UNIT-II

Pharmacodynamics :- What the drug does to the body. This includes physiological & Biochemical effects.

Adrenaline
↓
Interaction with adrenoceptors
↓
Stimulation of Adenylyl cyclase
↓
Teased intracellular cyclic AMP
↓
Cardiac stimulation, Hepatic glycogenolysis and Hyperglycemia

Principles of Drug Action :-

Drugs (except those gene based) do not impart new functions to any system, organ or cell, they only alter the pace of ongoing activity.

- Stimulation
- Depression
- Dual Action
- Irritation
- Replacement
- Antimicrobial effects
- Modification of Immune status.

① Stimulation :- Increase in the Activity of specialized cell is called stimulation.

eg:- ① Adrenaline stimulate heart
② Pilocarpine stimulate salivary glands.
③ Morphine " vagus + CTZ

However, excessive stimulation is often followed by depression of that function.

eg:- ① High dose of morphine depress the respiratory & cough centers.

② Depression :- Decrease in the Activity of specialized cell is called depression.

eg: ① Quinidine depresses myocardium.
② Barbiturates depress CNS
③ Benzodiazepam " CNS

③ Dual Action :- Certain drug stimulate one type of cells but depress the other.

eg:- ① Acetylcholine stimulates intestinal smooth muscle but depresses SA node in heart.

② Morphine stimulates vomiting centre and depress respiratory centre.

④ Irritation :- The term irritation indicates that a drug produce adverse effects on the growth, nutrition & morphology of living tissues.

Irritation is nonspecific phenomenon that can occurs in all tissues.

- It produces change in the cellular structure & can produce inflammation, corrosion & necrosis of cell.
- The cellular changes produced are -
  - ✓ Astringent effect
  - ✓ Dehydration

(5) Replacement :- This refers to the use of natural metabolites, hormones or their congeners in deficiency states.

eg: Insulin in diabetes mellitus
Iron in anaemia
Vitamins in vitamin deficiency

(6) Antimicrobial effects :- Drugs are used for prevention arrest & eradication of infections they act specifically on the causative organisms.

eg: Antibiotics like penicillin, chloroquine etc.

(7) Modification of Immune Status :- Vaccine, serat certain other agents (Levamisole, corticosteroids) act by altering (enhancing or depressing) the immune system.

Principles of Drug Action :-

Process	Drug	Site
Stimulation	Adrenaline	Heart
Depression	Morphine, Alcohol	CNS
Replacement	Hormones	Endocrine System
Irritation	Bitter, Purgatives	GIT
Cytotoxic	Antimicrobials Anticancer drugs	Parasitic cell

Mechanism of Drug Action :-

The term drug Action and drug effects often are used as synonyms - However drug Action always proceeds the drug effects.

- Drug action is the initial interaction of a drug with cells at the site of Action which result physiological & Biochemical consequences are the drug effects.
- The Drug Action & drug effects depends on drug concn achieved at the site, which is determined by :-
  - Absorption of drug after oral or parenteral administration.
  - First- Pass Metabolism
  - Biotransformation
  - Excretion.
  - Tissue affinity
  - Condition of body.

The Mechanism of drug Action has been classified into

① Non receptor Mediated
② Receptor Mediated

① Non Receptor mediated is further classified into -

(a) Physical Action
(b) chemical action
(c) Action through Enzymes
(d) Action through ion channels
(e) Action through Transporters.

In Receptor mediated Drug Action

(a) Receptors

(a) Physical Action :- Colour eg:. Tincture of cardamom

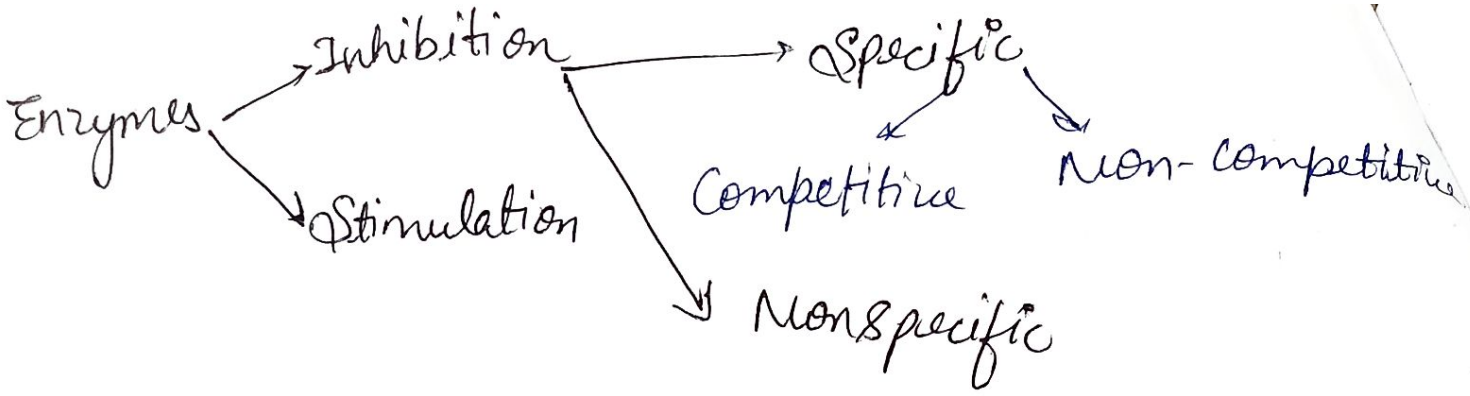
Physical mass :- Oral Agar absorb water, swell

Smell :- Peppermint oil used to mask unpleasant smell.

Taste :- Bitter taste.

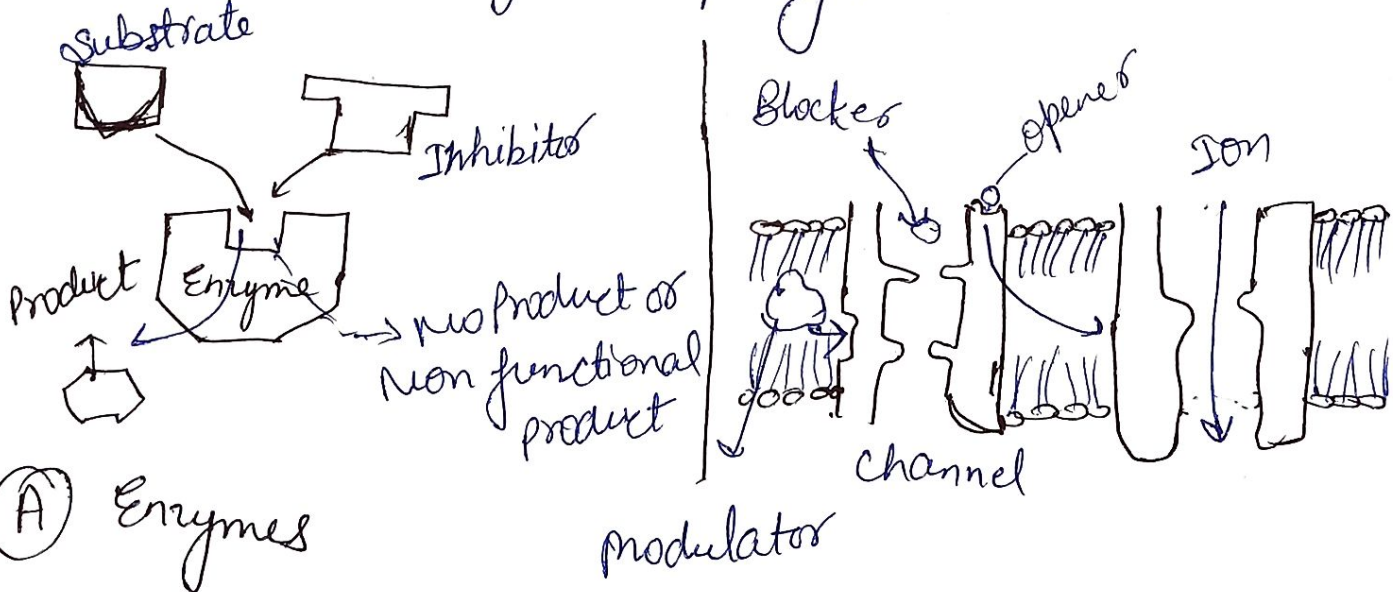
(b) chemical Action :- Antacids used in treatment of peptic ulcer.

(c) Enzymes :- Almost all biological reactions are carried out under catalytic influence of enzymes, hence enzyme are a very important target of drug Action.



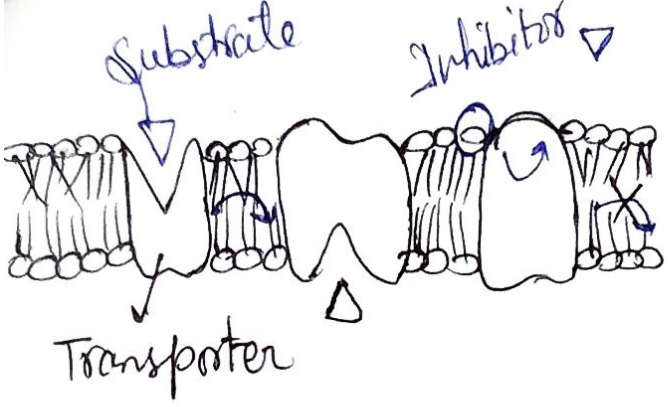
Competitive Enzyme:- The drug being structurally similar competes with the normal substrate for the catalytic binding site of the enzyme so that the product is not formed or a nonfunctional product formed.

Non-Competitive Enzyme:- The inhibitor reacts with an adjacent site and not with the catalytic site but alters the enzyme in such a way that it loses its catalytic property.

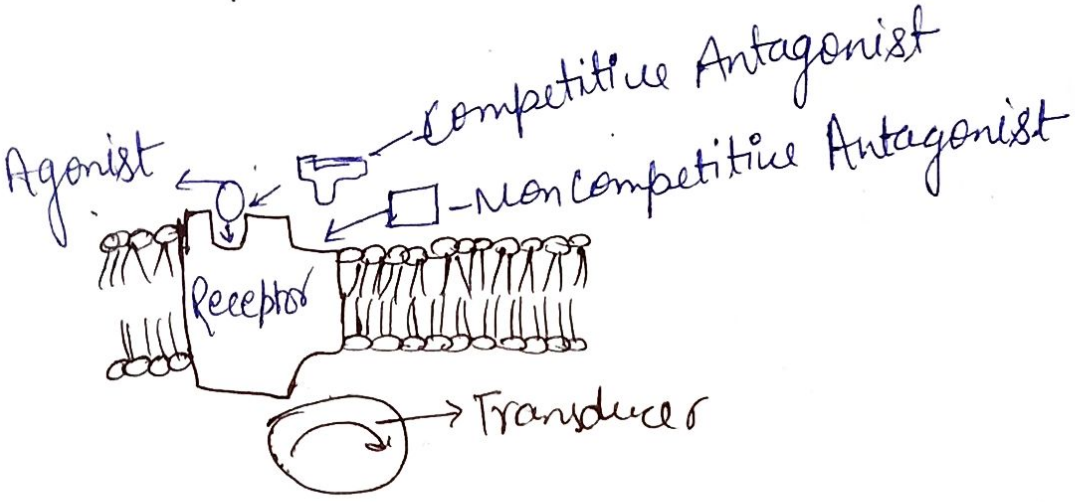


(A) Enzymes

(B) Transmembrane Ion channel



③ Transporter



④ Receptor

Receptor :- Receptor is special structure which is made up protein and it is present structure of organ. When drug bind the receptor then it form drug receptor complex ~~DR~~ complex & after formation of complex response is produce.

D + R → DR complex → Response

Affinity :- when drug bind receptor then it form complex and the ~~capacity~~ of drug bind with Receptor is called Affinity.

Types of Receptor :- on the Basis of Structure & functi

1. G-Protein Coupled Receptor (cAMP) Cyclic Adenosine monophosphate)
2. Enzyme linked Receptor
3. Ligand Gated Ion channel.
4. Receptor regulating gene Expression.
5. JAK - STAT binding receptor.

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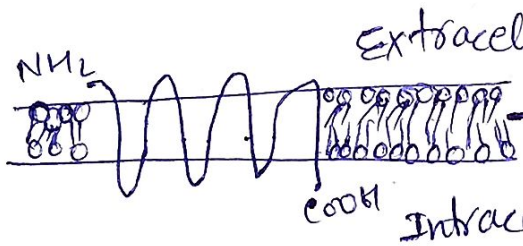
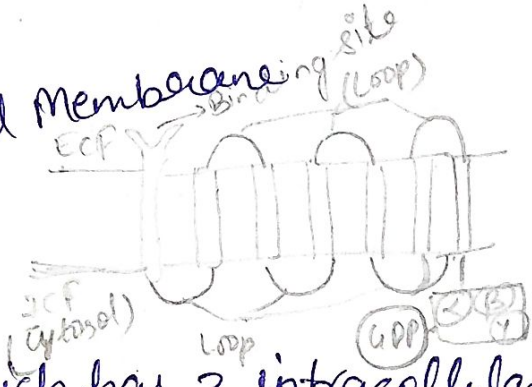
4. GPCR- G- Protein coupled Receptor

Also known as - Hepta helical Receptor
7- transmembrane Receptor
Metabotropic Receptor

G- Protein - Guanin nucleotide-binding proteins.

These are the cell surface receptor.





: 7 α helical Membrane which has 3 intracellular & 3 extracellular loops. G-protein present in trimeric complex form (α, β, γ) in which GDP is attached on α (alpha)

Mechanism :—

Drug (Agonist) bind with Receptor → Current flow through loops

↓

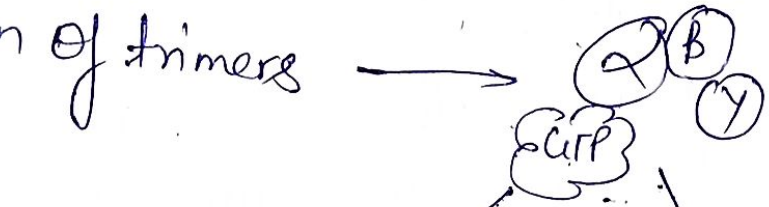
Activate G-protein

↓

GTP replace GDP

↓

Breakdown of trimers →



↓ Activate

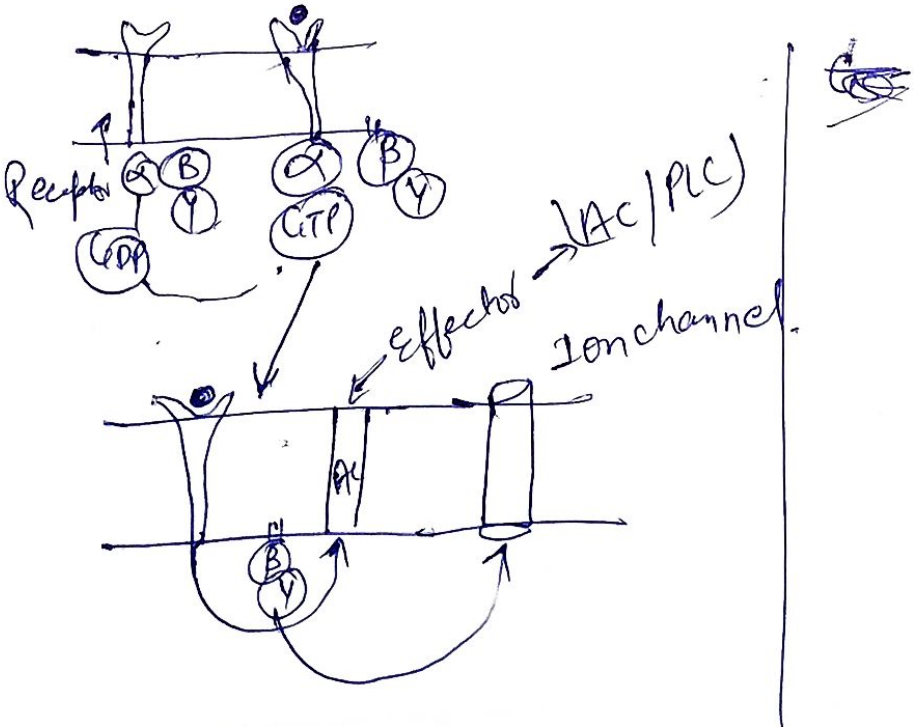
Effector enzymes

Adenylylcyclase phospholipase C

dimer

↓

Ion channel Regulation.



Types →

(i) G_s → Adenylyl cyclase Action, Ca^{2+} channel opening

(ii)(G_i) → Adenylyl cyclase inhibition, K^+ channel opening.

iii) G_o → Ca^{2+} channel inhibition

(iv) G_q → phospholipase C activation.

The GPCR produce their Action by three pathways :-

(i) cAMP (cyclic AMP) pathway (Adenylyl cyclase)

(ii) IP_3-DAG pathway (phospholipase C)

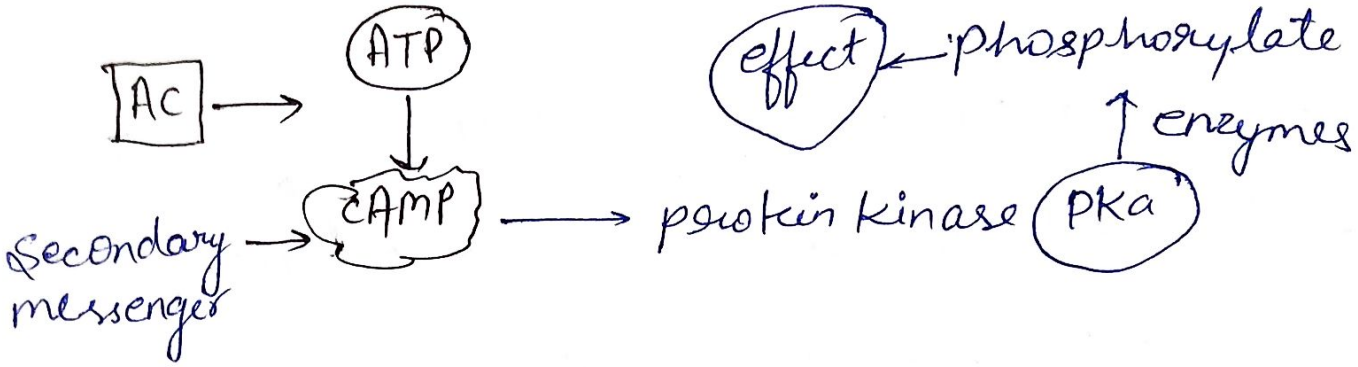
iii) channel Regulation.

(i) cAMP pathway :- • Activated by G_s
• Inhibited by G_i

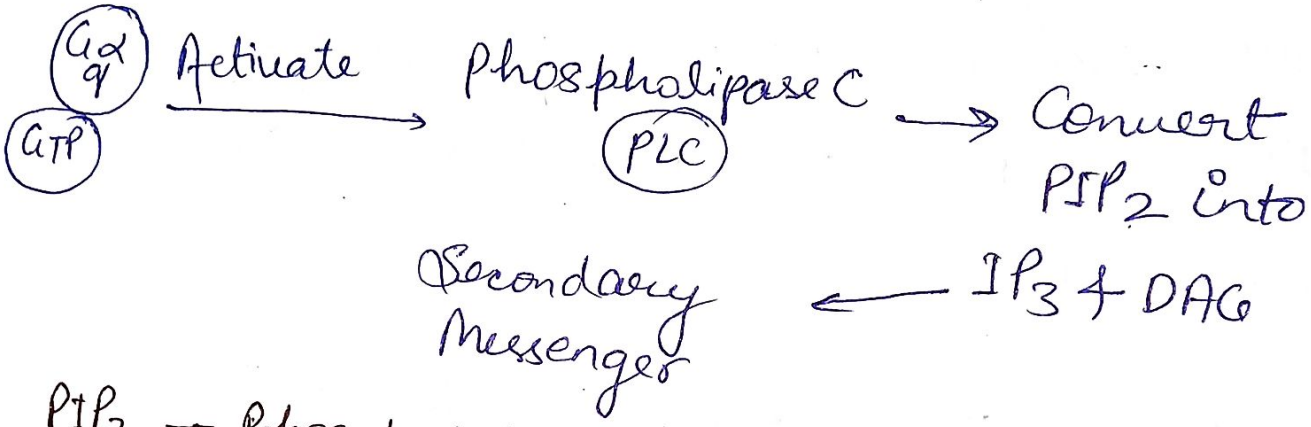
After Activation of AC, Adenylyl cyclase (AC) convert ATP into cAMP which further activate protein kinase. (PKa) enzyme also known as (AMP-dependent-protein kinase, then PKa phosphorylates and alter the function of many enzyme, ion channel etc.

Function :- ↓ LASH
Liver
Adipose tissue
Smooth muscles
Heart

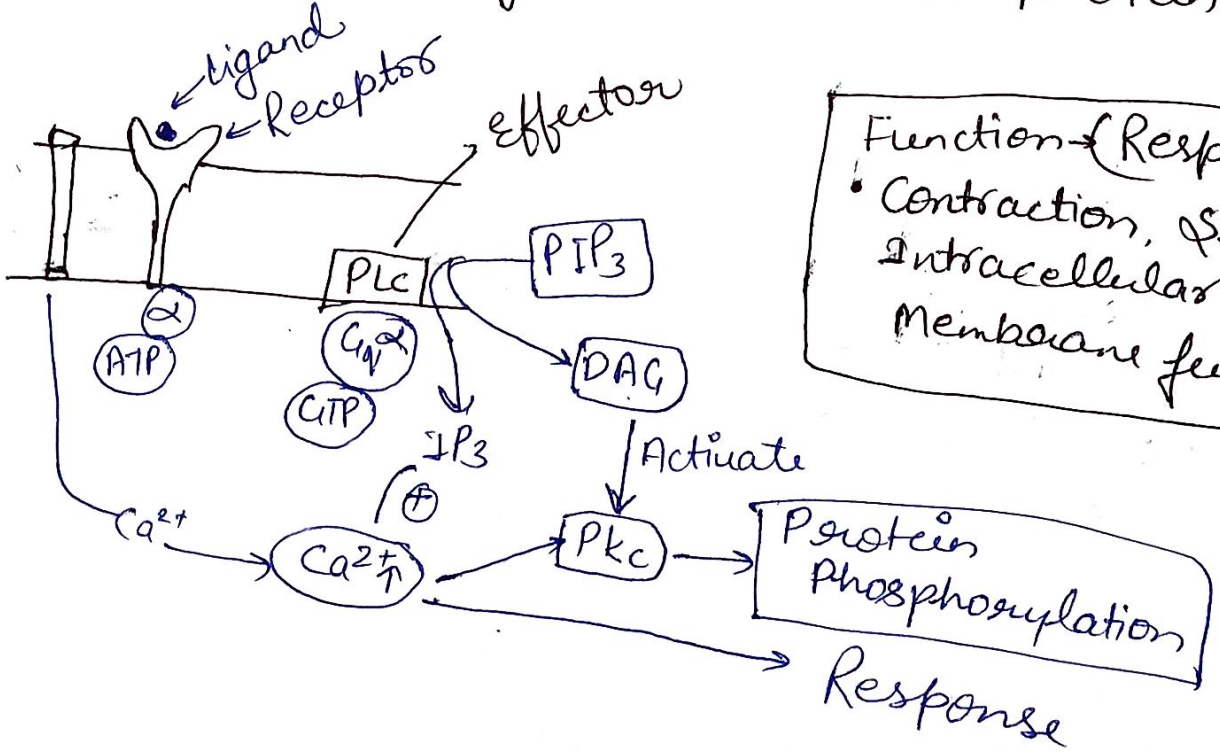
• Teased cardia contractility
• relaxation in smooth muscles.
• Glycogenolysis.
• open Ca^{++} channel in Heart, brain & kidney etc.



(11) IP_3 - DAG Pathway (phospholipase C) Activated by G_q



- PIP_3 → Phosphatidyl inositol 4, 5- biphosphate
- IP_3 → Inositol 1,4,5- triphosphate
- DAG → Diacylglycerol
- PKC - Protein kinase C



Function (Responses)
- Contraction, Secretion
- Intracellular movement
- Membrane function etc

(iii) channel Regulation →

Activated by Gs, Gi, Go

does not need secondary messenger

— Activated G-protein → can open channel

↓

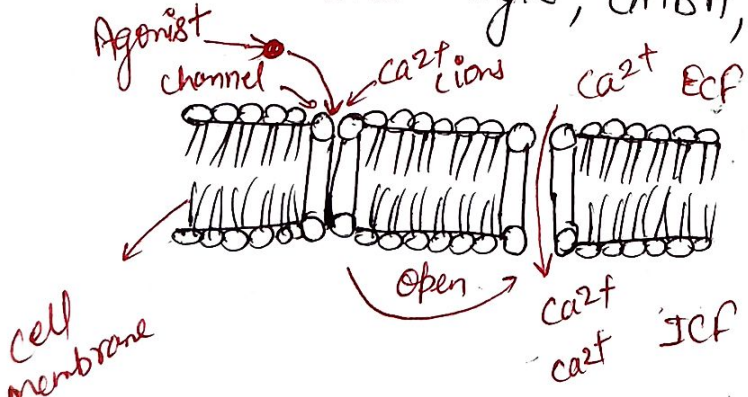
Movement of ions

- Gs open Ca^{2+} channel in myocardium.
- Gi & Go open K^+ channel in heart & smooth muscles.
- Responses such as inotropy, chronotropy. transmitter release & smooth muscle relaxation etc.

② ION CHANNEL RECEPTOR :-

It is also known as ligand gated ion channel. These are cell surface receptor. Ion selective channel for Na^+, K^+, Ca^{2+}, Cl^-

Mechanism :- Drug (Agonist) bind with in channel and open the channel. Responses such as depolarisation / Hyperpolarisation. Receptor includes in this category Nicotinic cholinergic, GABA, $5HT_3$ etc.



In these receptors the agonist directly operates ion channel (No requirement of secondary messenger)

The onset & offset of responses through this class of receptor is the fastest (in milliseconds).

③ Transmembrane Enzyme linked Receptors :-

These are plasma membrane receptor. Made up of single transmembrane chain, which has ligand binding domain in extracellular and Receptor tyrosine kinase's (RTKs) intracellular as a catalytic site with enzymatic property mostly peptide hormone are bind with receptor as a ligands

Mechanism :- Ligand bind with receptor (Hormone bind)

↓

Monomeric receptor move laterally in the membrane & form dimers.

↓

Dimerisation activates RTKs & RTKs activity of the intracellular domain.

↓

Autophosphorylate tyrosine Residue on each other.

↓

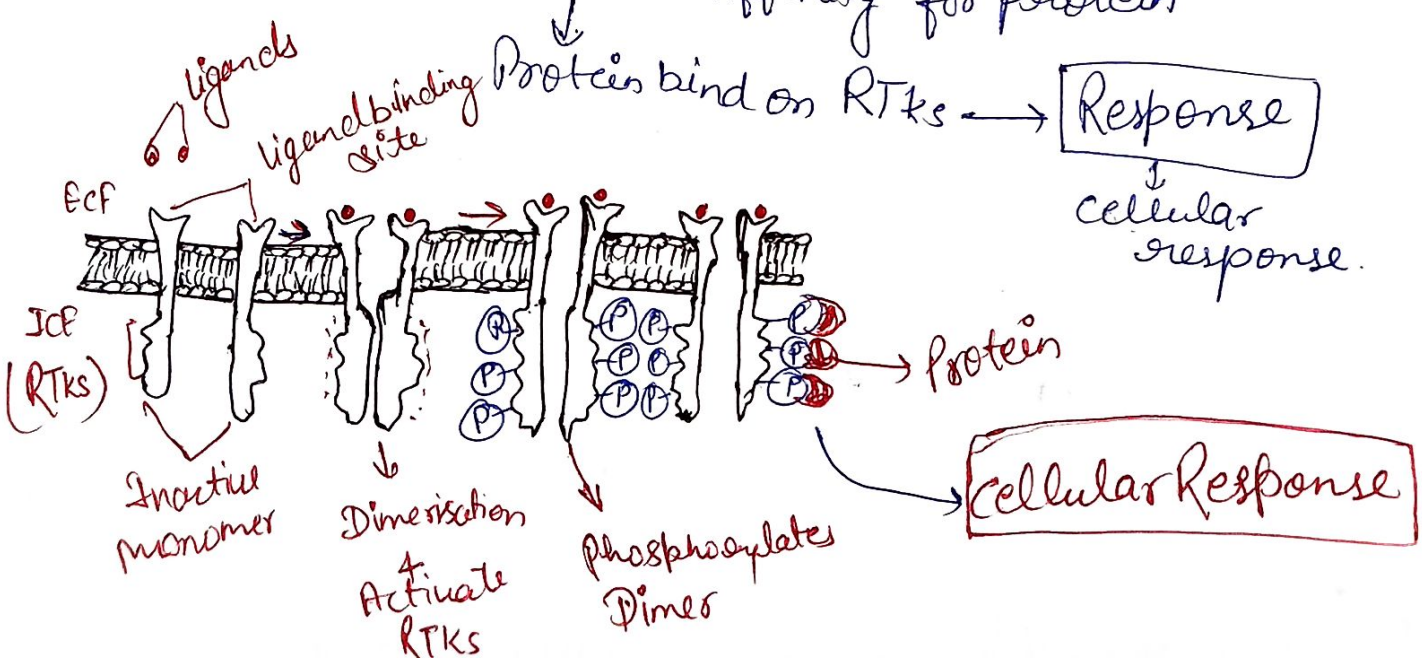
~~Inact~~ Increase Affinity for protein

↓

Protein bind on RTKs → Response

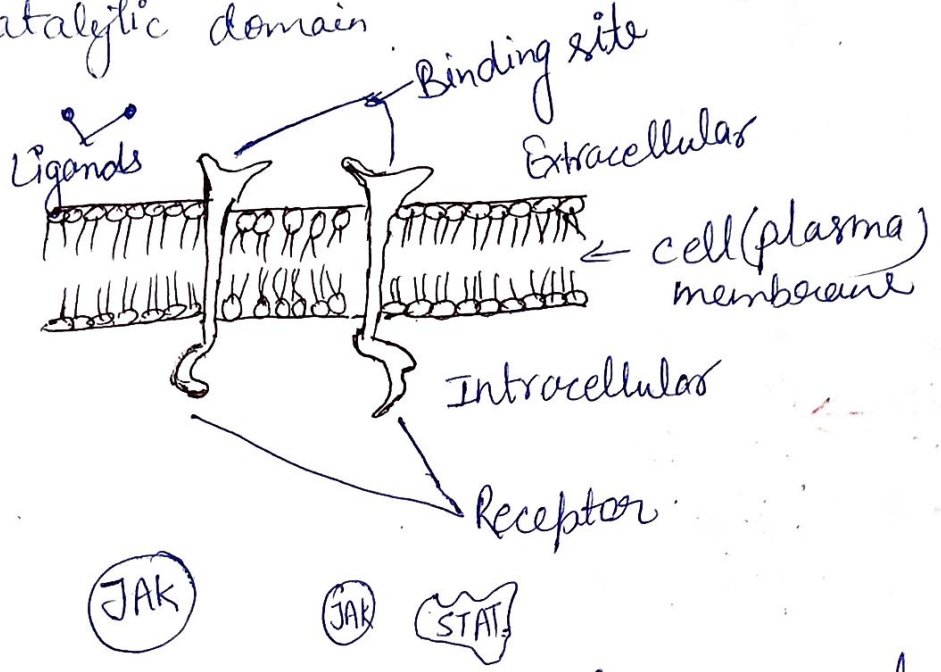
↕

cellular response.



4) Transmembrane JAK-STAT Binding Receptor :-

Similar as RTK's receptor, but they do not having any catalytic domain



Many cytokines, growth hormone, prolactin, interferons etc. act through this type of receptor.

Mechanism → Agonist binds & induced dimerization

↓

which alter the intracellular domain conformation to decrease its affinity for a cytosolic tyrosine protein kinase → JAK (Janus kinase)

↓

JAK gets Activated & phosphorylates tyrosine residues of the receptor.

↓

which now bind another free moving protein STAT (signal transducer and activator of Transcription) which is also phosphorylated by JAK.

↓

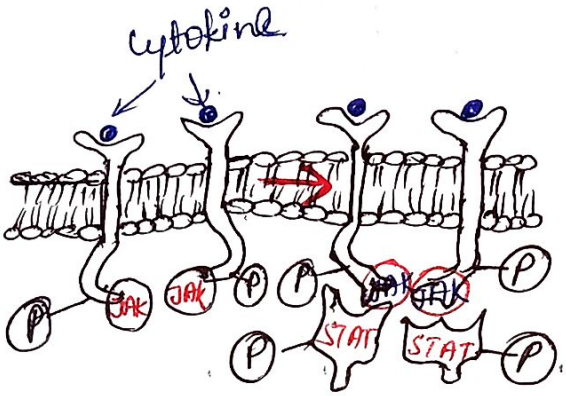
Pair of phosphorylated STAT dimerize

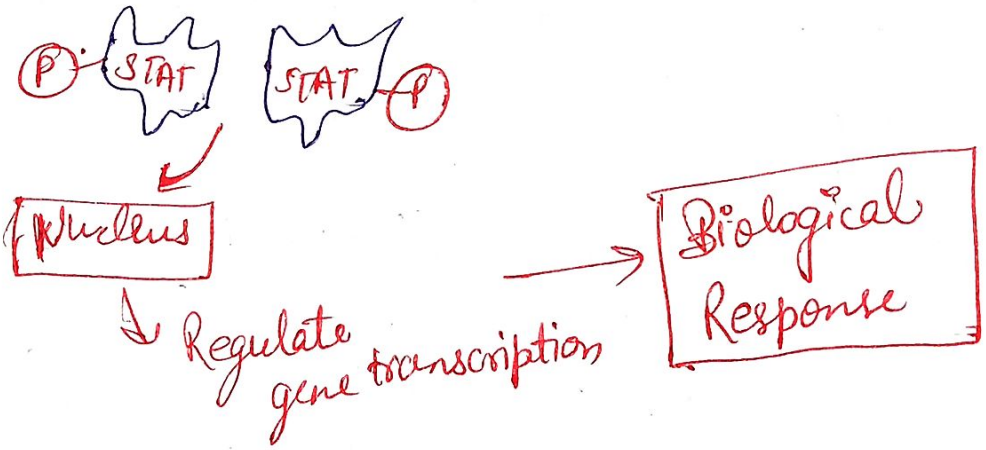
↓

Translocate to the nucleus to regulate gene transcriptio

↓

Biological Responses





(5) Receptor Regulating Gene Expression (transcription factor):-

These are intracellular receptor which are present inside the cell. They contain soluble protein which respond to lipid soluble chemical messengers that penetrate the cell. The receptor protein is inherently capable of binding to specific gene, but it attached proteins HSP-90 or any other to prevent it from adopting the configuration needed for Binding to DNA.

Mechanism:-

Hormone binds near the carboxy terminus of the receptor.

↓

The restricting proteins (HSP-90) are released

↓

The receptor dimerizes and the DNA binding regulatory segment folds into requisite conformation.

↓

The liganded receptor dimer moves to the nucleus & bind other co-activator / co-repressor proteins (which have capacity to alter gene function).

↓

The whole complex then attaches to specific DNA sequences of the target genes & facilitates or represses their expression.

↓

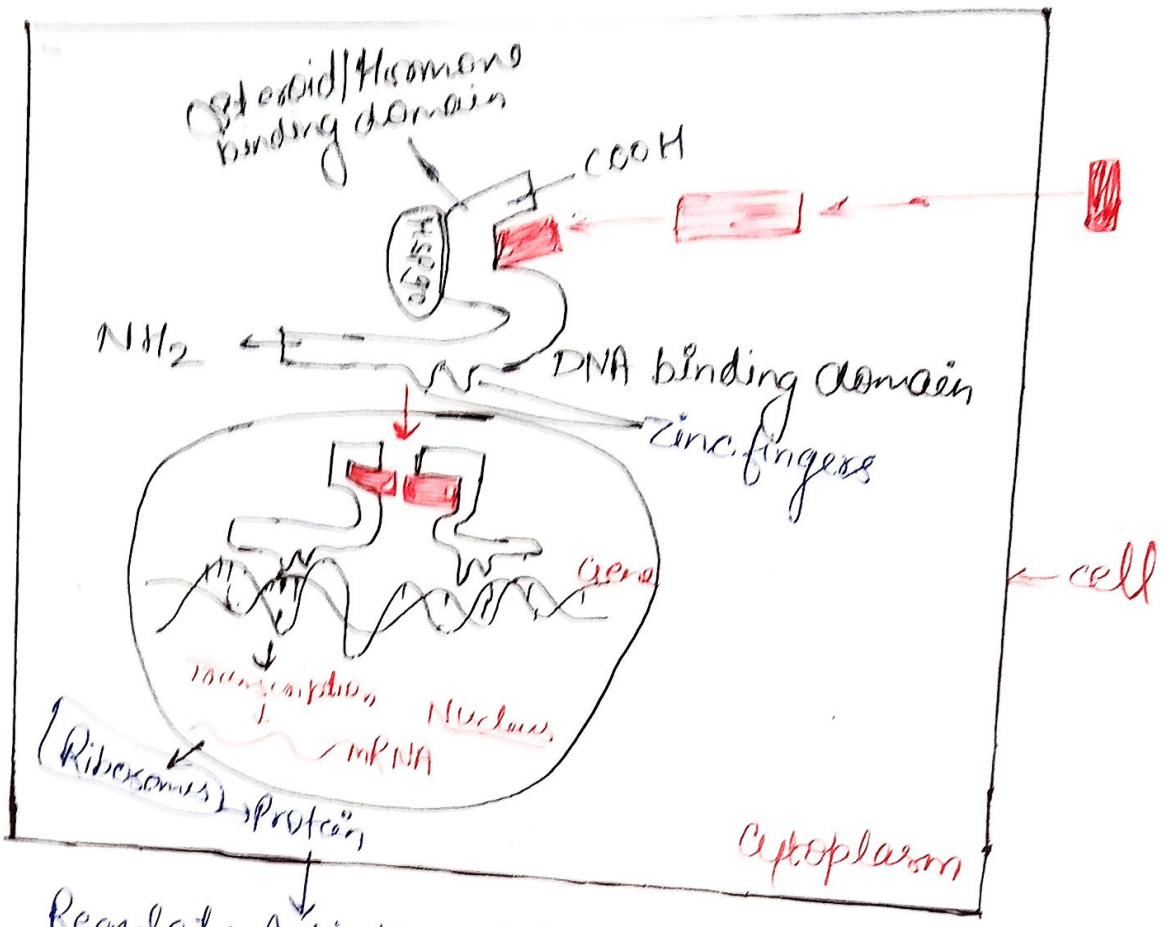
(Transcription) Specific mRNA is synthesized or repressed on the template of the gene.

↓

This mRNA moves to Ribosomes

↙

Synthesis of Specific Protein → Regulate Activity of target cell



Regulate Activity of target cells.

- All Steroidal hormone (Glucocorticoids, mineralocorticoids, androgens, estrogens, progestrone), thyroxine, vit D and vit A function in this manner.

HSP - Heat Shock protein 90

Dose - Response Relationship :-

When a drug is administered systemically, the dose-response relationship has two components; dose - plasma concentration relationship and plasma concentration - response relationship.

The response is quantitatively directly proportional to the plasma concentration as much as plasma concentration as much as the plasma concentration of drug is ↑ease there response will also be ↑ease and if the drug plasma concentration is decrease the response will aso be decrease.

$$Pc \propto Response$$

Dose Response Curve (DRC) :-

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

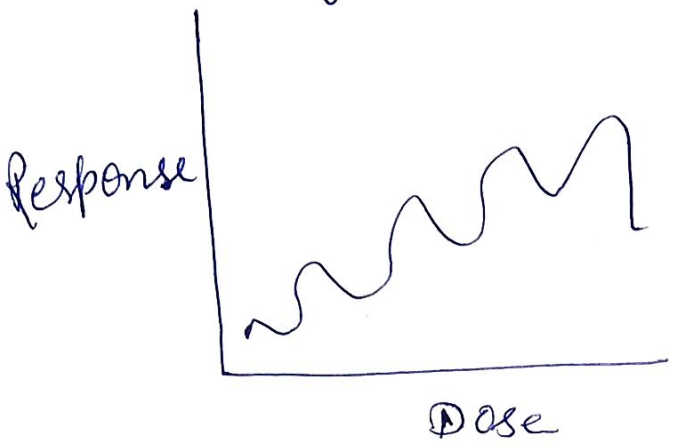
Type of DRC (Dose Response Curve)

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 ↑ease their response will also be ↑eases 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.

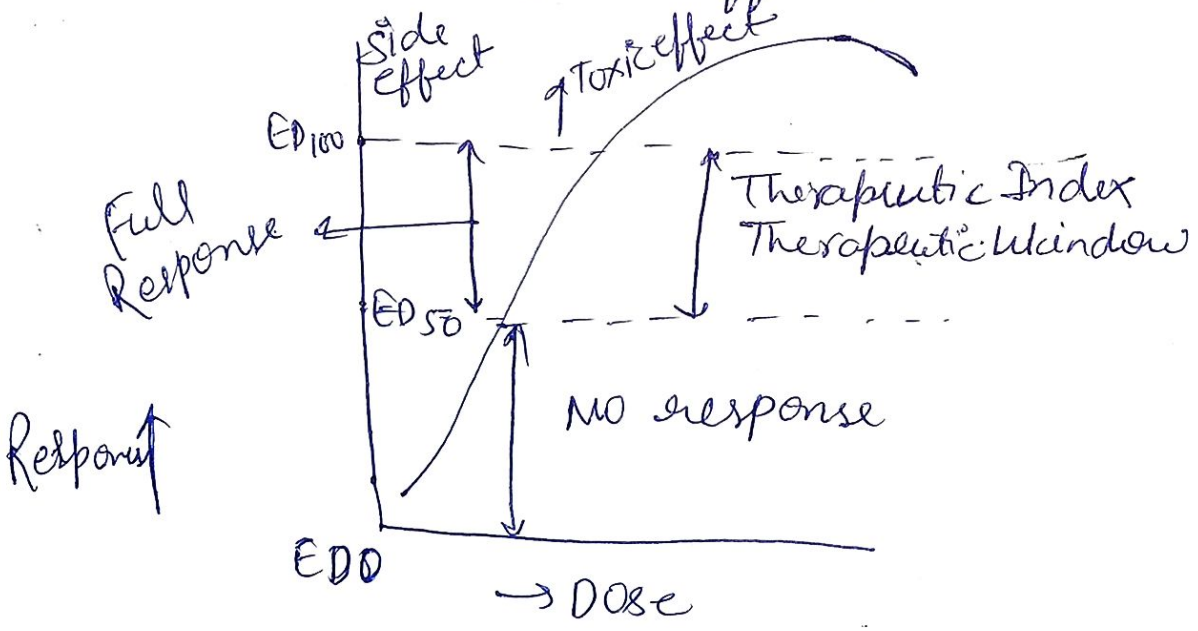
Potency:- Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude the concentration of drug producing 50% of the maximum effect is usually used to determine potency.

Efficacy - Efficacy is the magnitude of response a drug curves when it interacts with a receptor.

Maximal efficacy of a drug (Emax) assumes that all receptors are occupied by the drug. and no rease in response is observed if a higher concentration of drug is obtained.

Therapeutic Index :- The section between ED_{50} of ED_{100} of any drug in dose response curve is called therapeutic index or therapeutic (curve) windows.

- And in therapeutic Index and drug shows maximum response & less side effect.



$$TI = LD_{50} / ED_{50}$$

Combined effect of drugs :- when two or more drug given in combination then they either rease the effect of drug or they decrease the effect of drug.
On the basis of their effect, effect of combinations is of two type.

① Synergistic effect ② Antagonistic

① Synergistic effect :- when the two different drugs are given in combination then they enhence the Action of each other and the effect of drug is Increase is called Synergistic effect. It is of two types—

① Additive or Supra Addition
(ii) Potentiation (Supraadditive)

(i) Additive :- The effect of the two drugs is in the same direction and simply adds up :-

> Effect of drug A+B = effect of drug A + effect of drug B.

Ex:-
Aspirin + Paracetamol — as analgesic / Antipyretic

(ii) Supraadditive (Potentiation) :- The effect of combination is greater than the individual effects of the components :-

> Effect of drug A+B > effect of drug A + effect of drug B

Acetylcholine
Acetylcholinesterase | physostigmine

Acetyl choline + Physostigmine ⟶ Inhibition of Break down

Antagonism:- 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 Antagonistics effect.

It is of two type -

(a) Competative Antagonism

(b) Non Competative Antagonism

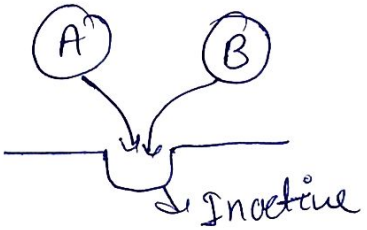
(a) Competative Antagonism (equilibrium type):-

The Antagonist is chemically similar to the agonist competes with it and binds to the same site to the exclusion of the agonist molecules; Because the Antagonist has affinity but no intrinsic Activity.

(b) Non-Competative Antagonism:-

When there are two different structure & shape of drug but they multiply the effect of each other they are called the Non-competative Antagonism.

Ex- Acetylcholine & Papperurine



Fixed dose combinations (FDCs) of drugs :- A large number of pharmaceutical preparations contain two or more drugs in a fixed dose ratio.

Advantages offered by these are :-

(1) Convenience and better patient compliance — when all the components present in the FDC are actually needed by the patient and their amounts are appropriate. It may also be cost saving compared to both/all the components administered separately.

(2) Certain drug combinations are synergistic. eg: isoniazid + rifampin

(3) Combined formulation ensures that a single drug will not be administered. This is important in the treatment of tuberculosis, HIV-AIDS and falciparum malaria.

Factors Modifying Drug Action :- Variation in response to the same dose of a drug between different patients & even in the same patient on different occasions is a rule rather than exception.

The factor modify drug action either :-

(a) Quantitatively :- The plasma concentration and /or the action of the drug is increased or decreased. Most of the factors introduce this type of change & can be dealt with by adjustment of drug dosage.

Qualitatively :- The type of response is altered.

eg: drug allergy or idiosyncrasy.

The various factors are discussed below-

) Body Size :- It influences the concentration of the drug attained at the site of Action.

$$\text{Individual dose} = \frac{\text{BW (kg)}}{70} \times \text{average adult dose}$$

$$\text{Individual dose} = \frac{\text{BSA } (m^2)}{1.7} \times \text{average adult dose}$$

) Age :- The dose of a drug for children is often calculated from the adult dose.

$$\text{child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose} \quad \text{(Young's formula)}$$

$$\text{child dose} = \frac{\text{Age}}{20} \times \text{adult dose} \quad \text{(Dilling's formula)}$$

③ Sex

④ Species & race

⑤ Genetics

⑥ Route of administration

⑦ Environmental factors & time of administration

⑧ Psychological factor ↔ Placebo / Nocebo

⑨ Pathological states - Not only drugs modify disease processes, several disease can influences drug disposition and drug Action.

(c) Other drugs :- Drug can modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them.

Adverse drug Reactions :-

Adverse effect is any undesirable or unintended consequence of drug administration.

Common causes of ADR :-

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

- Age :- children are often at risk because their capacity to metabolize drugs is usually not fully developed.

- Elderly :- ADRs including drugs interactions are a common caused of admission to hospitals in the elderly.

- Pregnancy :- • Sulfonamides :- Jaundice and brain damage in the fetus.

Warfarin :- Birth defects and Teased risk of bleeding problems in newborns & mothers.

- Breast feeding :- Many drugs can be passed from mother to infant via breast milk.
- Drug Related factors :- Dose, Duration, pharmacokinetic Properties, Pharmacodynamic Properties.

Types of ADR :-

Type A - (Atigmented)
" B - (Bizarre)
" C - (continuous)
" D - (Delayed)
" E - (Ending of use)
" 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 / Anticlate / Prolongation of Hospitalization is required.	Requires Treatment / change in treatment / prolongation by at least 1 day.	Requires intensive treatment, life threatening permanent damage.	Directly or indirectly contributes to death of the patient.

(Type A Reactions or Augmented) :- This type of Adverse drug reaction is predetermined and predefined. & this type of Adverse drug reaction can be minimize by using dose adjustment or other combination of drugs. overdosing causes

Ex:- Benzodiazepines - Sedation.
Insulin - Hypoglycemia. etc.

(Type B or Bizarre Reactions) :- This type-B Bizarre type of Adverse drug reaction is a type of reaction in which the effect of drug is not known and the appear suddenly. Not predicted. (Not reason) reaction.

→ Abnormal effects
→ Unrelated from the drugs known pharmacological action.

eg: Hypersensitivity reactions

(Type-C Reactions or continuous) :- Those type 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.

eg:- NSAIDS - Nephrotoxicity etc.

(Type-D Reactions or Delayed) :- In this type of Adverse drug reaction the Adverse effect of drug will be delayed after the prolong use of any medication. eg- Carcinogenesis etc (max dose) Teratogenicity

Type E Reaction or Ending of use :- This type of Adverse drug reaction is appear after the ending of dose or medication. withdrawal syndromes. suddenly stop the use of drug

eg :- Clonidine - Rebound hypertension.
Angina after atenolol.

Type F Reaction or Failure of efficacy :- This type of Adverse drug reaction is uncertain and this is the basically failure of efficacy.

In this type of reaction the drug can't shows their own response. eg: Underdosing of medications, Drug intractions.

Drug intractions :- 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 :-

(i) Drug - Drug interaction
(ii) Drug - Food interaction
(iii) Chemical - Drug interaction
(iv) Drug - laboratory test interaction
(v) Drug - Disease interactions.

Mechanism of drug Interactions :- The three mechanism by which an interaction can develop are -

1. Pharmaceutical Interactions
2. Pharmacokinetic Interactions

③ Pharmacodynamics Interaction.

(1) Pharmaceutical Interaction :- Pharmaceutical Interaction also called as incompatibility. It is a physicochemical interaction that occurs when drugs are mixed in IV infusions causing precipitation or inactivation of Active principles.

Ex- Ampicillin interact with dextran in solutions & 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.

(3) Pharmacodynamics Interactions - Pharmacodynamics Interaction are those in which the activity of the object drugs at its site of Action is altered by the precipitant.

Drug Discovery :- In the past most of drugs have been discovered either by identifying the Active ingredient from traditional remedies or by serendipitous discovery. In broader sense drug discovery & development can be defined.

serendipitous ↓ sudden profit

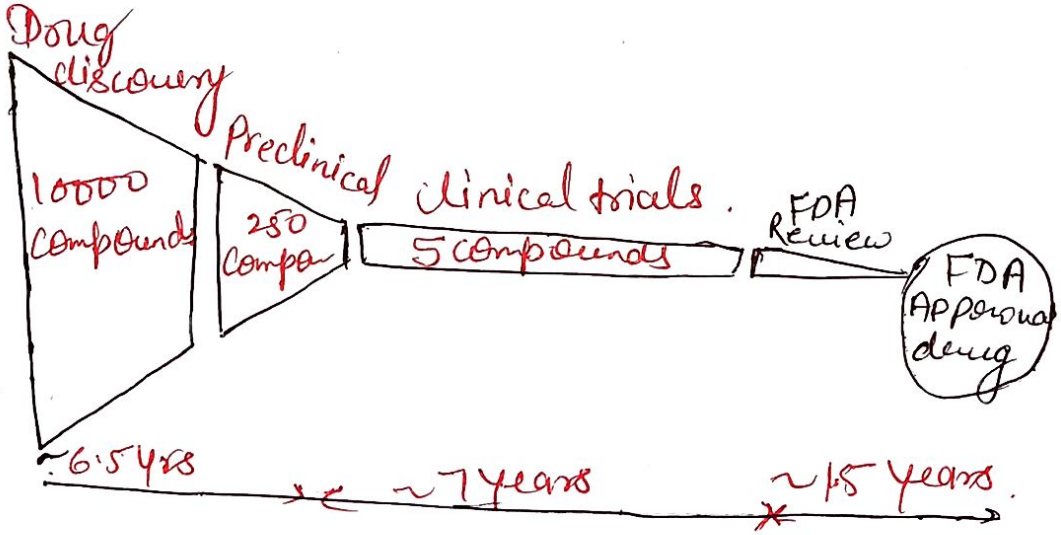
⇒ A Process that starts with the identification of disease and therapeutic identification and characterization in vitro. formulation & Animal pharmacological studies, pharmacokinetics and safety studies in animals & clinical studies in the human.

Different stages include.

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

Aim :- Safety, potency.

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 trials
8. New drug.

① Pre-Discovery :- To find out the problems or disease before the discovery of disease this is called pre-discovery.

② Target Identification :- Target identification is the second process of drug discovery in this phase. basically we find out the organ of body where the disease is occur and in that particular organ find out the particular receptor.

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 / chemical process / molecules in the body. Binding
(2) Association with a specific disease.

④ Lead discovery :- Lead finding / Lead generation - Approaches to new drug molecule
(1) Newer Techniques
  (i) Molecular Modeling
  (ii) Biotechnology
  (iii) Genetic Medicine
(2) Older techniques - Animals models as human disease Natural Products like plants animal & micro organism.

⑤ Lead Optimization :- Aim of this stage is -
Tease the potency of the compound on its target.
Tease its selectivity, Metabolic stability - short least of compounds
- functional Group Modification, SAR, Structure Modification, QSAR.
↓ functional gp attached

(6) Preclinical Testing :- After the lead optimization or lead finding the testing of these drug in animals is called preclinical testing. - Safety.

The Aims of Preclinical 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) Animal Studies :- Pharmacokinetic testing that is studies on absorption metabolism, distribution & elimination in laboratory animals like mice, chicken etc.

(3) Chemical & Pharmaceutical development :-
(a) Feasibility & large-scale synthesis & purification.
(b) Stability of the compound under various conditions
(c) To develop a formulation suitable for.

(4) Toxicology studies :- Extended programmes 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 preclinicals are over sensors are required to submit the Investigational New drug Application. It contains information regarding. - (1) Preclinical data, PK, PD & toxicological.

(2) Manufacturing data -

(3) Protocol of clinical trials.

(IND A) Investigational New Drug Application)

(7) Clinical Trials :- Set of procedures in medical research & drug development to study the safety & efficacy of new drug.

(i) phase 0 :- Microdosing study :

(ii) Phase I :- In this phase, drug is tested on 20-80 healthy volunteers. (Human Pharmacology & safety)

Main Purpose of this phase to check the safety and side effect (toxicity) of the drug.

(70% drugs passed this)

(ii) phase II : (Therapeutic exploration) :- In this study phase approx 100-500 patients are selected with that targeted disease. drug is tested on patients. length of this phase - (months - 2 years)

Main purpose of this phase to check the efficacy & side effect of drugs.

approx - 33% of drug are passed this phase & move to next phase.

Phase III :- (Therapeutic confirmation) In this phase, approx 1000 - 5000 patients is selected with that targeted disease. (1-4 years).

Purpose - long term safety
Drug Interaction
Assesment of safety & efficacy.

After completing the phase III trials, drug is undergoes for the approval of FDA (Food & Drug Administration).

4) Phase IV : (Post Marketing Surveillance / studies) :- In this phase collect data of drug that drug is safe or not.

purpose - Perform quality of life trials.
collection of long term safety information.

Pharmacovigilance

Pharmaco → drug

vigilance → Keep watching

Aim :- The main purpose of Pharmacovigilance is to reduce the drug related harm to the patients & protect patients and people to improve patient care & safety in relation to the use of medicine to improve public health & safety in relation to the use of medicines. Now, if any patients have any problems with any drug, patient informed the physician and fill the yellow form.