Pharmacodynamics- is the study of biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

Principles of Drug Action:-

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

The basic types of drug action can be broadly classed as:

① Stimulation: It refers to selective enhancement of the level of activity of specialized cells.
e.g- adrenaline stimulates heart, pilocarpine stimulate salivary gland.

② Depression: It means selective diminution of activity of specialized cells. eg. Barbiturates depress CNS, quinidine depress heart, omeprazole decrease or depresses gastric acid secretion.

③ Irritation:- This connotes a non-selective, often noxious effect and is particularly applied to less specialized cells (epithelium, connective tissue)

strong irritation results in inflammation, corrosion, necrosis and morphological damage.
This may result in diminution or loss of function.

④ Replacement - This refers to the use of natural metabolites, hormones or their congeners in deficiency state e.g. Levodopa in Parkinsonism, insulin in diabetes mellitus, iron in anaemia.

⑤ Cytotoxic action:- Selective cytotoxic action on invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure of infections and neoplasms, e.g. penicillin, Chloroquine. etc.

Mechanism of drug Action

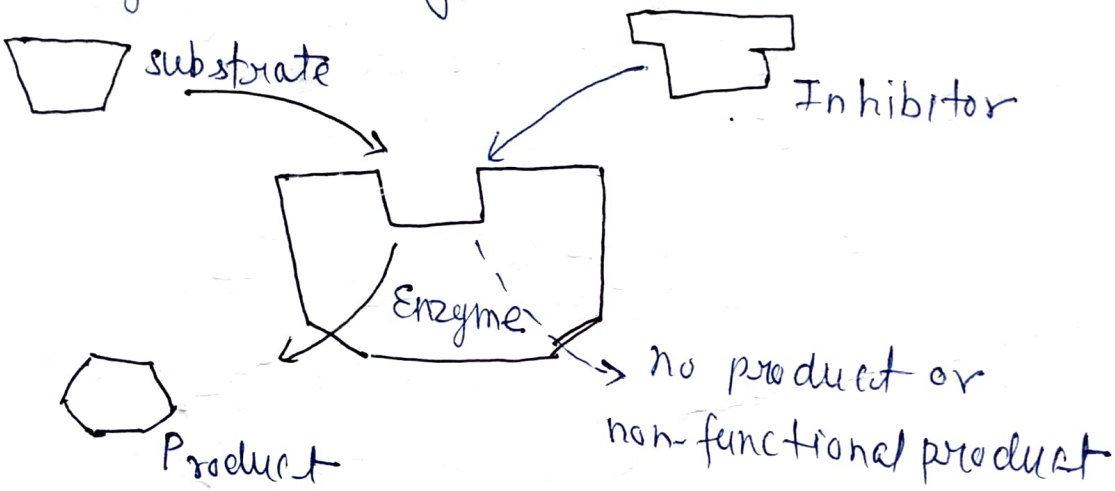
How any drugs produce their effect or action is known as mechanism of drug action.

- there are only some drugs which produce their effect/ action by virtue of their simple physical or chemical properties.
  eg- Laxatives (isaghula)
  Antacid (neutralization of gastric HCl).
- Most of the drugs produce their effect by interacting with a target biomolecules (proteins).

- Enzymes
- Ion channels
- Transporters
- Receptors.

① Enzyme – Almost all biological reactions are carried out under catalytic influence of enzymes; hence, enzyme are a very important target of drug action.

- Drugs can either increase or decrease the rate of enzymatically mediated reactions and also the biological activity.



- Enzyme Induction –

When drug bind with enzyme and increase its activity is known as enzyme induction.

- Enzyme inhibitor – When any drug decrease the activity of enzyme is known as enzyme inhibition.

– Competitive (structurally same as substrate so fight for same binding sites)

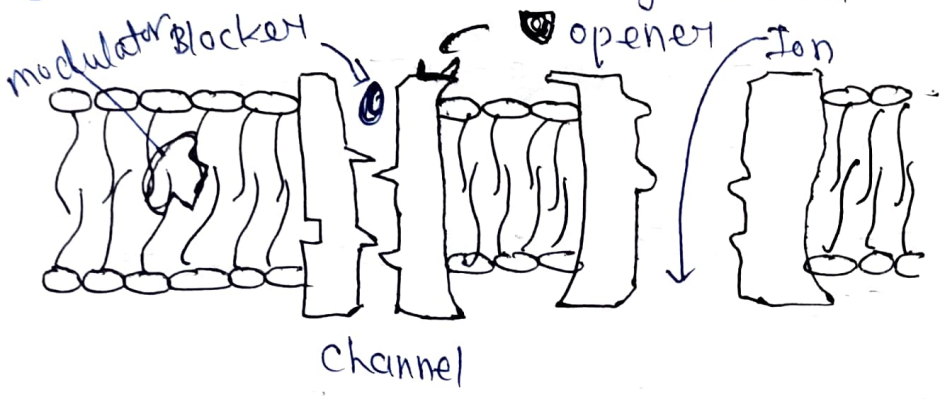
- Non-competitive (it decrease the enzyme activity by binding with adjacent site or allosteric site).

② Ion Channels-

Their are many ion channels in our body which helps transmembrane signaling and regulate intracellular ionic composition.

- Drug can affect ion channels, some of which actually are receptor because they are operated by specific signal molecules either directly and are called ligand gated channels.

eg. Quinidine blocks myocardial Na^+ channels.

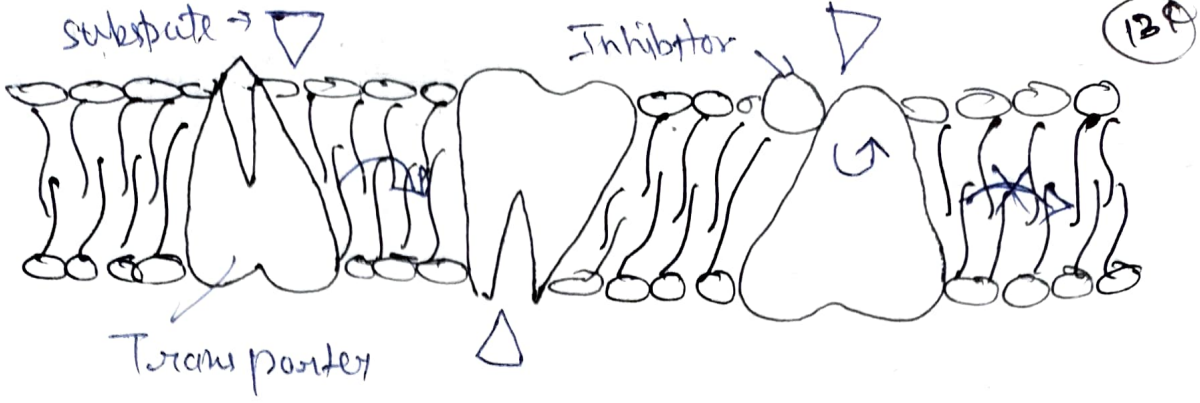


③ Transporters :-

Several substrates are move across membrane by binding to specific transporter (through facilitate diffusion).

- Many drugs effect this, they interact with solute carrier and inhibit the movement of metabolite/ ion (substrate)

eg- Amphetamine selectively block dopamine reuptake in brain neurons by dopamine transporter. (DAT)



④ Receptors –

Receptors are protein or binding site which present on surface and inside the cells. drugs bind with it, activate it and gived its pharmacological response.

Following terms are used in describing drug-receptor interaction:

- **Agonist** – An agent which activate receptor to produce effect.
- **Inverse agonist** – activate receptor but opposite action (effect).
- **Antagonist** – An agent which inhibit the action of agonist.
  - Competitive
  - Non-Competitive.

⇒ Receptor theories –

Drug + Receptor → Drug-Receptor Complex

↓

Effect (Response)

• these are following some theories -

i) Induced fit theory
ii) Occupation theory
iii) Rate theory
iv) Two state model

R_a R_i

i) Induced fit theory - It is based on "lock and key" concept.

• When drug mutually fit in the receptor is then gives its pharmacological (biological effects)
• Agonist induces full response
• Antagonist does not induce any response
• Partial agonist induce partial response.

ii) Occupation theory -

According to this theory, pharmacological response is depend on that how ~~All~~ much drug occupied the receptors.

Pharmacological effect of drug $\propto$ No. of Receptor occupied.

• Maximum response occurs when all the receptor are occupied.

iii) Rate theory -

• Acc. to this theory -

The response is proportional to the rate of drug-receptor formation.

Pharmacological effect of drug $\propto$ formation of Drug-receptor complex

• The more drug bind with receptors, the more receptor will be activated.

$$[D] + [R] \rightleftharpoons [DR] \rightarrow \text{Response}$$

iv) The two state receptor model –

The receptor is present in two states – Ra (active) and Ri (Inactive) and also is equilibrium.

$$Ra \rightleftharpoons Ri$$

• Now drug bind with these receptor and give its response

• Increase in the number of receptors on the surface of target cells.

• Increases of cellular components.

Due to → prolonged use of antagonists
↳ Drug effects ↑

Classification of Receptors –

- G- protein -coupled receptor
- Ion Channel receptor
- Enzyme Linked receptor
- JAK-STAT bind receptor
- Receptor that regulate transcription factors

Regulation of Receptors –

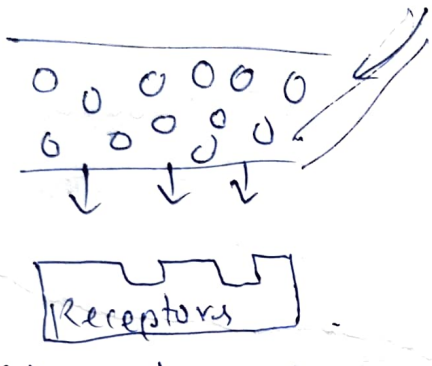
Maintain the homeostatic of receptors.

① → Up-Regulation
② → Down-Regulation.

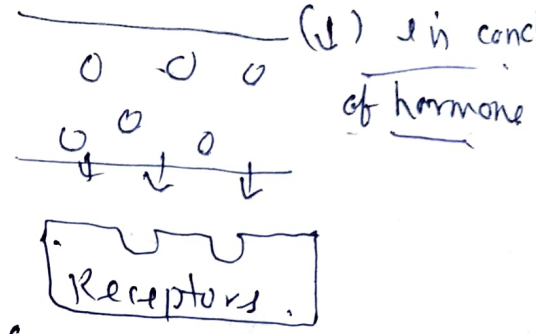
- → Activation
- → Deactivation
- → Destruction
- → Manufacturing.

① Up-regulation –

there are increasement or in sensitivity of receptors (hypersensitivity).



Normal condition



(Hormones decrease)

Up-regulation

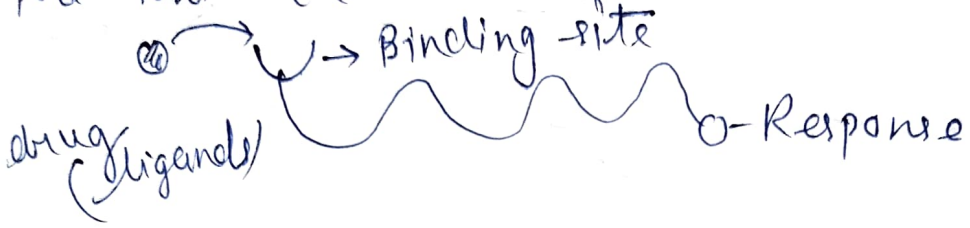
- Activation of inactive receptors.
- Increase sensitivity of receptors.

→ Agonists + Receptors → full response
→ Partial agonist + Receptors → less response
→ Inverse agonist + Receptors → opposite response
→ Antagonist + Receptors → No response (effect).

Signal transduction Mechanisms

It is the mechanism pathway by which receptor's activation is linked to the ~~recept~~ response.

eg- M cholinergic receptor acts through G- protein, while N-cholinergic receptor gates influx of Na^+ ions etc.



⇒ The transducer mechanism can be grouped into 5 major categories and also a receptor types —

① G- protein-couple receptors → imp
ii) Ion-channel receptors
iii) Transmembrane enzyme linked receptor
iv) Transmembrane JAK- STAT binding receptors
v) Receptor that regulate transcription factor.

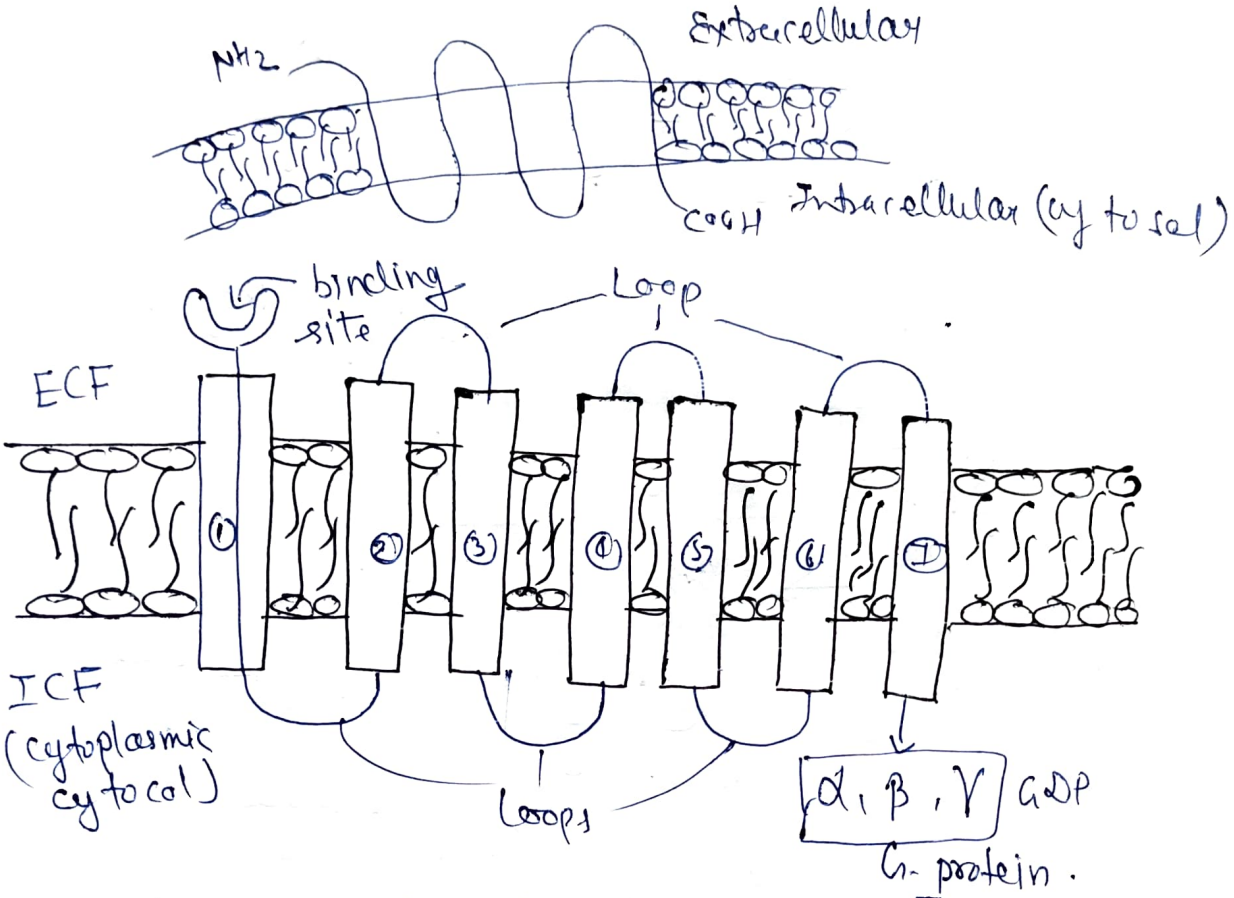
① GPCR.- G- Protein Couple Receptor

Also knows as → Hepta-helical Receptor
→ 7-transmembrane Receptor
→ metabotropic receptor.

⇒ G- protein – Guanin nucleotide-binding proteins.

- These are the cell surface receptors.

⇒ It constitute a large protein family of receptors that sense molecules (ligands) outside the cell (extracellular) and activate inside transduction pathway and give response.



⇒ It has 7 - α -helical membrane which has 3 intracellular and 3 extracellular loops.

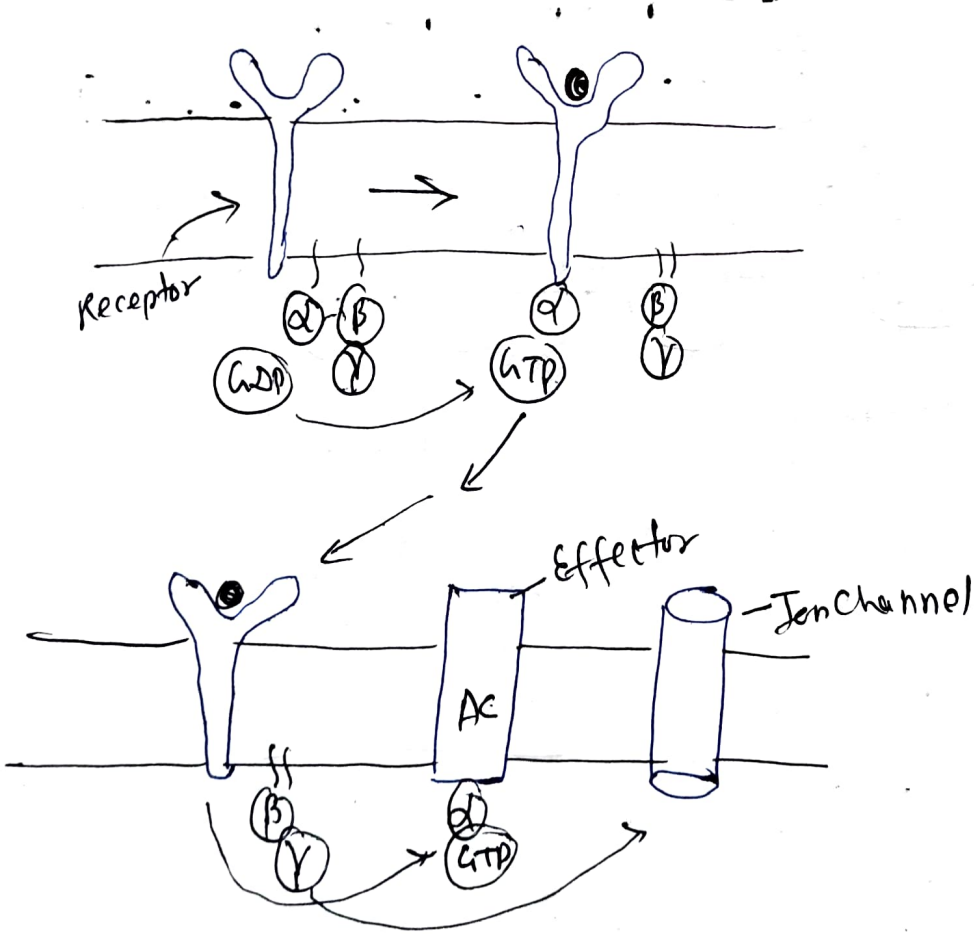
⇒ G- protein present in trimeric complex form (α, β, γ), in which GDP is attached on α (alpha).

⇒ The G- protein float in the membrane with their exposed domain lying in the cytosol.

Drug (Agonist) bind with receptor → Current flow through loops → Activate G- protein → GTP replace GDP → Breakdown of trimer → α, β, γ, GTP

α GTP → Activate Effector enzyme → Adenylyl cyclase / Phospholipase

Dimer (β γ) → 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 → Phosphalipase C activation.

→ The GPCRs produce their action by three pathways-

(1) cAMP (cyclic AMP) pathway (Adenylyl cyclase)
(2) IP_3-DAG pathway (Phospholipase C).
(3) Channel Regulation.

(1) ~~cAMP~~ cAMP pathway-

- Activated by G_s (Ca)
- Inhibited by G_i (K)

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

Function- increased cardiac contractility
LASH - relaxation in smooth muscles.
Liver, Adipose tissue, muscle, heart, smooth etc. Glycogenolysis, lipolysis, release of hormones
- open Ca^{2+} channel in heart, brain & kidney etc.

AC → ATP → cAMP → protein kinase (pkq)

effects ← phosphonylate ← enzyme

Secondary messenger

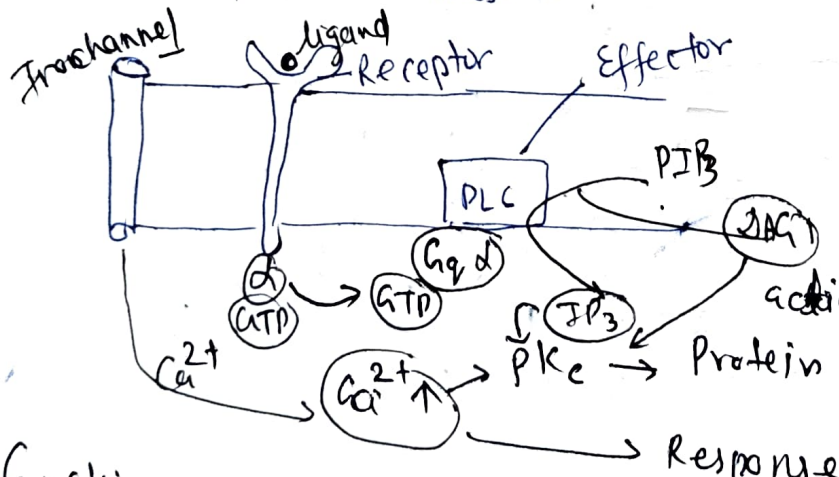
② IP_3 - DAG pathway (phospholipase C) :-

→ Activated by Gq.

Gq α + GTP → Activate → Phospholipase (PLC) → convert into PIP_2 into

Secondary messenger → IP_3 & DAG

- PIP_3 → phosphotidyl inositol 4, 5- biphosphate
- IP_3 → Inositol 1,4,5 - triphosphate
- DAG → Diacylglycerol.
- PKC → protein kinase C.



function.

— Contraction, secretion, intracellular movement, membrane function etc.

③ Channel Regulation :-

- Activated by G_s, G_i, G_o ...
- does not need secondary messenger.

- Activated G-protein → can open channel
  ↓
  movement of ions

⇒ G_s open Ca^{2+} channel in myocardium.

⇒ G_i & G_o open K^+ channel in heart & smooth muscle

⇒ Response such as inotropy, chronotropy, transmitter release & smooth muscle relaxation etc.

② Ion Channel Receptor

- Also known as ligand gated ion channel.
- These are cell surface receptors.
- Ion selective channel for Na^+, K^+, Ca^{2+} or Cl^-.

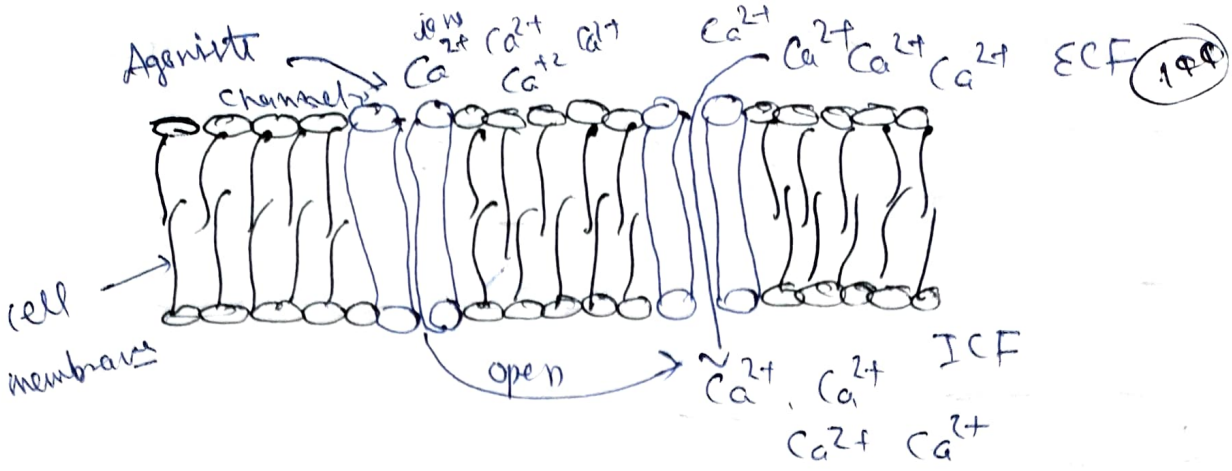
Mechanism -

- Drug (Agonist) bind with ion channel and open the channel
- Ion move inside the cytosol (intracellular).
- Changes in ionic composition.
- Responses such as depolarisation / hyperpolarisation.

⇒ Receptor includes in this category –

Nicotinic cholinergic, $GABA_A$, $5\text{-}HT_3$ etc.

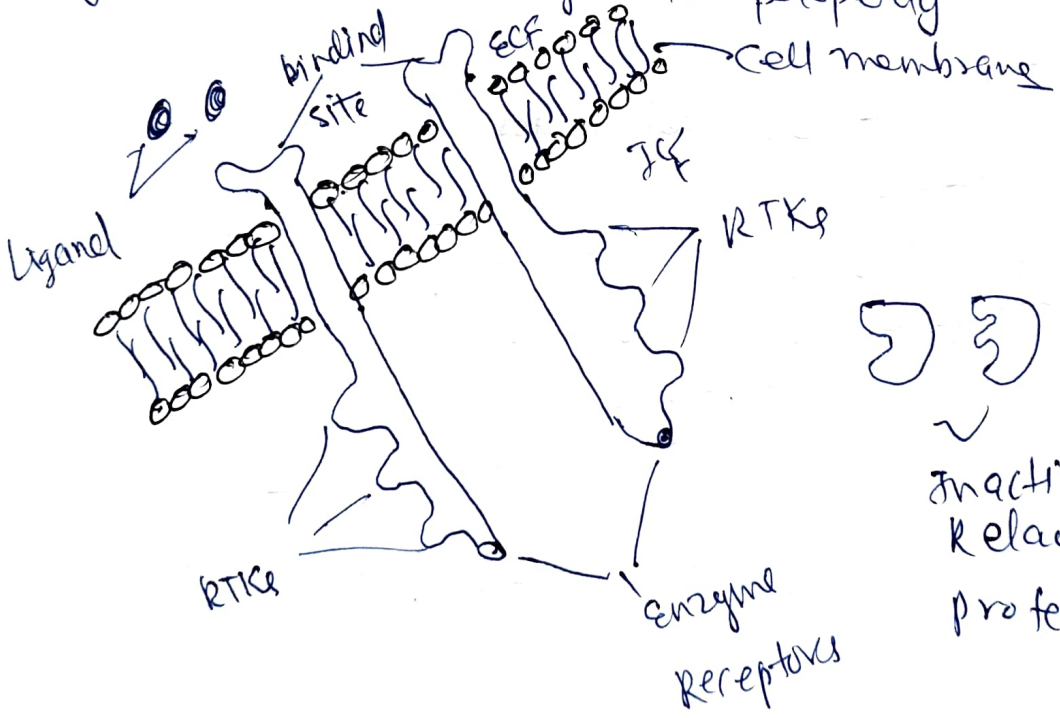
⇒ In these receptors the agonist directly operates ion channel (no requirement of secondary messenger)



* The onset and offset of responses through this class of receptors is the fastest (in milliseconds)

3. Transmembrane Enzyme Linked Receptors

- These are plasma membrane receptors.
- made up of single transmembrane chain, which has ligand binding domain in extracellular and Receptor tyrosine kinase (RTKs) intracellular as a catalytic site with enzymatic property.



- Mostly peptide hormone are bind with receptors as a ligands.
- When no ligands bind, Receptors are in monomeric state and "Receptor tyrosine kinase" (RTKs) are in inactive form.

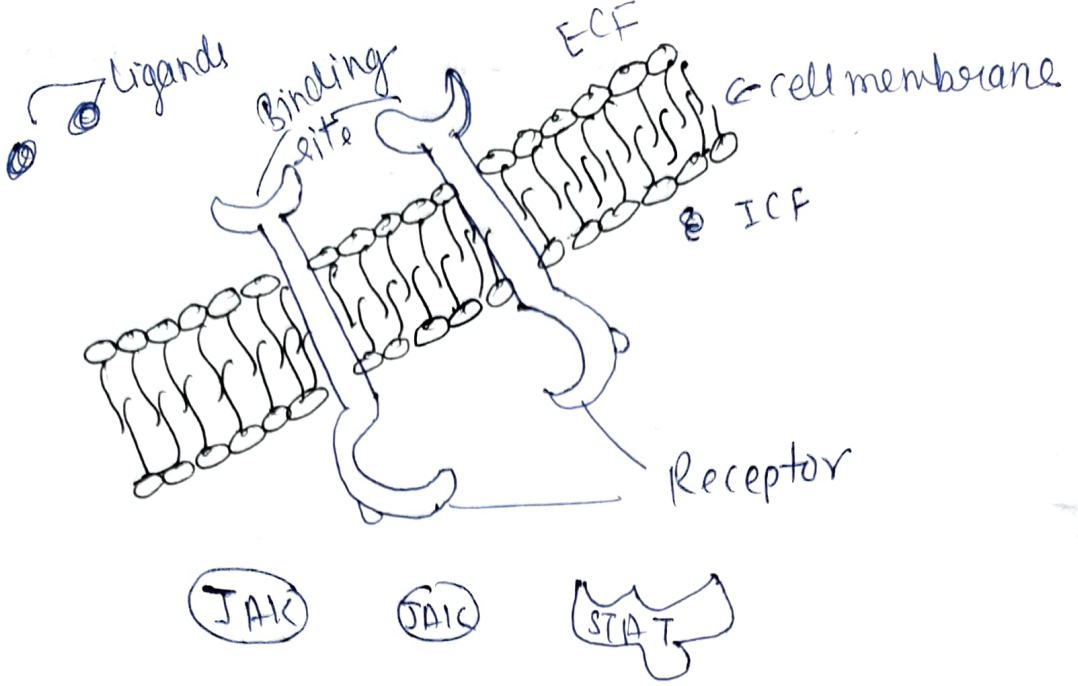
Mechanism.

Ligand bind with receptor (Hormone bind)
↓
monomeric receptors move laterally in the membrane and form dimers.
↓
Dimerisation activates RTKs & RTKs activity of the intracellular domain
↓
Autophosphorylate tyrosine residue on each other
↓
increase affinity for protein
↙
Protein bind on RTKs → Responses → Cellular Responses.

[4] Transmembrane JAK-STAT

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

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



Mechanism-

- Agonist binds and included dimerization

↓

which alter the intracellular domain conformation to increase its affinity for a cytosolic tyrosine protein kinase JAKs (Janus kinase).

↓

On binding, JAK gets activated and phosphorylate 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 transcription

↓

Biological Responses.

[5] Receptors that Regulate transcription factors (Gene expression)

- These are intracellular receptor which are present inside the cell.
- They contain soluble protein which responds to lipid soluble chemical messengers that penetrates 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 bind near the carboxy terminus of the receptor.

↓

the restriting protein (HSP-90) are released

↓

the receptor dimerized and the DNA binding regulatory segment folds into requisite conformation. ← necessary for regulation.

↓

The liganded receptor dimer moves to the nuclear and 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 and facilitates or repress their expression

↓

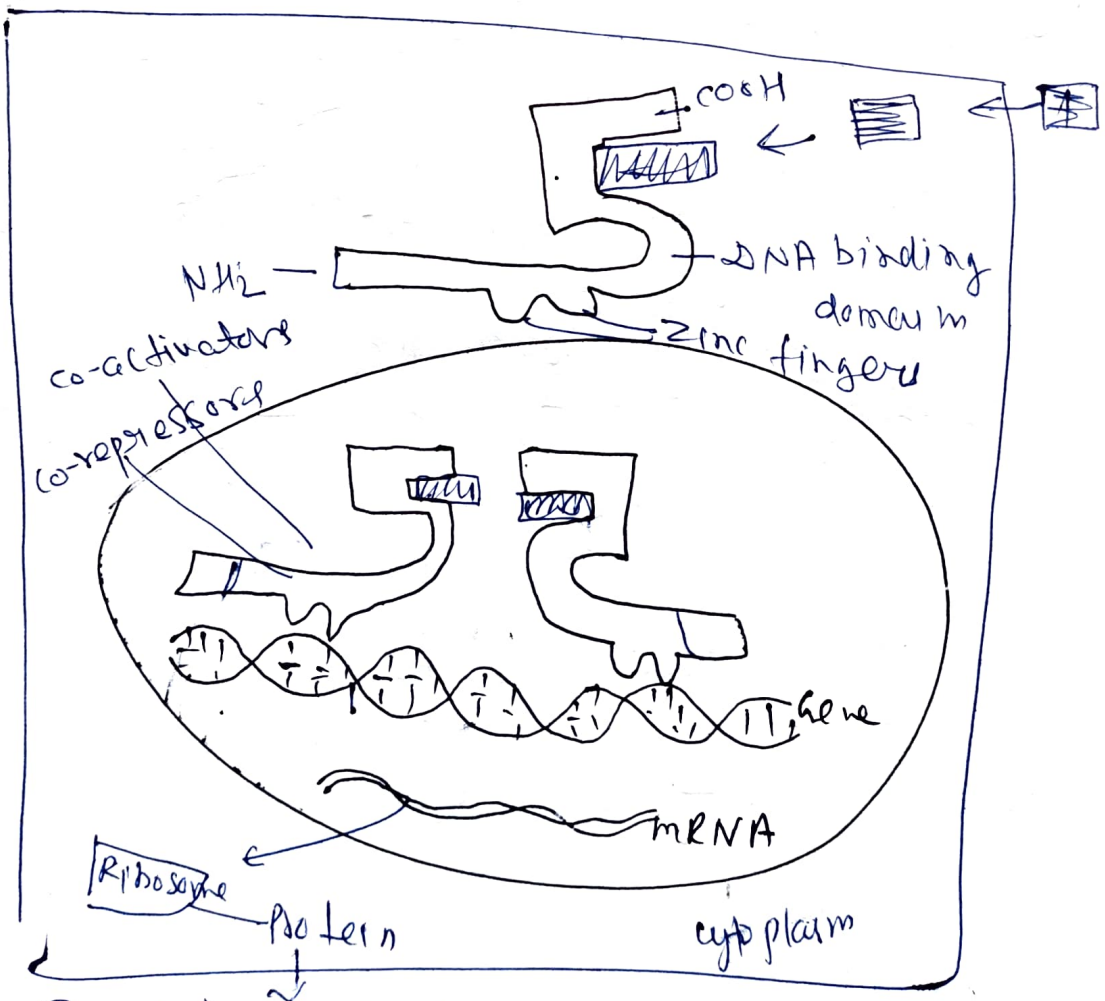
(Transcription) Specific mRNA is synthesized or repressed on the template of the gene

↓

This mRNA moves to Ribosomes

↙

Synthesis of Specific protein → Regulate activity of target cells.



Regulate Activity of target cells.

All steroidal harmones (Glucocorticoids, mineralocorticoids, androgens, estrogens, progesterone, thyroxine, vit D and vit. A function in this manner.

Dose - Response Relationship

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

(i) Dose - plasma concentration relationship &

(ii) Plasma concentration - response relationship.

Generally, the intensity of response increases with increase in dose concentration at the receptor, but at higher doses, the increase in response progressively becomes less marked and the dose-response curve is a rectangular hyperbola.

This is because drug-receptor interaction obeys law of mass action,

$$E = \frac{E_{max} \propto [D]}{K_D + [D]}$$

Where,

E = observed effect

D = Dose

E_{max} = maximum response,

K_D = Dissociation constant of the drug-receptor complex.

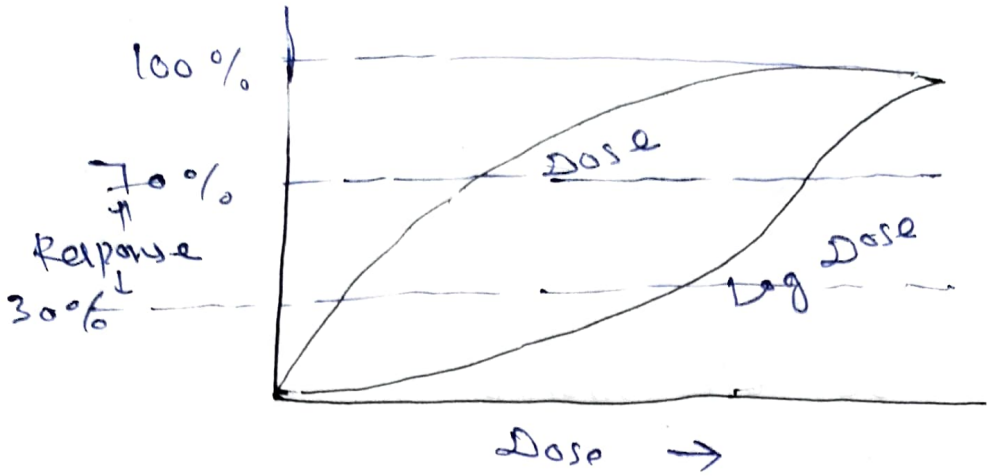


Fig - Dose - response and log dose - response curves.

Drug potency – the amount of drug needed to produce a certain response (which is required to cure and also safe)

Drug efficacy - maximum response produced by a drug.

Therapeutic index –

The ratio of the dose of that produces a toxic (lethal) effect to the desired therapeutic effect.

* The gap between the therapeutic effect DRC and the adverse effect DRC defines the safety margin or the therapeutic index of a drug.

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

or

$T.I. = \frac{LD_{50}}{ED_{50}}$ ⇒ LD_{50} = that dose which kill 50% recipients (animals)

ED_{50} = that dose which produced specified effect and cured 50% individuals.

Combined effects of drugs

When two or more drugs are given in combination, then they either increase or decrease the effect of the drugs.

divided into two parts —

i) Synergism.

ii) Antagonism.

i) Synergism — Greek → Syn → together
ergon → work.

When two or more drug is given in combination then the action of one drug is increased by other

① Additive
- effect of the two drugs is in same direction and simply adds up :-
- effect of drug A + B =
effect of drug A
+
effect of drug B

– Supraadditive (Potentiation)
- effect of combination is increase multitimes.
- Effect of A + B > effect of A + Effect of B

eg - Aspirin + paracetamol
↓
an analgesic / antipyretic

- Nitrous oxide + halothane
↓
as general anaesthetic

eg - Acetylcholine + physostigmine
↓
inhibition of break down

- Levodopa + carbidopa / benserazide
↓
inhibition of peripheral metabolism.

ii> Antagonism

anti → opposite
ergon → work

When one drug decreases the action of other, they are said to be antagonistic:

effect of drug A + B < effect of drug A + effect of drug B.

Usually in an antagonistic pair one drug is inactive as such but decrease the effect of the other.

Depending on the mechanism involved, antagonism may be:

ⓐ Physical antagonism
ⓑ Chemical antagonism
ⓒ Physiological / functional antagonism
ⓓ Receptor antagonism
- Competitive antagonism
- Non-competitive antagonism.

ⓐ Physical antagonism - Based on the physical property of drugs.
eg. Charcoal adsorbs alkaloids and can prevent their absorption → used in alkaloidal poisoning.

ⓑ Chemical antagonism –

Two drugs react chemically and form an inactive product.

eg: Tannins + alkaloids → insoluble alkaloidal tannate is formed.

· $KMnO_4$ oxidizes alkaloids → used for gastric lavage in poisoning.

ⓒ Physiological antagonism –

The two drugs act on different receptors or by different mechanisms, but have opposite overt effect on the same physiological function.

eg – Histamine & adrenaline on bronchial muscles and on BP.

ⓓ Receptor antagonism – One drug (antagonist) blocks the action of other drug (agonist).

– Competitive antagonism –

· Antagonist shape is similar as agonist and bind with the same receptor and inactive receptor.

eg· Acetylcholine → Atropine (antagonist)

· Morphine → Naloxone etc.

– Non-competitive antagonism –

· Antagonist bind with another site (allosteric) of receptor and inactive it. So drug does not give any effect.

eg· ⊛ Diazepam → Bicuculline etc.

Factors Modifying drug Action

Variation in response to the same dose of a drug between different patient and even in the same patient on different occasions is a rule rather than exception.

One or more of following categories of differences among individuals are responsible for the variation in drug response:-

① Individuals differ in pharmacokinetic handling of drug: attain varying plasma/target site conc^{n}. of the drug.

② Variations in number or state of receptors, coupling proteins or other compounds of response effectuation.

③ Variations in neurogenic/hormonal tone or conc. of specific constituents, e.g. atropine tachycardia depends on vagal tone.

The factors modify drug action either:

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

ⓑ Qualitatively - The type of response is altered, eg. drug allergy.

This is less common but often precludes further use of that drug in the affected patient.

⇒ The various factors are discussed below —

① Body size – It influence the conc. of the drug attained at the site of action.

The average adult dose refers to individuals of medium built.

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

② Age: The dose of a drug for children is often calculated from the adult dose.

$$\text{child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose [Young's formula]}$$

$$\text{child dose} = \frac{\text{Age}}{20} \times \text{adult dose [Dilling's formula]}$$

③ Sex – Females have smaller body size and require doses that are on the lower side of the range.

~~Maintai~~ Maintenance treatment of heart failure with digoxin is reported to be associated with higher mortality among women than among men.

④ Species and race – There are many examples of differences in responsiveness to drug among different species; rabbits are resistant to atropine, rats & mice are resistant to digitalis and rat is more sensitive to curare than cat.

⑤ Genetics.
⑥ Route of administration
⑦ Environmental factors and time of administration.
⑧ Psychological factor.
⑨ Pathological states.

Adverse Drug Reactions

ADRs is an undesirable effect of drug in our body which we does not want.
- It may include all kind of noxious effect such as trivial, serious, even fatal.
- Adverse effects may develop instantly or only after prolonged medication or even after stoppage of the drugs.

Cause -
- Expire medicine
- Overdosing
- Allergies to the particular medicine
- Idiosyncrasy
- Take other's medicines etc.

Classification (Types) -

Adverse drug reactions are classified into ~~six~~ six type -

i) Type A
ii) Type B
iii) Type C
iv) Type D
v) Type E
vi) Type F

i) Type A [Augmented, predictable reaction] -

- These reaction occurs in case when amount of drug is increase in body.
- This type of adverse drug reaction can be ~~minize~~ minimize by using dose adjustment or other combination of drugs.
- Effect - include side effect, toxic effects and consequence of drug withdrawal.
- They are more common, dose related and mostly preventable, predictable and may be reversible

eg ⇒ Benzodiazepines → sedation
Insulin → Hypoglycemia etc.

ii) Type B: [Bizarre] unpredictable reaction -

- This types of reaction occurs suddenly with unknown reason and effect of drug is not known.
- It include allergy and idiosyncrasy.
- they are less common, often non-dose related, generally more serious and require withdrawal of drugs. It is unpredictable.

Example-
- Allergy due to hypersensitivity
- Hemolytic anemia etc.

iii) Type C [Continuous] -

- These types of ADR occurs due to use of any dose or drug for a long time.
- chronic use of any drugs.

Example- NSAIDs → Nephrotoxicity etc.

iv) Type D [Delayed] -

In this type of ADRs, the effect of drug will be delayed after the prolonged use of any medication.

eg. carcinogensis, → terotogenicity → thalidomid etc
(Cause cancer) (during pregancy)

⇒ medicine → women → fetus
↓
side effect (harmful)

v) Type E [End of use]

This type of ADRs occurs when we suddenly stop use of any drug which we take from a long time

"OR"

this type of effects appear after ending of any medication.

Eg. Angina after atenolol
- Rebound hypertension after clonidine etc.

vi) Type F [failure of efficacy] -

- This type of ADRs occurs when drug failed to show their efficacy.
- In this, drug does not show their own response.

example - Drug interactions.
- Antagonism etc.

- Some other Adverse effects -

→ Side effect, toxic effects, secondary effects, Intolerance, Idiosyncrasy, Drug allergies, Photosensitivity, Teratogenicity etc.

⇒ Prevention of adverse effects to drugs -

- It can be minimized but not eliminated -
- Avoid all inappropriate use of drugs.
- During medication, consider previous history of drug reaction.
- Check history of allergic disease
- Rule out possibility of drug interaction when more than one drug is prescribed.
- Augmented - excess of drug.
- Drug intolerance - ADRs due to low dose
- Iatrogenic - ADRs due to physician.
- Drug dependence - Depend of any drug (particular)
- Teratogenicity - during pregenacy; effect on fetus / child.

- Carcinogenesis - cause cancer.
- Drug abuse - misuse of drug (cocaine etc).
- Drug withdrawl system - suddenly stop use of drugs.

Drug Interactions

When one drug alter the action or physiochemical properties of any other's drug by interact with it is known as Drug interaction.

-Types:-

Pharmacokinetics
- What does body do to the drug.
- affects ADME

Pharmacodynamics
- What does drug do to the body.
- Affects mechanism and action of drug.

Drug interactions includes —

① Drug - drug interaction
② Food - drug interactions.
③ chemical - drug interaction
④ Drug - laboratory test interaction
⑤ Drug - disease interactions.

① Pharmacokinetics —

These are those interaction in which any drug alter the ADME properties of other drug —

i) 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 and more or less complete drug absorption. Major mechanisms of absorption interactions are –

- Complexation & adsorption.
- Alteration in GI pH.
- Inhibition of GI enzymes.

ii) Distribution interactions – are those where the distribution pattern of the object drug is altered. The major mechanism for distribution interaction is alteration in protein-drug binding.

iii) Metabolism interactions – are those where the metabolism of the object drug is altered. Mechanisms of metabolism interaction include –

(a) Enzyme induction - increased rate of metabolism

(b) Enzyme inhibition - decreased rate of metabolism. It is the most significant interaction in comparison to other interactions and can be fatal.

iv) Excretion interactions – are those where the excretion pattern of the object drug is altered. Major mechanisms of excretion interactions are –

(a) Alteration in renal blood flow.
eg- NSAIDs reduce renal blood flow

(b) Alteration of urine pH – eg - antacid with amphetamine.

② Pharmacodynamic interaction – these are those interaction in which the effect of one drug are changed by the presence of another drug at its "site of action."

- Atropin opposes the effect of physostigmine
- Naloxone antagonize morphine.

-& Classified → Synergism, Antagonism] Page No. - 151-152

③ Drug-food interaction – when drug interact with food inside the stomach, resulting change in their effects.

Example – Iron tablets and antibiotics.

→ Tetracyclin + milk → Bioavailability ↓

Drug Discovery and Clinical Evaluation of New drugs

Drug discovery is the process in which new medicines are identified and introduced into market.

- It involves two stages :–

i) Drug discovery ii) Drug development.

- It will be take approx. 10-15 years and lots of money for a new drug.
- Drug is discovered on the basis of disease.

Aim- ⇒ Drug should be - safe
- Effective, potent &
- less or without toxic effect

⇒ Drug discovery and development involves total six steps -

① Target identification
② Target validation
③ Lead identification
④ Lead optimization
⑤ Preclinical trials
⑥ Clinical trials.

(①–④) → Drug discovery
(⑤, ⑥) → Drug development
↳ phase - I, II, III, IV.

① Drug discovery phase -
(i) Target identification (ii) Target validation
(iii) Lead identification (iv) Lead optimization.

⇒ In drug discovery phase, we have to identified the disease or problems then identified the drug which is used to cure that disease.

① Target identification - Firstly we have to identified the disease or problems for which we have to find out the drug.

• In this step identified the disease

Cause
- reason behind the disease.

organ involved
- that particular organ which involve or defective due to disease.

- It can be any organ, gene, tissue, protein etc.

(ii) **Target validation -**

Now, in this step choosen target is analyze and validate that above information is correct or not.

- Short listed the causes and affect of disease
- Also checks the drug ability
  ↓
  Can a target actually bind to the drug.

(iii) **Lead identification -**

In this step, identified the drugs that is actually used to cure that disease (Lead compound).

- It can be synthesized in laboratory.
- Identified that drug which have potential to bind to the identified target successfully.
- Approx. 5000 - 10000 compound should be choosen.

(iv) **Lead optimization -**

After succesfully choose lead compound, now optimize it.

⇒ Modify compound for increase its effectiveness and safety.

⇒ Drugs can be optimized through various method -

- Functional group modification
- SAR (Structure activity relationship)
- ~~QSAR~~ QSAR.
- Approx. 250 compounds send for ~~this~~ pre-Clinical trials.

(2) Drug development phase -

In this phase, drug is develop for the market use -

- It involve two steps -

(i) Pre- clinical evaluation phase
(ii) Clinical trials phase.

i) Pre- clinical trial phase -

Before testing a drug on peoples, we have to confirm that drug is safe and it does not give any harmful effects to the peoples.

- For this purpose firstly drugs is tested on animals instead of humans.

Aim -

- to check the safety and effectiveness of drug.
- to checks the drug's pharmacokinetic properties.
- check toxicalogy.
- Evaluation of therapeutic index.

=> two types of preclinical testing -

i) In- vitro - Experiment are conducted outside the animal. In this collect animal's tissue, plasma etc. and test drug on that is laboratory.

ii) In- vivo - Experiment are conducted inside the animals by ~~increase~~ introduce drug inside animals.

- Animals used for trials -
  - Guinea pigs, mice, rats, dogs, monkeys, cat etc.

- IND - Investigational New Drug Application is applied after the pre-clinical studies show success and if the IND submission is accepted the product is further forwarded to the clinical trials.
- Both drug discovery and priclinical phase take approx. 6.5 years
- Now approx. 5 compound send in the clinical trials.

ii) Clinical trial phase -

In this phase, drug is applied on humans.

- It involves four phases -

① **Phase I** - In this phase, drug is tested on 20-80 healthy volunteer.
- Main purpose of this phase to check the safety and side effect of the drug.
- purpose → studies of PK (pharmacokinetic) and PD, pharmacological effect, tolerability, side effect and toxicity at different doses (70% drugs passed this).

② **Phase II** : (Therapeutic exploration) investigation study.

- In this phase, approx. 100-500 patients are selected with that targeted disease.
- Now drug is tested on patients.
- Length of this phase (~~math~~ months - 2 years)

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

Purpose

- Finding the dose range (minimum and maximum effective dose)
- Effectiveness for the treatment of the disease.
- Maximum tolerated dose (MTD).
- Common short time side effects

→ approx. 33% of drugs are passed this phase and move to next phase.

③ Phase III - (Therapeutic confirmatory)

In this phase, approx. 1000 - 5000 patients is selected with that targeted disease.

- Now drug is tested on patients
- Length of this phase (1 - 4 years)

purpose -

- long term safety.
- Tolerability - common side effects
- Drug interaction
- Assesment of safety and efficacy.

⇒ After completing the phase III trails, drug is under-goes for the approval of FDA (Food and drug Administration)

- After FDA approval, the product is lunched into market.

④ Phase IV (Post marketing therapeutic use)

- 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

Pharmacovigilance < pharmaco → drug
vigilance → keep watching.

" The science and activity relating to the detection Assesment, understanding and prevention of adverse effect or any other possible drug-related problem.

Aim- The main purpose of pharmacovigilances is to the reduce the drug related harm to the patients and protect patient and peoples.

- to improve patient care and safety in relation to the use of medicine.
- to improve public health and safety in relation to the use of medicines.
- Now, if any patients have any problem with any drug, patient informed the physician and fill the yellow form.

- yellow form formate -

- Brand name
- Manufacture by
- Batch no.
- Expiry date
- Dose used (amount of mg.)
- Route of administration
- Frequency.
- Reason for prescription
- Therapy date

- Strict pharmacovigilance should be carried out by healthcare professions.
- Patients with high risk of ADRs and should be closely monitored —

- Renal or hepatic impairment.
- In case of any allergies or Idiosyncrasy.

- All ADRs related information of any drug is collected to the pharmacovigilance centres.