

CONCEPT OF DRUG ACTION

1. **Local action:** action is produced at the site of drug administered.
E.g. skin and mucous membrane - external.
drug on gastro intestinal tract-internally
 2. **Systemic action:** action on the system, action is generally seen only after absorption.
 - a) **Selective action:** post-pituitary hormone (ADH at the dose of 0.00001 mg to animal results in inhibition of water diuresis in man. Chloroform as CNS depressants. Iodine in Thyroid gland.
 - b) **Non-selective:** General action, Toxin, irritants Action.
1. **Primary action:** Action of the drug brought about in its unaltered state.
Eg. Adrenaline on B.P., digitalis on myocardium.
 2. **Secondary action:** Action following primary and due to it.
 - a) Adrenalin 1/u rise of BP at its zenith of the rise of BP there is cardiac slowing due to vagal action and fall of BP to a little extent. This later effect is the secondary action.
 - b) Nitrites: fall of BP followed by a rise of BP to a certain extent.
 - c) Digitalis diuresis.
 - d) Ammonium chloride rendering the urine acidic is secondary.

Action:

1. Direct action:

2. Indirect action: when a drug enhances or decreased the response to a second drug (or) an endogenous chemical messenger.

Eg: inhibitor of cholinesterase would allow endogenous acetylcholine to accumulate and act at increased concentration for an extended duration.

3. Reflex action: camphor in oil subcutaneous.

Cold water sprinkling on face to stimulate CNS (respiration).

Drug action: method by which drug influences a cell (or) alteration (or) change caused by the drug.

1. **Visible action:** Action extends at organism level.

Eg. chloroform as depressant

Strychnine as CNS stimulant.

2. **Appreciable action:** action at organ level or cellular level or molecular level.

Mechanisms of drug action

The basic mechanism of drug effect is often difficult to explain. The bio-chemical & bio-physical mechanisms viz. Salines as purgatives (osmosis) Kaoline as internal astringent (mechanical coating), Acid against alkali (physiological antagonism), Tannic acid as astringent (precipitation of proteins) can be easily explained.

However the actions cannot be elucidated so easily in all cases e.g. action of anesthetics producing unconsciousness and the action of digitalis

on heart. This is because very little is known of cellular physiology, which alone will permit an interpretation of the mechanism of drugs resulting in the modification of cellular function.

1. **Inhibition of enzymes theory:** suggest that many drugs extent their action by inhibiting specific cellular enzymes. Often the action of a drug itself provides a research tool in tracing the intricate pattern of catalyzed cellular reactions.

Eg. 1. Physostigmine salicylate acts by inhibition of cholinesterase.

2. CNS depressants acting by inhibiting or inactivating respiratory enzymes.

3. Mercurial diuretics acting by inhibition of SH group of enzymes necessary for tubular reabsorption.

2. **Theory of cellular response:** No drug can impart a new function to a cell. Drugs can either stimulate or depress cellular activity, the intensity of action being adjusted for therapeutic purposes by varying the dosage. eg. CNS depressants producing an action ranging from sedation to general anesthesia depending on dosage.

3. **Selective action theory:** suggests that most drugs are selective in that they affect only a specific tissue or a group of effector cells. Eg: epinephrine stimulates the myoneural junction of the sympathetic innervation to the arterioles.

Curare selectively paralyzes the motor end plate of skeletal muscle innervations. Similarly the antidiuretic principle of the posterior pituitary is so highly selective that one millionth of mg of ADH inhibits water diuresis without producing any other effect.

4. **Anti-metabolic theory:** or theory of competitive antagonism or substrate competition (Woods fields theory).

Certain drugs can affect an organism by virtue of structural similarity to essential cellular metabolites. Eg. sulphonamides by their resemblance to P.A.B.A an essential metabolite required for synthesis of pteroyl glutomic acid, exert their anti-bacterial action by interfering with the utilization of PABA by the Bacterial cell.

5. **chlelation:** A process in which an organic group combines with or binds another substance usually metallic ion. Such chelates are not dissociable and therefore the metallic ion is effectively removed from biological medium.

Eg. Ca² EDTA in arsenical poisoning.

Mode of action of drugs that are not mediated by receptors.

Drug can act by various properties like physical, chemical, physiological etc.

Physical properties:

1) **Taste:** certain compounds have a bitter taste and by virtue of this taste, they reflexly increase the flow of hydrochloric acid in the stomach and improve the appetite. Eg. quassia, chirata etc.

2) **Physical Mass:** Here a drug may not have any intricate action but by its mechanical action, it produces the effect. Eg. Taking isapgol orally increases the bulk in the intestines so as to produce laxative effects.

- 3) **Osmosis:** certain substances as such are inert but by virtue of their osmosis draw out water and produce the necessary action. For example osmotic diuretics like mannitol and purgatives like mag. Sulph.

Saline cathartic (sodium sulfate, mag. Sulfate) give orally retain an osmotic equivalent of water within lumen of the gut. The increased intraluminal volume stimulates motility reflexively.

- 4) **Adsorption:** Kaolin particles adsorb water on its surface and there by reduces gut motility. This action is useful to control diarrhea.
- 5) **Soothing effect:** By soothing the surface, irritation can be prevented, which may be useful in the treatment of cough. eg. Syrups, Elixir.
6. **Electrolytic action:** Drug can undergo partial disintegration into electrically charged particles called ions. Some bear a positive charge and are called cations, while others bearing a negative charge are known as anions. There when drug exhibits an ionic action, it may be an anionic or cationic. Heamatinic drug like ferrus carbonate, Ferrus sulphate: action is due to Fe^{+} cation, and anions carbonate, and sulphate are inert.

Sodium sulphate, Sodium tartarate Purgative action in due to anion sulphate or tartarte (-) not by cation - Na^{+} is inert.

Such anionic action is influenced by the extent of its ionization and temperature, PH, enzyme action and substrate concentration affect its activity.

7. **Radioactivity:** The radioactive substances eg: ^{131}I are commonly used in treatment of cancer.
8. **Perturbation of membrane:** General anesthetic agents are diverse in chemical nature, and it is generally accepted that they affect most biologic cells in a nonspecific fashion. It has been hypothesized that the cell membrane is the major site of action. This interaction is thought to be dependent only on the physicochemical properties of the anesthetic molecule, which yield a perturbation of membrane components resulting in the phenomenon of anesthesia.

Chemical properties:

1. **Neutralization:** substances like aluminum hydroxide neutralizes acid in the stomach and hence is used as antacids.
2. **Chelation:** It is another biochemical process for drawing out ions of heavy metals, which may be toxic to the body. A substances like ethylene Diemnine tetra acetic acid (EDTA), British anti/lewisite (BAL) and Penicillamine, deferoxamine etc. are good chelating agents that can excrete out poisonous substances like lead, arsenic, mercury, iron etc. from the patient's body and spare the animal of their toxicity. Heavy metal antagonists are chelating agents, posses the common property of forming co-ordination complexes (chelates) with the heavy metal, thereby preventing or reversing the binding of metallic cations to tissue ligands (mostly SH groups). A chelate is defined as a coordination complex formed between a metal and a compound containing two or more potential ligands. (eg. Ethylene diamine).
3. **Oxidative phosphorilation:** In Kreb's cycle, oxygen is used to promote energy rich phosphate bonds. The process involves coupling of two

actions, drugs like barbiturates perhaps act by uncoupling the two processes.

4. **Metabolism:** Enzymes like trypsin digests proteins, thrombokinase helps in clotting of blood, hyaluronidase increases cell permeability and facilitates quicker absorption.
5. **Chemical antagonism:** any drug that counteracts the effect of an agonist can be called antagonist. In chemical antagonism, the antagonist does not cause its effect by an interaction with tissue receptor sites but interacts with its agonist, as a consequence loses its ability to be effective (antagonism by neutralization). Neutralization of the anti-coagulant activity of heparin by protamine is an example of this type of interaction. Protamine a low molecular weight protein forms a stable complex with a strongly acidic heparin, and then heparin loses its anti coagulant activity.

Physiological actions:

1. **Stimulation:** certain drugs increase the activity of specialized cells. This is called stimulation. Eg. theophylline present in tea stimulates diuresis, caffeine stimulates the brain cortex.
2. **Depression:** This is the decrease in the activity of specialized cells. Eg. quinidine (an antiarrhythmic drug) depresses the myocardium of heart.
3. **Irritation:** Here, drugs produce effects on growth, nutrition or morphology of the living tissues. For example precipitation of proteins (astringent effect) of alcohol, irritation of gastro intestinal tract by Senna (purgation). Sometimes drug is applied locally to the skin to relieve deep-seated pain. This is referred to as counter-irritation. Eg. Rubbing of methyl salicylate.
4. **Replacement:** Drugs may be used for the replacement of some endogenous substances, for example hydrocortisone in Addison's disease, insulin in diabetes mellitus, and thyroxin in myxedema.
5. **Modification of Immune status:** Resistance against infection can be built by vaccines, toxoids etc. The process is called Immunization. There are two methods of producing immunity.
 - a) Active immunity: to produce antitoxin and antibodies in the body (vaccine, toxoids).
 - b) Passive immunity: to inject readymade antibody rich sera for the particular disease. The plasma has agglutinins, precipitins and bacteriolysins for its defense against respective Diseases

RECEPTOR

The term receptor has been used operationally to denote any cellular macro molecular to which a drug binds to initiate its effects. Among the most important drug receptors are cellular proteins whose normal function is to act as receptors for endogenous regulatory ligands, particularly hormones growth factors, neurotransmitters and autacoids.

Two functions of a receptor are the ligand binding and message propagation; to deliver above functions receptor contains a ligand-binding

domain to which receptor binds to agonist and effector domain from which propagates its biochemical effects.

The regulatory actions of a receptor may be exerted directly on its cellular target(s), effector protein(s), or, may be conveyed to cellular targets by intermediary cellular molecules, transducers. The receptor, its cellular targets and any intermediary molecules are referred to as a **receptor- effector system, or, signal transduction pathway**. Even effector protein may not be the ultimate cellular component affected, but may synthesize, or, release another signaling molecule, usually a small metabolite, or, ion known as a second messenger.

Receptors also act as integrators of extra cellular information as they coordinate signals- from multiple ligands with each other and with metabolic activities of the cell.

An important property of physiological receptors is that they act catalytically and hence are biochemical signal amplifiers. The catalytic nature of receptor is obvious, when the receptor itself is an enzyme, but all physiological receptors are formally catalysts. For example, when a single ligand molecule binds to receptor that is an ion channel and opens it, many ions flow through the channel. Similarly, a single steroid hormone molecule binds to its receptors and initiates the transcription of many copies of specific mRNAs, which in turn can give rise to multiple copies of a single protein.

Receptors are the macromolecular specific cellular components with which drugs combine chemically to evoke the biological response. Receptors can be counted in a particular tissue.

Agonist

A drug combines with the receptor and may initiate a sequence of effects. The ability of drug to combine with the receptor to form the drug receptor complex is defined as **affinity**. The ability of drug to initiate the effect is termed as **intrinsic activity or efficacy**.

Agonist is the drug that possesses both affinity as well as efficacy.

Antagonist

Certain drugs possess only affinity but have no intrinsic activity. Such drugs are not capable of producing any effect of its own but prevent the effect of the agonist; such drugs are referred to as antagonist. There are two types of antagonism: 1) Competitive. 2) Non competitive.

Competitive antagonism

If the antagonist binds reversibly to the receptor and its inhibitory effects are overcome by increasing the dose of the agonist. Maximum response can be obtained. In dose response curves rightward shift occurs.

Non-competitive antagonism

If the binding of antagonist is irreversible or non specific (i.e. site of action is different) then the antagonist is known as non-competitive. In this type of curves increasing the dose of the agonist cannot attain maximum response. The slope of curve is changed. There is no

parallel shift of dose response curve. The maximum response is decreased on increasing the dose of antagonist.

Classification of Receptors

1. Receptors as enzymes or Receptor protein Kinase

Receptors for peptide hormones that regulate growth, differentiation, and development (and in some cases acute metabolic activity.) are frequently plasma membrane-bound protein kinases that act by phosphorylating target proteins. These targets may be enzymes (including other kinases), regulatory proteins, or structural proteins and phosphorylation may either alter their individual activation, or influence their interactions with other regulatory proteins, or effectors. Many receptor protein kinases phosphorylate specific tyrosine residues on their target proteins, but a few phosphorylate serine, or, threonine residues.

Tyrosine protein kinase receptors: receptors of Insulin epidermal growth factor, platelet derived growth factor certain lymphokines.

Serine/ Threonine protein kinase: isoforms of receptors for transforming growth factor B.

The extra cellular hormone-binding domain is connected to an intracellular protein kinase catalytic domain by a relatively short sequence of hydrophobic amino acid residues that cross the plasma membrane. Because of the homology among the protein kinase domains in this family, active chimeric receptors have been constructed from different intracellular (catalytic) and extra cellular (hormone binding) regions. These chimeras display specificities for hormones and substrates.

Receptors for neurotrophic peptides and multisubunit antigen receptors on T&B lymphocytes elicit tyrosin phosphorylation (protein kinase). These receptors lack intracellular enzymatic protein kinase.

2. Receptors with other enzymatic activity

The receptors for atrial natriuretic peptides and the peptidoguanlylin, the intracellular domain is guanylyl cyclase, which synthesizes the second messenger, cyclic Gmp.

3. Ion channels

Receptors for several neurotransmitters are agonist regulated, ion-selective channels in the plasma membrane, termed as ligand-gated ion channels. Which convey their signals by altering the cell's membrane potential or ionic composition. This group includes the nicotinic cholinergic receptors. The GABA/A receptors and receptors for glutamate, aspartate and glycine.

They are all multi subunit proteins with each subunit predicted to span the plasma membrane. The mode of association of the subunits appears to form the channel.

4. G protein Coupled receptors

Many receptors in the plasma membrane regulate distinct effector proteins through the mediation of a group of GTP-binding proteins known as

G proteins. Receptors for biogenic amines, eicosanoids, and many peptide hormones utilize G protein-coupled receptors. Receptors in this group act by facilitating the binding of GTP to specific G proteins. GTP binding activates the G protein that in turn can regulate the activity of specific effectors. The **effectors** include enzymes such as adenylyl cyclase and phospholipase A₂, C, D, ion channels that are specific for Ca²⁺, K⁺, or, Na⁺, and certain transport proteins.

The G proteins are bound to inner face of the plasma membrane. They are heterotrimeric molecules (sub units are designated as alpha, beta, gamma), and their classification is based on their identity of their distinct alpha sub units. These polypeptides have highly homologous guanine nucleotide binding domains and have distinct domain for interactions with receptors and effectors. When the system is inactive GDP is bound to the alpha sub unit. An agonist receptor complex facilitates GTP binding to the alpha sub unit in part by promoting the dissociation of bound GDP. Binding of GTP activates the alpha sub unit and the alpha-GTP sub unit is then thought to dissociate from the beta, gamma sub units and interacts with a membrane bound effector. The beta, gamma sub units also can interact with and influence effector activity independent of, or, in parallel with alpha-GTP sub unit effects. Termination of signal transmission results from hydrolysis of GTP to GDP by a GTPase that is intrinsic to the alpha sub unit and the resulting reassociation of alpha, beta and gamma sub units. These G proteins serve as regulated molecular switches capable of eliciting, bifurcating signals through alpha and beta, gamma sub unit effects. The switch is turned on by the receptor and turns itself off within a few seconds a time sufficient for considerable amplification of signal transmission.

5. Transcription factors

Receptors for steroid hormones, Thyroid hormone, vitamin D, and the retinoids are soluble DNA binding proteins that regulate the transcription of specific genes. They are part of a larger family of transcription factors whose members may be regulated by phosphorylation, association with other protein factors, or by binding to metabolites or cellular regulatory ligand. These receptors act as dimmers. Some as homodimers and some as heterodimers, with homologous cellular proteins, but may be regulated by higher order oligomerization with other regulating molecules. They provide striking examples of conservation of structure and mechanism. They are assembled as three largely independent domains. The region nearest to the carboxyl terminus binds hormone and serves a negative regulatory role; that is removal of this domain leaves a constitutively active fragment that may be nearly as effective in regulating transcription, as is the intact hormone-ligand receptor. Hormone binding presumably also relieves this inhibitory constraint. The central region of the receptor mediates binding to specific sites on nuclear DNA to activate or inhibit transcription of the nearby gene. These regulatory sites in DNA are likewise receptor-specific. The function of the amino terminal region of the receptor is less well defined. But its loss decreases the receptors regulatory activity.

Cytoplasmic second messengers

Cytoplasmic second messengers are chemical substances or ions, which are synthesized or released from various sites within the cell by the stimulation of receptor. Cytoplasmic second messengers are synthesized by transducers or by some other enzymes or released from intracellular sites. There are relatively few recognized second messengers. Their synthesis or release reflects the activities of many pathways. Second messengers

influence each other both directly by altering others metabolism and indirectly by sharing intracellular targets. Thus physiological signals also are integrated with in the cell as a result of interactions between second messenger pathways.

1. Cyclic AMP

The first recognized second messenger and is synthesized by adenylyl cyclase in response to activation of many receptors. Stimulation is mediated by G_s and inhibition is by one or more closely related G proteins termed G_i . There is ten tissue-specific adenylyl cyclase isozyms are there, each with its unique pattern of regulatory responses. Several adenylyl cyclase isozyms are inhibited by the G protein β, γ subunits, which allows activation of G proteins other than G_s to inhibit cyclase activity. Other isozyms are stimulated by G β, γ subunits, but this stimulation is dependent upon concurrent stimulation by the α subunits of G_s . Still other isozyms are stimulated by Ca^{2+} - calmodulin complexes.

The hydrolysis of cyclic AMP is catalyzed by several phosphodiesterases and the extrusion of cyclic AMP from the cell is accomplished by at least one regulated active transport system.

In most cases cyclic AMP functions by activating cyclic AMP-dependent protein kinase, which regulate numerous intracellular proteins by catalyzing their phosphorylation.

2. Cytoplasmic concentration of Ca^{2+}

Calcium ions are the ubiquitous second messenger, is controlled by regulation of several different Ca^{2+} -specific channels in the plasma membrane and by its release from intracellular storage sites. Ca^{2+} channels can be opened by electrical depolarization, by phosphorylation, by cyclic AMP dependent protein kinase, by G_s or K^+ or by Ca^{2+} itself. Opening can be inhibited by either G protein G_i and G_o . One channel may respond to several of these inputs.

3. Inositol 1,4,5-triphosphate (IP_3)

This second messenger mediates release of calcium ion from intracellular stores. IP_3 is product of hydrolyses of membrane lipid, phosphatidylinositol 4,5-bis phosphate (PIP_2). This reaction is catalyzed by a phospholipase C (PLC). IP_3 acts on Ca^{2+} storage vesicle and channels to release Ca^{2+} .

4. Protein Kinase C

It is like cyclic AMP dependent protein kinase it has several proteins as substrates. The activation of protein kinase C by Ca^{2+} is potentiated by diacylglycerol; the other second messenger product of the phospholipase C catalyzed reaction that liberates IP_3 .

5. Cyclic guanosin monophosphate (c-GMP)

Cyclic guanosin monophosphate is another intracellular messenger, synthesized by the enzyme guanylate cyclase. This concentration can be shown to increase in response to a wide rang of mediators some of which also act via adenylyl cyclase Eg. Dopamine, histamine and vasopressin.

6. Protein mediators

Calcium ions regulate cellular activity by interaction with several protein mediators. Salient examples are protein kinase C and calmoduline.