
- Antacids combining Al & Mg are used to lower stomach acid w/o producing undesirable constipation or diarrhea



CHEMICALLY REACTIVE AGENTS

Chelation:

- Dimercaprol: coordination complexes with mercury & heavy metals
- EDTA: Ca^{2+}
- Calcium sodium edetate : Pb^{2+}
- Penicillamine: Cu^{2+}
- Desferrioxamine : Iron



CHEMICALLY REACTIVE AGENTS

Oxidation:

- Potassium permanganate

Ion exchangers:

- Anion exchange resin: cholestyramine exchanges chloride ions from bile salts cholesterol lowering
- Cation exchange resin: reduce sodium absorption from intestine



PHYSICALLY ACTIVE AGENTS

Colour:

- Psychological effect: pleasant colour.
- Eg: tincture of cardamom

Physical mass:

- Water absorption & size: peristalsis & laxative effect
- Eg: agar, ispaghula, psyllium seeds



PHYSICALLY ACTIVE AGENTS

Smell:

- Volatile oils: peppermint oil, mask the unpleasant smell of mixtures.

Taste:

- Compounds with bitter taste ↑ HCl flow: improve appetite.

Osmolality:

- Diuretic: mannitol
- Purgative: MgSO_4



PHYSICALLY ACTIVE AGENTS

Adsorption:

- Kaolin & activated charcoal: antidiarrhoeal
- Methylpolysiloxane & simethicone: antifatulent

Protective:

- Various dusting powders



PHYSICALLY ACTIVE AGENTS

Soothing demulcent:

- Coat inflamed mucous membrane: soothing effect
- Pectin: antidiarrhoeal preparations
- Menthol, syrup vasaka: Pharyngeal demulcents in cough
- Calamine lotion: eczema



PHYSICALLY ACTIVE AGENTS

Reduction in surface tension:

- Cationic surfactants: cetrimide

Electrical charge:

- Strongly acidic heparin- exerts action due to negative charge

Radioactivity:

- I₁₃₁ : hyperthyroidism



PHYSICALLY ACTIVE AGENTS

Radio-opacity

- BaSO_4 : barium meal
- Organic iodine compounds: urinary & biliary tracts Absorption of UV rays
- Para amino benzoic acid: topical use in sunscreen preparations



PHYSICALLY ACTIVE AGENTS

Physical form:

- Dimethicone – antifoaming agent
- petroleum jelly

Astringents:

- Precipitate & denature mucosal proteins: protects mucosa – firms up the surface
- Tannic acid- gum paints



PHYSICALLY ACTIVE AGENTS

Saturation in the biophase:

- Cellular sites/ biophase of CNS: saturated by general anaesthetics
- Packed between membrane lipids- hinder metabolic functions/ disrupt membrane organisation



COUNTERFEIT / FALSE INCORPORATION MECHANISMS

- Artificial analogues of natural substrates
- No effect on enzymes: but incorporated into specific macromolecules by the cell
- Cell: altered biologic activity/ susceptibility to destruction
- 5-bromouracil: ↑ mutation rate & chromosomal disturbances-antineoplastic
- Sulfa drugs : non functional folic acid bacteriostatic



PROTOPLASMIC POISONS

- Germicides & antiseptics: phenol , HCHO
- Death of bacteria



FORMATION OF ANTIBODIES

- Vaccines: induce antibody formation & stimulate defense mechanisms
- Active immunity: against small pox & cholera
- Passive immunity: antisera against tetanus & diphtheria



PLACEBO ACTION

- Pharmacodynamically inert & harmless: dosage form resembling actual medication
- Physician: good patient confidence- dramatic relief to subjective symptoms: psychological
- Starch/ lactose: solid dosage forms
- Double blind clinical trials



TARGETING SPECIFIC GENETIC CHANGES

- Inhibitors of *ras*- modifying- enzyme farnesyl transferase: reverses malignant transformation of cancer cells with *ras* oncogene
- Inhibitors of specific *tyrosine kinase* – block the activity of oncogenic kinases

Promising approaches:

Delivering genes to cancer cells: more sensitive to drugs

Delivering genes to healthy cells : protect from chemotherapy

Tag cancer cells with genes that make them immunogenic



CLASSIFICATION OF MECHANISM

I. On the cell membrane

- *Specific receptors* - agonists & antagonists on adrenoceptors, histamine receptors etc.
- Interference with selective passage of *ions across membranes* - calcium channel blockers
- Inhibition of membrane bound *enzymes & pumps* – membrane bound ATPase by cardiac glycoside, TCAs blocking pumps of amine transport



CLASSIFICATION OF MECHANISM

II. Metabolic processes within the cell

- *Enzyme inhibition*: COX by aspirin, cholinesterase by pyridostigmine, xanthine oxidase by allopurinol
- Inhibition of *transport processes*: blockade of anion transport in renal tubule cell by probenecid- delays penicillin excretion & enhances urate elimination



CLASSIFICATION OF MECHANISM

- Incorporation into larger molecules: 5-FU into mRNA in place of uracil
- Altering metabolic processes unique to microorganisms:
Interference with cell formation by penicillin
- **III. Outside the cell**
 - Direct chemical interaction: chelating agents, antacids
 - Osmosis: purgatives, diuretics like mannitol



THANK YOU



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