÷ Unit-2 ÷

÷ Pharmacodynamics ÷

→ The pharmacodynamics is the second part of pharmacology. which is derrived from two ward. Pharmacodynamics.

- The term pharmaco means drugs and dynamics means motion or effect.

→ It means the drug which produce the diff-2 action inside the body. this is pharmacodynamics.

→ Pharmacodynamics decide what drug does to the body.

→ The termpharmacodynamics means the study of mode of action of any drug. or any biochemical & Physiochemical changes which is occurs by the drug it is also study under the pharmacodynamics.

→ Pharmacodynamics is also reffer to the drug effect and drug action.

Drug Effect → What responce produce by the drug.

Drug Action - How effect is produce by the drug.

÷ Site of Action ÷

The site of action of any drug is defiend as those particular organ or tissue where drug shows their action and produce some effect.

→ Some time two different drug can produce same resfponce but their side of action may be different.

→ For example pilocorpin and marphin both drug shows miasis in eye but pilocorpin bind with the circular muscle. and marphine bind with the third cranial nerves.

Pilocorpin — Circular Muscle
Morphine — 3rd Cranial Nerve
} Miasis.

:- Types of site of Action :-

→ The site of action of any drug it is of three type.

(i) Extracellular
(ii) Cellular
(iii) Intracellular

(i) Extracellular :- When the drug shows their action and responce in extracellular fluid outside the surface of the cell. then this is called extracellular side.

→ For example antacid drug neutralized the acidity in inside the stomach which is the ecf

(ii) Cellular :- Those drug which bind on the receptors on the surface of cell membrane they are called cellular site.

- For Example Acetylcholine, Adrenyline, Pilocorpine, Atropin. They are bind with the receptor on the present on the surface of the cell and they produce the responce.

(iii) Intracellular :- When the drug cross the cell membrane and goes inside the intracellular fluid and produce responce inside the cell organilies. and produce the action on cell organilies. they are called intracellular site.

→ For example Sulphonamide drug cross the cellmembrane. and inside the cellmembrane they inhibit the formation of fallic acid. so the bacteria are kill this is called intracellular site.

:- Principle of drug action :-

→ Any drug cannot produce any new type of responce in our body but it can only stimulate or depress the action of any organ.

(1) Stimulation.
(2) Depression.
(3) Irritation.
4) Replacement.
5) Cytotoxic
6) Modification of Immune status.

(1) Stimulation :-

→ When any drug produce any responce for the excitatory to any organ this is called stimulation.

→ When any organ shows less responce or their efficiency of work is reduce or they become depress that time stimulation is require.

→ Ex:- → Adrenyline increase the heart beat.
- Pilocarpine stimulate the saliva secreation.
- Caffine stimulate the CNS (Central nervous system)

(2) Depression :-

→ To depress the higher activity of any organ or higher stimulation of any organ. depression resfonce is produce.

Ex:- → Barbiturate depress the CNS.
- Quinidene depress the heart rate
- Morphine depress the Respiratary.

(3) Irritation

→ When any drug bind with the receptar or any organ and produce any inflametory resfonce. or Inflamation this is called Irritatation

Ex:- Plant bitter increase saliva secreation.

(4) Replacement :-

→ When any organ fail to produce their original resfonce by secreating their chemicals, hormons or Enzyme. then some others drugs are given to replace that hormons and enzyme and it produce new resfonce this is called Replacement action. Ex- Levodopa - Parkinsonism disease

(5) Cytotoxic :-

→ Cytotoxic action are those action in which drug kill the cell, which creating disease in human body.

for Example:- Antibiotics kill the cell of bacteria; virus & protozoa. so it help in recovery for disease.

→ For the treatment of cancer in chimotherapy. we kill the its own oumcogenic cell. Ex- Anticancer drug.

(6) Modification of Immune status :-

→ Some of the most drug increase the immune systems of body. to helps fighting against the disease this is called modification of Immune status.

Ex- Antibiotics and Antiviral.
Vaccine - Sera.

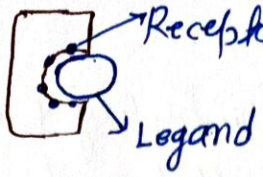
Receptor

Receptor is special structure which is made up protein and it is present surface of organ.

→ Receptor and drug structure is like lock and key and when drug is bind with receptor then is produce responce.

- Any molecule which bind with receptor and give certain responce is called legand molecule.

→ when drug bind the receptor then it form drug receptor complex CDR complex and after formation of complex responce is produce.



D + R → DR Complex → Responce.

÷ Affinity ÷

When drug bind receptor then it farm complex and the compacticity of drug bind with Receptor is called Affinity.

÷ Efficacy ÷

After formation of DR complex drug produce some responce and the lavel of responce produce is called efficacy of drug.

Types of legand ÷

On the basis of Affinity and efficacy legand is of faur types

(1) Agonist → A↑E↑

(2) Antagonist → A↑ E X Zero

(3) Partial Agonist → A↓ E↓

(4) Inverse Agonist → A↑E↓

(1) Agonist ÷

Agonist are thoes legand molicule which have similar structure and action to the Natural drug there affinity 100% and efficacy is also 100%.

(2) Antagonist ÷

Thoes legand molicule whose affinity is 100% but efficacy 0% so they bind with the receptor completely but produce no responce.

÷ Partial Agonist ÷

→ Those legand molicule which is not completely bind with the receptar and produce less Resfonce is called partial Agonist their Affinity and efficaly is less then 100%.

÷ Inverse Agonist ÷

Those legant malioule which completely bind with the receptar and produce opposite resfonce, so there affinity is a 100% and efficacy is also 100%. but Resfonce is opposite.

÷ Types of Receptar ÷

On the basis of structure and function structure of faur types.

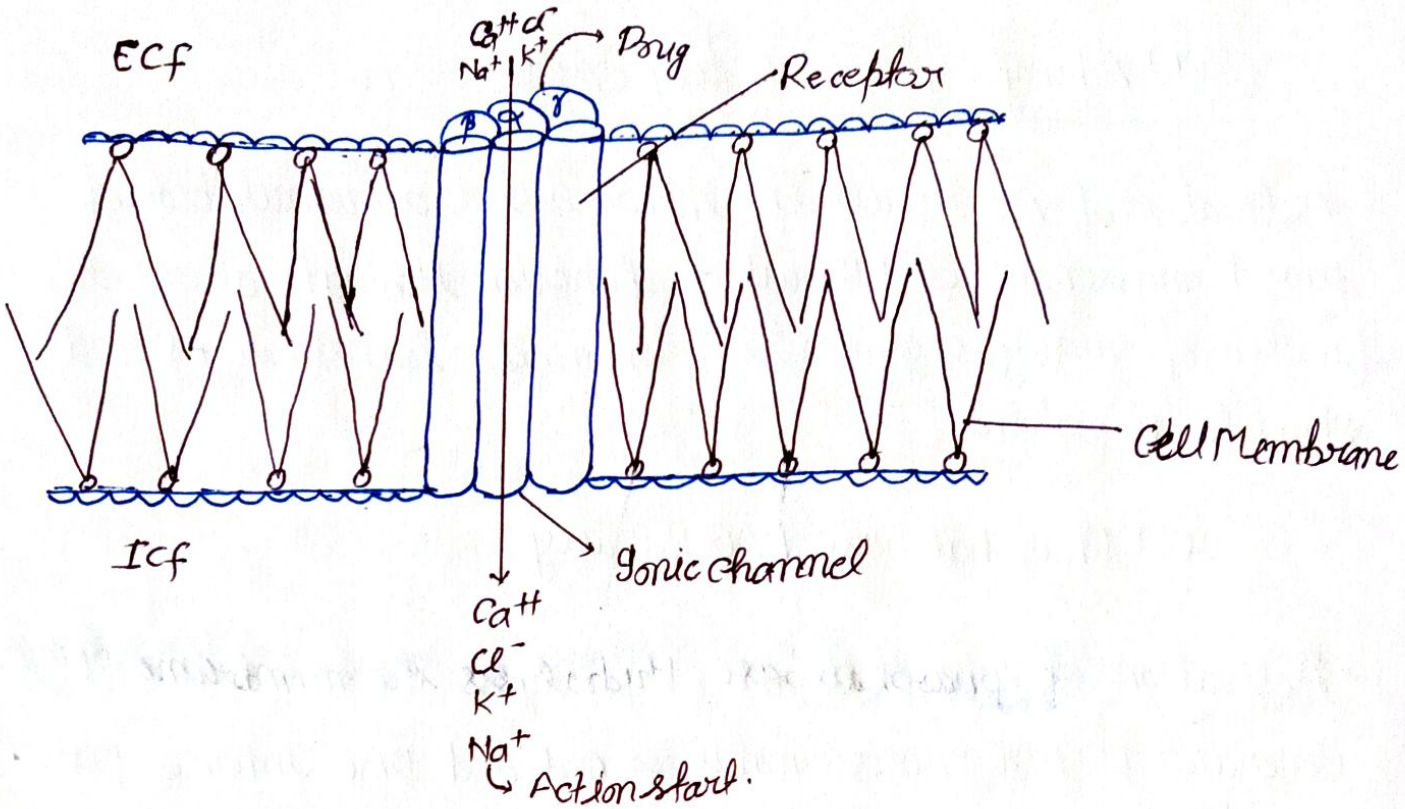
(1) Ionic Receptar / Legand Gated Receptar / Ion channel Receptar
(2) GPCR - G-protein couple receptar.
(3) Enzyme linked Receptar.
(4) Receptar regulating gene expression.

(1) Ionic Receptar or Legand Gated Receptar or Ion channel Receptar ÷

Ionic receptar is present on the surface of cell membrane. This receptar produce the action due to moovement of respective ions like - Na ion, K ion, cl ion, and Ca ion etc.

→ So it is called ionic receptar ionic receptar is present Arround the ionic channel and when drug bind with the Receptar then ionic channels are open and the moovement are ion takes place from Ecf to Icf and action is jenerated.

Ex÷ Chlinergic, Adrenergic, and dofaminergic Receptar are the ionic Receptar.



÷ GPCR ÷

÷ G-Protein Couple Receptor ÷

GPCR Receptor is a family of cell membrane Receptor which is Activated by G-Protein this Receptor is made up by Seven Helical sparing membrane which are connected each other.

- In this helical channels three sigment Run in extra celluler and three run intra celluler when drug agonist by is bind with the Amine group of extra celluler then G-protein is Activated and G-protein bind with the Receptor and produce action.

- The GPCR Receptor produce action by following three pathway

(1) Adenyl Cyclase pathway cAMP

(2) IP_3 DAG Pathway

(3) Ion channel Regulation.

(1) Adenyl Cyclase Pathway cAMP Systems:-

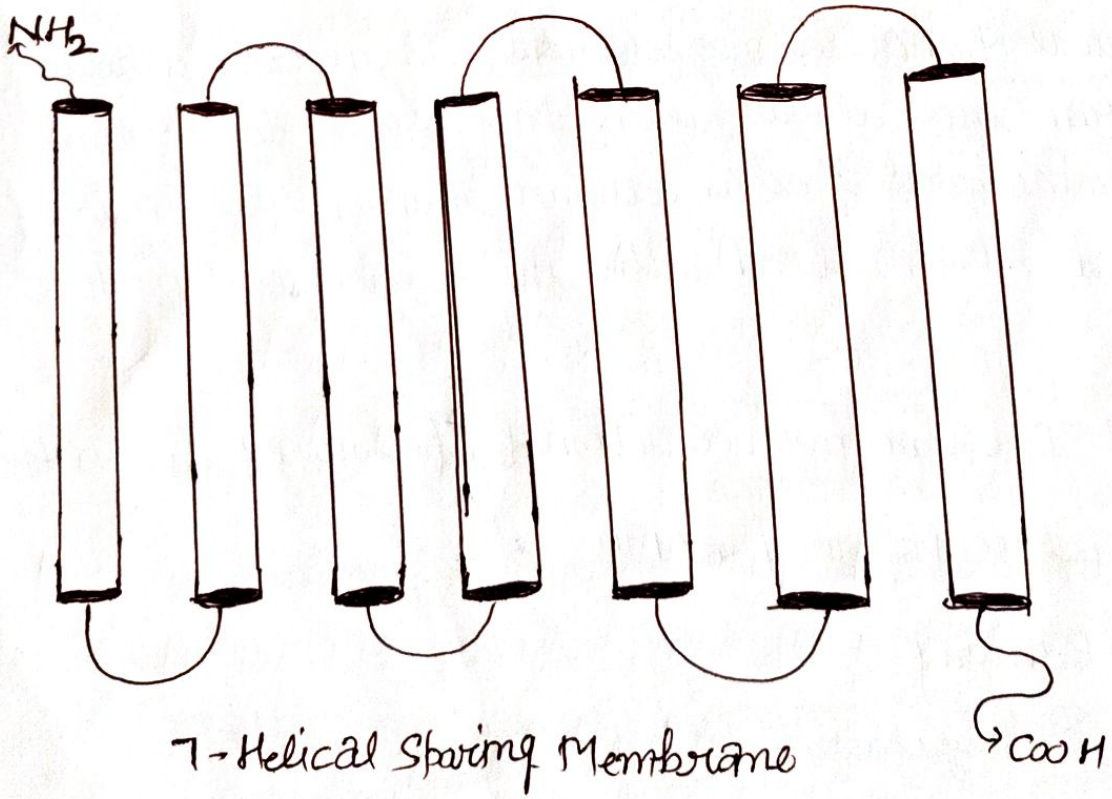
Activation of Ac result in intracellular accumulation of second massenger cAMP which function through alters the function of many enzymes, ion channels transproteins and structural proteins.

(2) Phasphalipase DAG Pathway:-

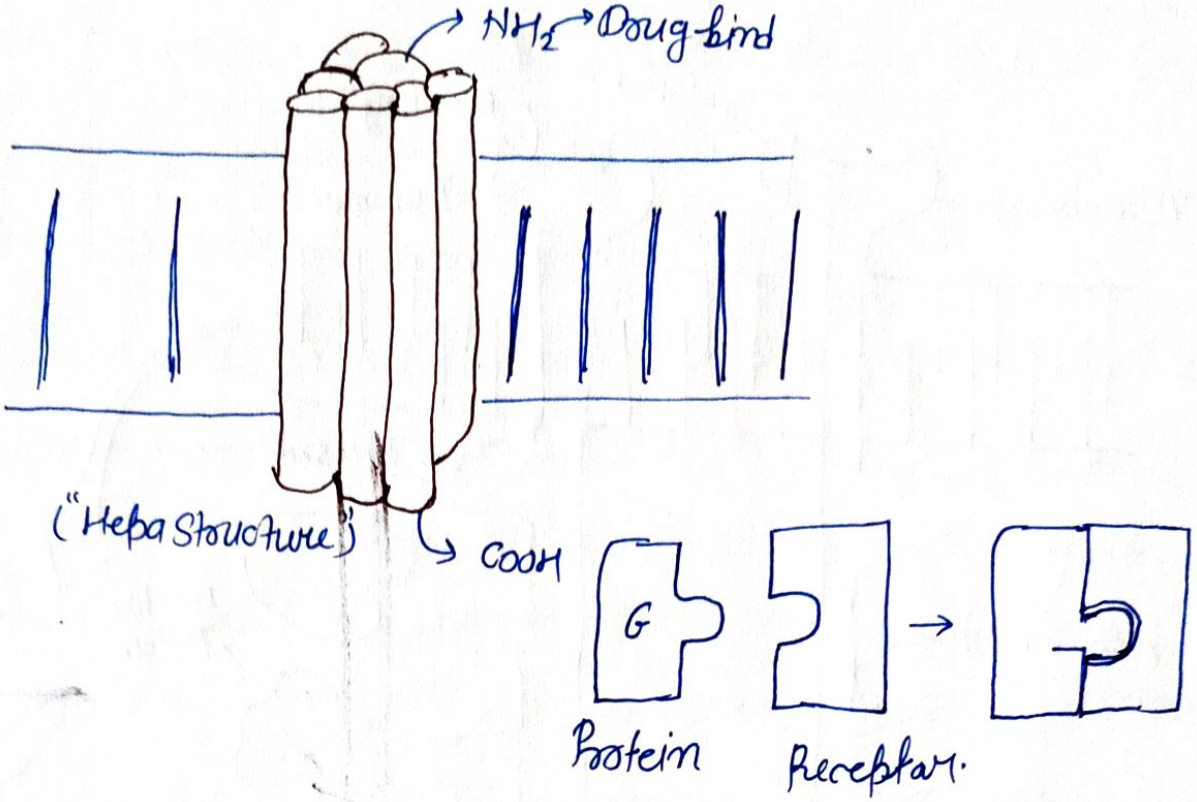
→ Activation of phasphalipase, Hydrolysis the membrane PIP to Generate IP and DAG. IP mobilizes Ca+ and DAG inhances protein kinase activation by ca+

(3) Ion Channel Regulation:-

→ The activated G-protein can also open or close ioning channels specific for ca+, K or Na without the intervention of any second massenger like cAMP or IP and bring about depolarization Hyperpolarization. changes in intracellular ca+.



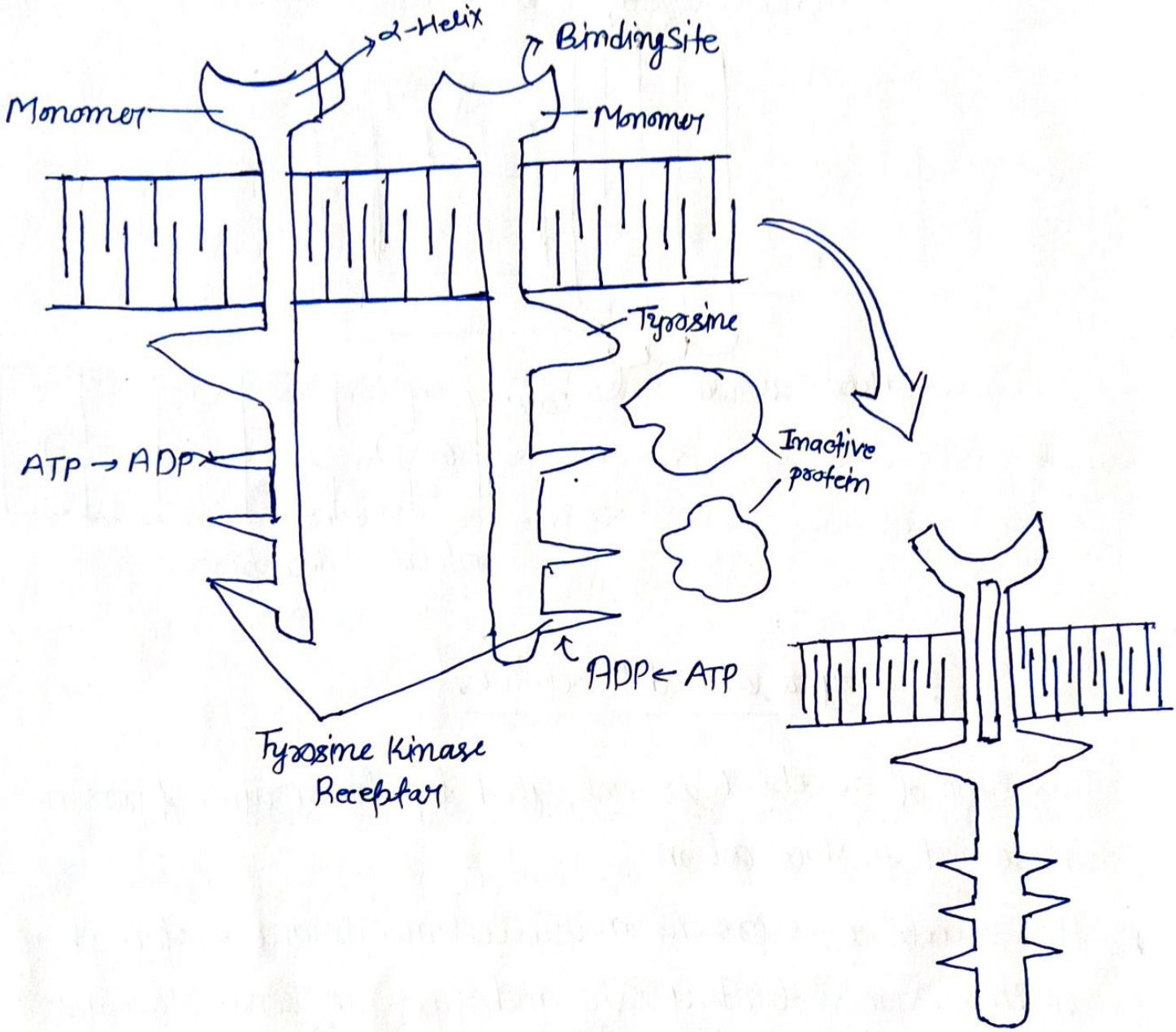
7-Helical Spaning Membrane



÷ Enzyme linked Receptor ÷

This type of receptor is activated by the enzyme tyrosin kinase and produce action.

- This receptor is present on the cell membrane surface it contains Agonist binding site and tyrosine kinase. Receptor this receptor are monomer form when it inactive.
- When drug agonist is bind with the binding site a α helix than it join and form dimer.
- Some inactive protein are present in ICf but when drug bind with the receptor it becomes active.
- Now protein by bind with the tyrosine receptor and produce different responce by phasphorelation.



∴ Dose Responce Relationship ∴

Dose:- Dose may be defind as the minimum amount of the drug which is require for the effect in body. is called dose.

Responce:- Responce may be defind as the all pharmacological effect which produce after binding of the drug with receptor is called responce.

→ In dose responce relationship it depends upon two component

(1) Drug Plasma Concentration Relationship.

(2) Plasma Concentration Responce Relationship.

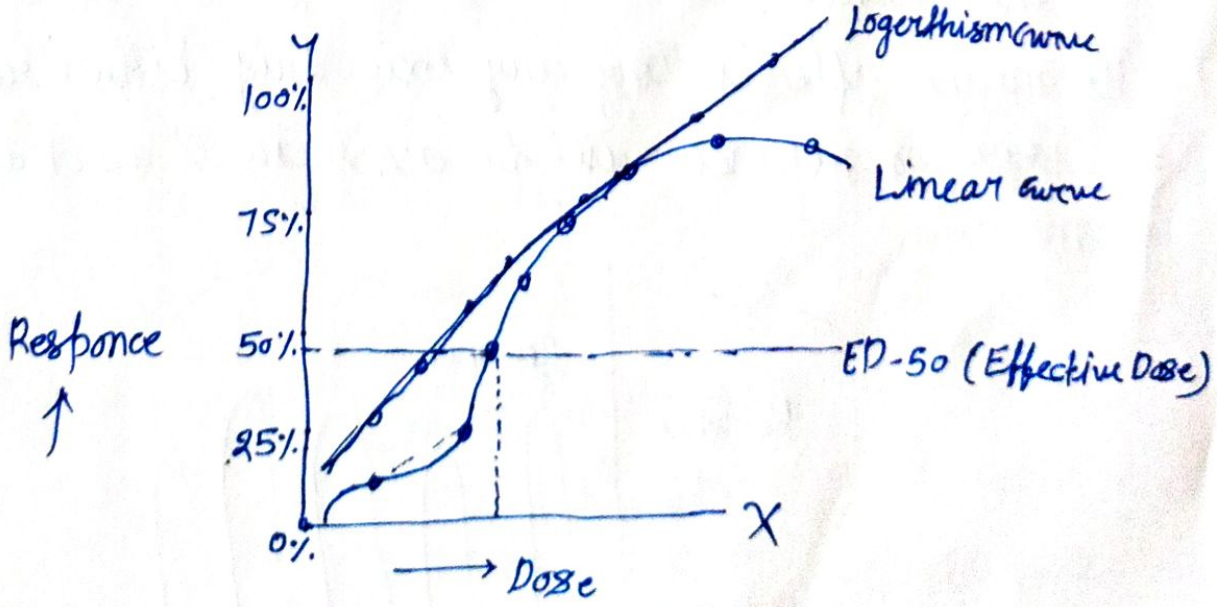
→ The responce is quantitatively directly proportional to the plasma concentration as much as plasma concentration as much as the plasma concentration of drug is increase. there responce will also be increase. and if the drug plasma concentration is decrease. the responce will also be decrease.

Pc ∝ Responce

Dose Responce Curve (DRC)

→ When we plot the relationship of dose and responce. on to the graph. then this graph is called dose responce curve.

→ In dose responce curve dose is plated on x-axis and responce is plated on y-axis.



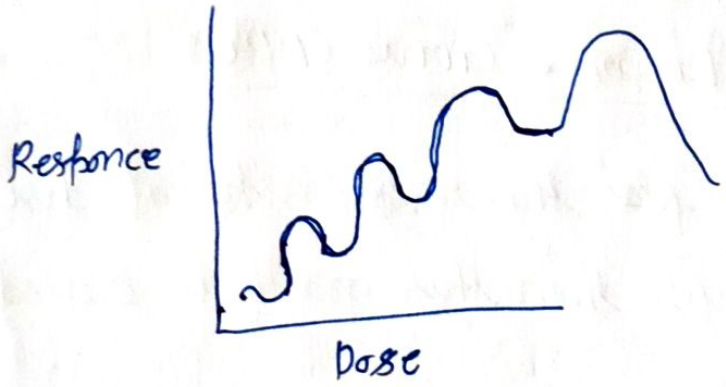
Types of DRC (Dose Response curve)

→ DRC is of two type :-

(1) Graded curve
(2) Quantal curve

(1) Graded curve :-

→ This type of curve is depends on the quantitative relationship as well as the dose of drug is increased then response will also be increases. this is quantitative directly proportional relationship.



(2) Quantal curve :-

→ The quantal curve is depends on the "all or none" principle. -It means after taking any toxic drug either response will be 100% or response will be 0%, there is no chances of less or more.

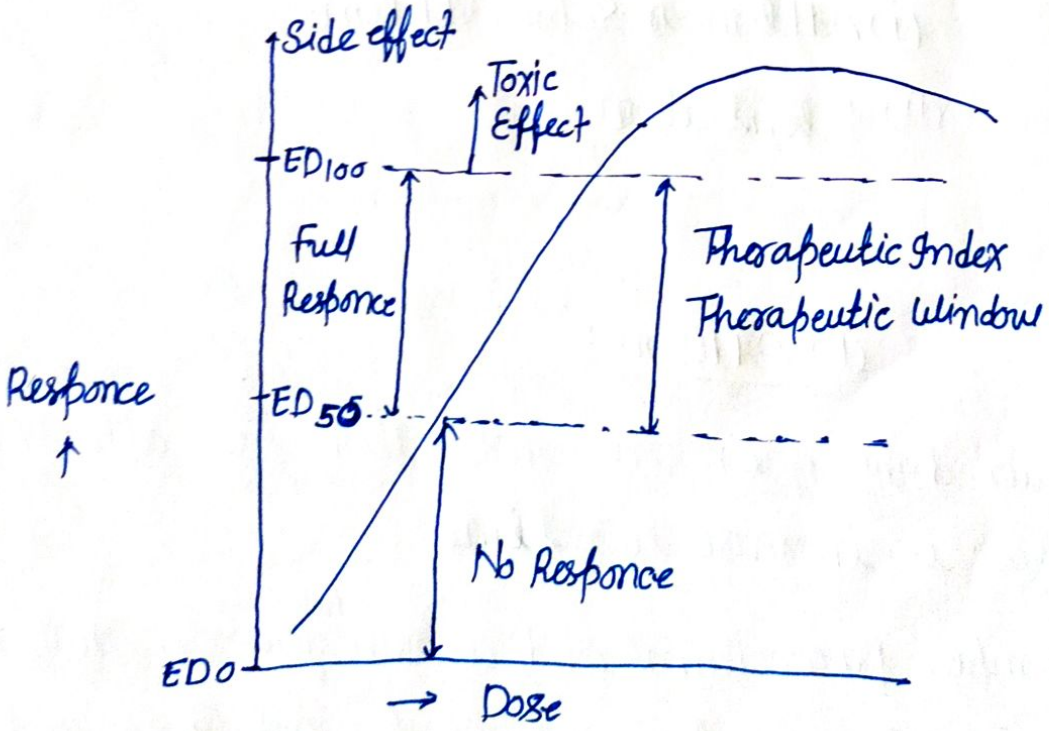
÷ Therapeutic Index ÷

LD-50 Dose (Lither Dose-50) ÷ On which dose the 50 % of animal were killed that dose is called LD_{50} dose.

ED_{50} Dose (Effective dose) ÷ On which dose the 50 % of animal were cure that dose is called ED_{50} dose.

Therapeutic Index ÷ The section between ED_{50} and ED_{100} of any drug in dose responce curve is called therapeutic index or therapeutic (curve) window.

→ And in therapeutic index and drug shows maximum responce and less side effect.



÷ Combined effect of Drugs ÷

→ When two or more drug given in combination then they either increase the effect of drug or they decrease the effect of drug.

- On the basis of their effect, effect of combination is of two type.

(1) Synergistic
(2) Antagonistic.

(1) Synergistic Effect ÷

When the two different drug are given in combination then they inhence the action of each other and the effect of drug is increase is called synergistic effect.
it is of two types -

(i) Addition or Supra Addition.

(ii) Potentiation.

(i) Addition ÷

When two drug given in combination then after Addition their effect is increase two time

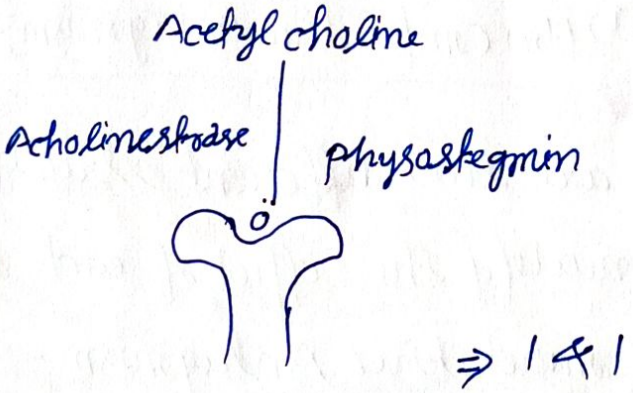
→ for example paracetamol and asprin both given in combination. then it increase effect two time for Analgesic and Anti-pyretic effect.

Ex- 1 & 1 = 2

Potentiation

When two drug given in a combination then they increase the their effect multiple number of time. this effect is called potentiation effect.

→ When acetylcholine and physostegmin drug are given then physostegmin drug block the effect of Acholinestrase enzyme so Acetylcholine can bind with the receptor. And the effect can increase multible number of time. this is called potentiation effect.



$\Rightarrow 1 < 1 = 11$

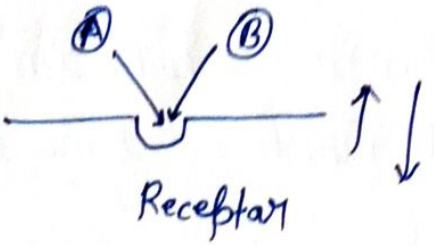
(2) Antagonistic effect :-

→ When the two different drug are given in combination then they inhibit the action of each other and the effect of drug is decrease or stop is called Antagonistic effect. it is of two type :-

(i) Competative Antagonism.

(ii) Non competative Antagonism

(i) Competative Antagonism:



I & I > 0

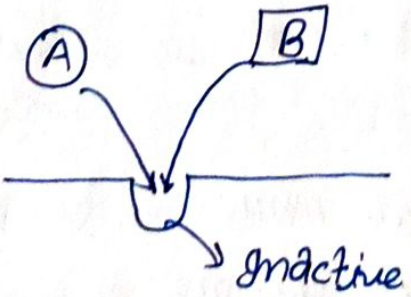
Ex- Antihypertesive.
Antiacholinergic.
Antithyroid. (Antithyroid)

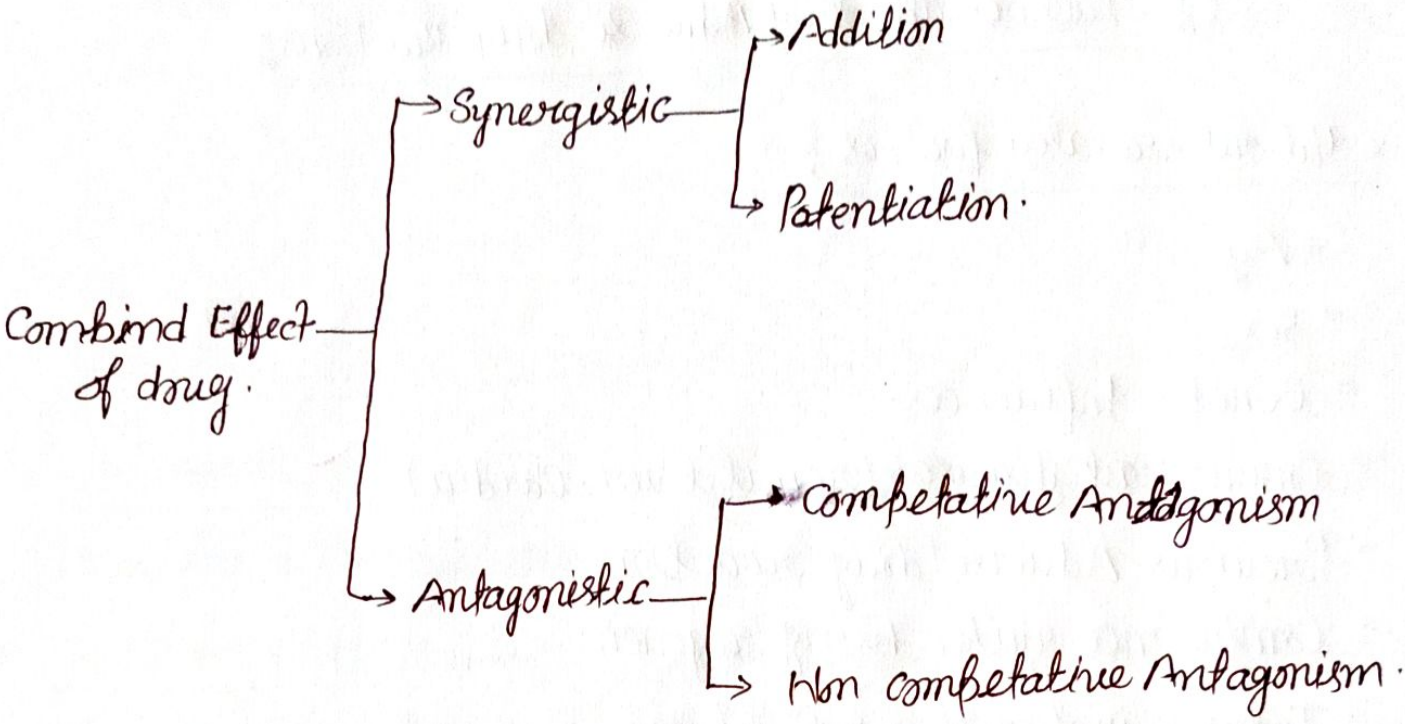
(ii) Non Competative Antagonism:

→ When there are two different structure and shape of drug but they nullify the effect of each other they are called the non competative Antagonism.

→ In this type of antagonist the other drug inactivate the receptor of organ.

Ex:- Acetylcholine & Papperverine





÷ Adverse drug Reaction ÷

Any unwanted medical occurrence that may present during treatment with medicine, but which may not have causal relationship with the treatment.

Common Causes of ADRS

- Failing to take the correct dosages at the correct time.
- Overdosing.
- Allergies to chemical components of the medicine.
- Combining the medicine with alcohal.
- Taking other drugs or preparations that interact with the medicine.
- Taking a medicine that was prescribed for someone else.

Factors affecting Adverse drug Reactions

* Patient-related factors

- Age
- Sex
- Genetic Influences.
- Concurrent diseases (renal, liver, Cardia)
- Previous Adverse drug reaction.
- Compliance with dosing regimen.
- Total number of medications.
- Misc. (diet, smoking, environmental exposure.

Age

- Children are often at risk because their capacity to metabolize drugs is usually not fully developed.
- Children younger than 18 may be at risk of developing Reye's syndrome if given acetylsalicylic acid (aspirin) while infected with chickenpox or influenza.

Elderly

- ADRs, including drug interactions are a common caused of admission to hospitals in the elderly.
- Reasons for ADRs in the elderly -
  (i) Concomitant use of several medications.
  (ii) Decreased drug ADME activity due to age

(3) These conditions are exacerbated by malnutrition and dehydration common in the elderly.

÷ Pregnancy ÷

→ Sulfonamides → Jaundice and brain damage in the fetus

→ Warfarin ÷ Birth defects. and increased risk of bleeding problems in newboons and mothers

→ Lithium ÷ Defects of the heart (Ebstein's Anomaly) lethargy reduce muscle tone and underactivity of the thyroid gland

÷ Breast feeding ÷

→ Many drugs can be passed from mother to infant via breast milk.

→ Amantadine (Antiviral)

→ Cyclophasphamide (Antineoplastic)

→ Cocaine (Schedule 2 FDA drug)

→ Carisoprodol (Skeletal muscle relaxant)

÷ Drug Related Factors ÷

→ Dose

→ Duration

→ Inherent toxicity of the agent

→ Pharmacodynamic properties.

→ Pharmacokinetic Properties.

÷ Types of ADR ÷

Type-A – (Augmented

Type-B – (Bizarre)

Type-C – (Continuous)

Type-D – (Delayed

Type-E – (Ending of use)

Type-F – (Failure of Efficacy)

÷ Types based on onset ÷

Onset of event ÷

→ Acute ÷ Within 60 minutes

Sub-acute ÷ 1 to 24 hours.

Latent ÷ > 2 days

÷ Severity of ADR ÷

Minor	Moderate	Severe	Lethal
No treatment/ Antidote / prolongation of hospitalisation	Requires Treatment / Change in treatment / prolongation by at least 1 day	Requires intensive treatment, life threatening permanent damage	Directly / Indirectly contributes to the death of the patient

÷ Type-A Reactions or Augmented ÷

→ This type of adverse drug reaction is predetermined and predefind.

→ And this type of Adverse drug reaction can be minimize by using dose adjustment or other combination of drugs.

Pharmacological properties of a drug ÷

Extension effects ÷

→ Predictable

- Dose-Related responses.

→ Prevention- Adjustment of dosage regimen

Ex ÷ → Benzodiazepines → Sedation

→ Furosemide → Water and electrolyte imbalance.

→ Heparin, Warfarin → Spontaneous bleeding.

→ Insulin → Hypoglycemia.

÷ Type-B Reactions or Bizare ÷

The type-B Bizare type of Adverse drug reaction is a type of reaction in which the effect of drug is not known and the appear suddenly.

→ Abnormal effects

→ Unrelated from the drugs' known pharmacological Action

Ex:- → Hypersensitivity reactions.
⇒ Stevens-Johnson's Syndrome.
⇒ Hemolytic Anemia.

Type-C Reaction or Continuous

These types of Adverse drug reaction which was appear in human body by taking continuous dose of any drug for long duration is called type-c Adverse drug reaction.

⇒ Long term effects are usually related to the dose and duration of treatment.

Ex:- Ethambutal - Retinopathy

NSAIDS - Nephrotoxicity.

Type-D Reaction or Delayed

In this type of Adverse drug reaction the Adverse effect of drug will be delayed after the prolong use of any medication.

Ex:- → Carcinogenesis
- Teratogenesis.
- Thalidomide.

÷ Type-E Reaction or Ending of use ÷

This type of adverse drug reaction is appear after the ending of dose or medication.

→ Withdrawal syndromes.

Ex ÷ Benzodiazepines — Reboumd insomnia Agitation
Clonidine — Reboumd hypertension.
Corticosteroids — Acute Adrenal Insufficiency.

÷ Type-F Reaction or failure of efficacy ÷

→ This type of Adverse drug reaction is uncertain and this is the basicaly failure of efficacy.

→ In this type of reaction the drug can't show their own responce

Ex ÷ → Counterfeit Medicines.
→ Underdosing of Medications.
→ Drug intractions

÷ Drug Interactions ÷

Drug interaction is defined as the pharmacological Activity of one drug is altered by the concominant use of another drug or by the presence of some other substance.

÷ Types of drug interaction ÷

(1) Drug - Drug interaction.
(2) Drug - Food interaction.
(3) Chemical - Drug interation
(4) Drug - Laboratary test interaction.
(5) Drug - Disease interactions.

÷ Factors Contributing to drug interaction ÷

(1) Multiple drugs therapy.
(2) Multiple prescribers.
(3) Multiple pharmacological of drug.
(4) Multiple disease / Predisposing illness.
(5) Poor patient compliance.
(6) Advancing age of patient
(7) Drug - related factors.

∴ Mechanism of drug interactions ∴

The three mechanism by with which an interaction can develop are. -

(1) Pharmaceutical Interaction.

(2) Pharmacokinetic Interaction

(3) Pharmacodynamic Interaction.

(1) Pharmaceutical Interaction

Pharmaceutical Interaction also called as incompatibility. It is a physicochemical interaction that occurs when drugs are mixed in IV (Intravenous) Infusions causing precipitation or inactivation of active principles.

Ex∴ Ampicillin, Chlorpromazine & barbiturates interact with dextran in solutions and are broken down or from chemical compounds.

(2) Pharmacokinetics Interactions ∴

These interactions are those in which ADME properties of the object drug is Altered by the precipitant and hence such interactions are also called as ADME interactions

- The resultant effect is altered plasma concentration of the object drug.

These are classified as :

(1) Absorption Interactions
(2) Distribution Interactions.
(3) Metabolism Interactions.
(4) Excretion Interactions.

(1) Absorption Interaction :-

Absorption Interaction are those where the absorption of the object drug is altered.

The net effect of such an interaction is -

→ Faster or Slower drug absorption.
= More or Less complete drug absorption.

:- Major Mechanism of absorption interaction are :-

(1) Complexation and absorption.
(2) Alteration in Gastro Intestinal pH.
(3) Alteration in gut motility.
(4) Inhibition of Gastro Intestinal enzymes.
(5) Alteration of Gastro Intestinal micro flora.
(6) Malabsorption symptome.

Object drug	Precipitant Drugs	Influence on object drug

(1) Complexation and Absorption :-

Cephrofloxacine penicillamine	Antacids, Food & Minerals Supplements containing Al, Mg, Fe, Zn & Ca Ions	Formation of Poorely Soluble and Unabsorable Complex with such Heavy metal ions.

(2) Alteration in GI pH :-

Sulphonamides Aspirin Ferrous Sulphate	Antacids; Sodium Bicarbonate, Calcium Carbonate	Enhanced Dissolution and Absorption Rate.
		Decreased Dissolution and Hence Absorption.

(3) Alteration in Gut Motility :-

Aspirin Diazepam Levodopa, Mexiletine	Metoclopramide	Rapid Gastric Emptying, Increased Rate of Absorption.
Levodopa Lithium carbonate Mexiletine	Anti Cholinergics	Delayed Gastric Emptying, Decreased Rate of Absorption.

(4) Alteration of GI Microflora :-

Digoxin	Antibiotics	Increased Bioavailability Due to Destruction of bacterial flora that inactivates Digoxin in lower intestine.

(5) Malabsorption Syndrome :-

Vitamin A, B_{12}, Digoxin	Neomycin	Inhibition of Absorption Due to Malabsorption.

(2) Distribution Interaction :-

Distribution interation are those where the distribution pattern of the object drug is altered.

- The major mechanism for distribution interaction is alteration in protein drug binding.

Competitive displacement Interactions :-

:- Displaced drug	displacer :-	
Anti Coagulant	Phenylbutazone, Chloral hydrate.	Increased clotting time increased risk of hemorrhage
Tolbutamide	Sulphonamides	Increased hyperglycemic effect.

(3) Metabolism Interactions :-

Metabolism interaction are those where the metabolism of the object drug is altered.

Mechanisms of metabolism interactions include

(1) Enzyme induction :- Increased rate of metabolism.

(2) Enzyme inhibition :- Decreased rate of metabolism.

It is the most significant interactions in comparison to other interactions and can be fatal.

(1) Enzyme Induction :-

Corticosteroids, oral Contraceptives, Coumarins, phenylbutazone	Barbiturates	Decrease Plasma levels, Decreased efficacy of object drugs.
Oral, Contraceptives Oral Hypoglycaemics	Rifamicin	Decreased plasma levels.

(2) Enzyme Inhibition :-

Tyramine Rich food	Mao Inhibitors	Enhanced Absorption of un metabolised Tyramine
Coumarins	Metronidazole Phenyl Butazone	Increase Anticoagulant Activity.
Alcohal	Disulfiram Metronidazole	Increased in plasma Acetaldehyde Levels.

:- Excretion Interactions :-

Excretion Interaction are these where the excretion pattern of the object drug is altered.

Major Mechanism of excretion interactions are

- → Alteration in renal blood flow.
- → Alteration of urine pH
- → Competition for active secretions.
- → Forced diuresis.

(1) Change in Active tubular secretion :-

Penicillin Cephalosporins, Nalidixic Acid	Probenicid	Elevated plasma levels of Acidic Drugs.

(2) Changes in urine pH

Amphetamine	Antacids, Thiazidesa Cetazolamide	Increased passive Reabsorption of basic drugs increased risk of Toxicity.

(3) Changes in renal blood flow :-

Lithium Bicarbonate	NSAIDs	Decreased Renal Clearance of Lithium Risk of Toxicity

Pharmacodynamics Interactions

Pharmacodynamic Interaction are those in which the activity of the object drugs at its site of action is altered by the precipitant.

Such interactions may be direct or Indirect.

These are of two types :-

(1) Direct pharmacodynamic Interactions

(2) Indirect pharmacodynamic Interactions.

÷ Direct Pharmacodynamic Interaction ÷

In which drug having similar or opposing pharmacological effects are used concurrently.

- The three consequences of direct interactions are -

(1) Antagonism

(2) Addition or Summation

(3) Synergism or Potentiation.

(1) ÷ Antagonism ÷

The interacting drug have opposing actions.

Ex ÷ Acetylcholine and noradrenaline have opposing effects on heart rate

(2) Addition or Summation ÷

The interacting drugs have similar actions and the resultant effects is the some of individual drug responses.

Ex ÷ CNS depressants like sedative and hypnotics etc.

(3) Synergism or potentiation

It is an enhancement of action of one drug by another

Ex ÷ Alcohal enhances the analgesics activity of aspirin.

÷ Indirect pharmacodynamic interaction ÷

In which both the object and the precipitant drugs have unrelated effects but the latter in some way alters the effects but latter in some way alerts the effects of the former.

Ex:- Salicylates decrease the ability of the platelets to aggregate thus impairing the homeostasis if warfarin induced bleeding occurs.

÷ Drug discovery ÷

Introduction:- In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery.

→ But now we know disease are controlled at molecular and physiological level.

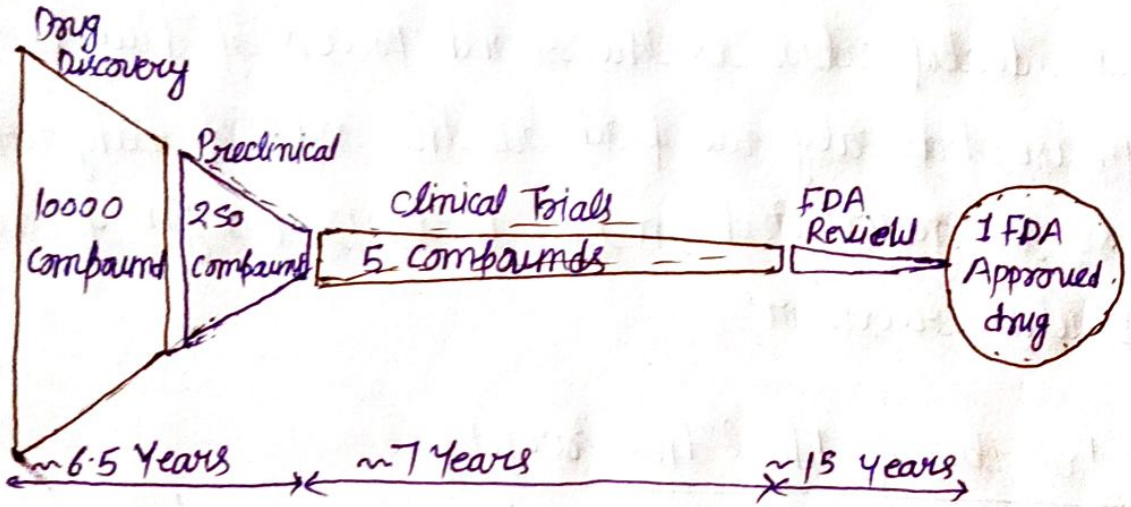
→ Also shape of an molecule at atomic level is well understood.

→ In broader sense drug discovery and development can be defind.

→ A process that starts with the identification of disease and therapeutic identification and characterization in vitro, formulation and animal pharmacological studies, pharmacokinetic and safety studies in animals and clinical studies in the human " Different stages include.

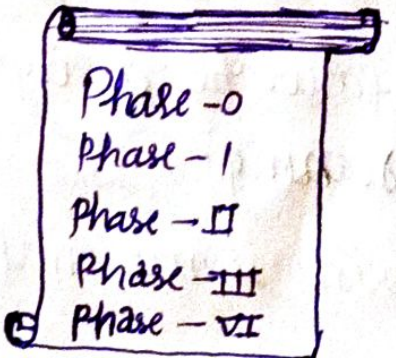
* Basic research
* Feasibility studies
* Programme
* Non-clinical development
* Clinical development.

Drug discovery & development timeline



÷ Process of drug discovery ÷

1 Pre-discovery.
(2) Target identification.
(3) Target Validation
(4) Lead discovery.
(5) Lead optimization.
(6) Preclinical Testing.
(7) Clinical Trial
(8) New drug.



÷ (1) Pre-Discovery ÷

To find out the problems or disease before the discovery of disease. this is called pre-discovery.

→ This can be done by laboratory method.

(2) Target Identification ÷

→ Target identification is the second process of drug discovery in this phase. basicaly we find out the organ of body where the disease is occur. and in that particular organ find out the particular receptor.

÷ Properties of Ideal drug target ÷

→ Target is disease-modifying and/or has a proven function in the pathophysiology of a disease.

→ Modulation of the target is less important under physiological conditions or in other disease.

→ If the druggability is not obvious (exa. as for kinases) a 3D-structure for the target protein or a close homolog should be available for a druggability assessment.

→ Target has a favorable assayability enabling high through put screening.

→ Target expression is not uniformly disbributed throughout the body.

→ A target / disease-specific biomarker exists to monitor therapeutic efficacy.

÷ Various target of drug action ÷

→ The majority of drug targets are →

(A) G-Protein Coupled receptors · 5000 → (Est total

(B) Nuclear receptors > 150 → (Est total)

(C) ion channels → (Est total 1000)

(D) Enzymes Uncertain. → (Est total.)

→ Currently we are exploiting only 120 distinct drug targets.

÷ Target identification strategies ÷

* Gene Expression profiling → Genomics
* Focussed → Proteomics.
* Metabolic pathways analysis → Molecular biology.
* Phenotype Analysis.
* Genetic Association.

÷ Inverse Docking ÷

It is a computational docking program in which a specific small molecule of interest is tested against a library of receptor structures.

÷ Bioinformatics ÷

→ It derives knowledge from computational analysis of biological data.

→ It includes information stored in genetic code, patients statistics and scientific literature.

→ In the earlier times, the complex biological responses of chemical were first seen.

- And then the drug targets were explored for those chemicals.

→ Now target identification has become the first step of drug discovery.

÷ Limitation ÷

Drug which do not act through receptors → Antacids, osmotic, diuretics, Alkylating agent, Psoralens and Activated charcoal can not be recognised.

(3) Target Validation ÷

→ To identify the most useful target among the various identified targets. Target validation is done -

- Identified targets are analysed and compared for

(1) Ability to regulate biological and chemical process / Molecules in the body.

(2) Association with a specific disease.

- It is done using genetic knockout.

÷ (4) Lead discovery ÷

Lead finding / Lead generation ÷ Approaches to new drug molecule –

(1) Newer Techniques ÷

- → Molecular Modeling.
- → Combinatorial chemistry.
- → Biotechnology.
- → Genetic Medicine
- → Immunopharmacology ÷

} → Biologics or Biological Compound.

→ **Definition ÷** Lead compounds are the those active compound. which are responcible for the treatment of disease. which is later are known as drug.

(i) Molecular Modeling ÷

- → AKA Rational drug designing.
- → Aided by three dimensional computer graphics.
- → Allow design of structure based on new & known molecules
- → Highly selective targeted compounds are created by enhancing desired properties of known molecules.

(ii) Combinatorial chemistry :-

→ It is systematic and repetitive covalent connection of set of different building blocks of varying structures to each other to yield a large array of diverse molecular entities.

→ This process is :-

(1) Faster, more efficient and cheaper

(2) Millions of compounds can be synthesized; chemical compounds.

(iii) Biotechnology :-

→ Therapeutic agents produced by biotechnology rather than conventional synthetic chemistry are called biopharmaceuticals.

→ Involve the use of recombinant DNA technology / genetic engineering to clone & express human genes.

→ To produce large amount of hormones like insulin.

(iv) Genetic Medicine :-

→ Transfer of Genetic material :-

(1) A single gene which is typical for gene therapy.

(2) Fragments of coding sequences (as in RNA modification therapy - MC being anti sense oligonucleotide strategy)

(3) Entire genome (as in the case of SSC and ESC Therapy.

→ Vectors are viruses and liposome plasmid complex.

→ Diseases Addressed: Hereditary diseases like SCID, Haemophillia etc.

(V) Immunopharmacology :-

Deals with finding the biological immune modifiers or immunomodulating agents that cause selective up-regulation or down regulation of specific immune responses.

Examples - Include-

(i) Rituximab - Anti CD 20 monoclonal antibody for RA

(ii) Adalimumab - Anti TNF-α inhibitor antibody for RA.

(2) Older techniques :-

→ Animal models as human disease.

→ Natural Products like plants, animal & micro organism.

(1) Random screening approach.

(2) Ethnobiological approach.

→ Traditional Medicines

→ Modification of structure of known drugs to develop "Me-too derivative medications follow-up drugs" drugs.

÷ Source of leads Plant ÷

- Papaver somniferum → Morphin
- Atropa belladona → Atropine
- Rauwolfia serpentina → Reserp
- Digitalis Ganata. → Digoxin
- Strychnos toxifera. → d-TC
- Pilocarpus microphyllus → Pilocarpine
- Salix alba (Willow bark) → Aspirin
- Bark of Yew tree → Paclitaxel
- Cinchona tree → Quinine.

(5) Lead optimization ÷

The aim of this stage is -

(1) Increase the potency of the compound on its target.

(2) Increase its selectivity

(3) Increase its metabolic stability.

→ usually one project out of five passes this stage

÷ Various steps of lead optimization ÷

(i) Identification of the "pharmacophore" (Relevant group on a molecule that interact with a receptor and are responsible for the biological Activity.

(2) Functional Group Modification :

→ Modification of the group may enable or disable certain biological effects.

(3) Structure Activity relationship : Some of these features are important for the activity and the others are not.

(1) NH_2 and sulfonyl (R) should be para

(2) NH_2 should be unsubstituted

(3) Benzene ring should not be replaced by other ring systems.

(4) Structure Modification : To increase potency and therapeutic index.

(A) Homologation → A homologous series is a group of compounds that differ by a constant unit, usually CH_2

(B) Chain branching.

(C) Ring chain transformation Affects -

(1) Lipophilicity.

(2) Interaction with the enzyme or receptor. It could increase or decrease drug potency and therapeutic index.

(D) Bioisosterism.

(5) Quantitative Structure Activity relationships
(QSAR - rational drug design)

→ Based on the fact "the biological properties of compounds are a function of its physico-chemical parameters.

- Fundamental Physico-chemical parameters -

(a) Electronic effects → Hammett equation.
(b) Lipophilicity effects → Hansch equation.
(c) Steric effects → Taft equation.

(6) preclinical Testing :-

→ After the lead optimization or lead finding the testing of these drug in animal is called preclinical testing.

:- Preclinical development :-

→ Usual time duration — 15 years
→ Usual no of compounds - 20 years
→ The aims of pre clinical testing are -

(1) Pharmacokinetics
(2) Short term toxicology.
(3) Formulation.
(4) Synthesis scale up.

÷ Work falls in four categories ÷

(1) Safety pharmacology ÷ Pharmacological testing to check that the drug does not produce any hazardous side effects.

(2) Preliminary toxicological testing to eliminate genotoxicity and to determine the maximum non toxic dose of the drug (usually when given daily for 28 days, and tested in two species)

(3) Animal studies ÷ Pharmacokinetic testing that is studies on absorption metabolism, distribution and elimination in laboratory animals like Mice, chicken monkeys, and guinea pigs.

(4) Chemical and Pharmaceutical development ÷

(A) Feasibility of large-scale synthesis and purification.

(b) Stability of the compound under various conditions.

(c) To develop a formulation suitable for.

(5) Toxicology studies ÷ Extended programme in animals studies these could be acute, sub Acute or chronic toxicity studies

(1) Acute → 24-28 hours

(2) Sub Acute → Few week

(3) Chronic → For months.

What after preclinical phase:

Once the preclinical trials are over sponsors are required to submit the Investigational New drug application

→ It contains information regarding.

(1) Preclinical data PK, PD & Toxicological

(2) Manufacturing data → Composition Manufacturing process stability & shelf life.

(3) Protocol of clinical trials.

(7) Clinical Trials:-

→ Set of procedures in medical research and drug development to study the safety and efficacy of new drug.

→ Essential to get marketing approval from regulatory authorities.

→ May require upto 7 years.

Phas - I

→ Clinical pharmacalogic Evaluation.

→ First stage of testing in human subjects.

→ 20-50 healthy valunteers.

- Concerned with → • Human toxicity
  • Tolerated Dosage Range
  → Pharma-cology/dynamics.

÷ Phase-II ÷

→ Controlled clinical Evaluation.

→ 50 to 300 patients.

→ Controlled single-blind Technique.

→ Concerned with → Safety
→ Efficacy
→ Drug Toxicity & drug Interaction.

÷ Phase-III ÷

→ Extended clinical trials

→ Most expensive & time consuming.

→ 250 - 1000 patient

→ Controlled double blind technique.

Concerned with → Safety, Efficacy.
→ Comparism with other drugs
→ Package Insert.

÷ Phase-IV ÷

→ Post Marketing Surveillance.

→ Designed to detect any rare or long term adverse effects.

→ Adverse drug reaction Monitoring.