General pharmacology -II

Unit-II

10×1 = 10
2×5 = 10
2×1 = 2
} 22 Must know

2×1 = 2
} 2 Desriable to know

24 Marks

Pharmaco dynamics
↓ ↓
Drug motion / effect

→ The Pharmacodynamics is the second Part of Pharmacology. which is derrived from the two word.

→ The Term Pharmaco means drug and dynamic means motion or effect.

→ It means the drug which Produce the different action inside the body.

→ Pharmacodynamics decide that what drug does do with body.

→ The term Pharmacodynamics means the Study of mode of Action of any drug on any biochamical and Physiochemical changes which is ~~om os~~ occours by the drug in our body.

→ Pharmacodynamic is also refter to the drug effect and drug Action.

Drug effect :- what responce Produce by the drug
Drug Action :- How effect is Produce by the drug.

② Site of Action :-

→ The site of Action of Any drug is defined as those Particular organ or tissue where drug shows their Action and Produce Some effect.

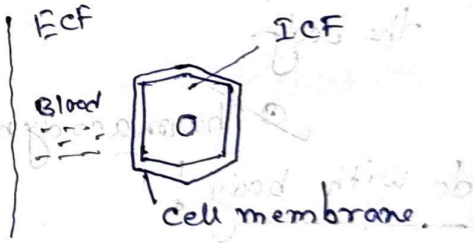
→ Some time two different drug can Produce Same responce but their Site of Action may be different.

eg:- for example Pilocarpin and Morphin both drug shows miosis in eye but Pilocarpin bind With circular Muscle and morphine bind With 3rd cranial nerves.

Pilocrapin → circular Muscle
Morphine → 3rd cranial nerves
→ Miosis

Types of Site of Action :-

1. Extracellular
2. cellular
3. Intracellular



① extracellular :-

When the drug shows their Action and Responce in Extra cellular fluid out side the surface of the cell then is called extracellular Site

eg:- Antacid drug Neutralized the Acidity inside the Stomach which is ECF.

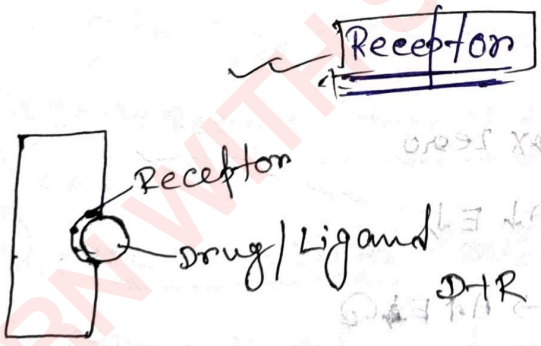
(i) Cellular :- Those drug which bind on the ~~res~~ receptors on the surface of cell membrane they are called cellular site.

eg:- Acetylcholine, Adrenyline, Atropin they are bind with Receptors on the Present on the surface of the cell and they Produce Responce.

(ii) Intracellular :->

When the drug crosss the cell membrane and goes inside the intracellular fluid and Produce Responce inside the cell and Produce Responce.

eg:- Sulphonamide drug crosss the cell membrane and inside the cell membrane they inhibit the formation of folic Acid, so the bacteria are kill this is called Intracellular site.



D+R → DR complex → Responce
affinity
efficacy

-> 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 the drug is bind with receptor then is Produce Responce.

->

→ When the drug bind the receptor then it form drug Receptor complex and after formation of complex Response is produce.

* **Affinity:-**
When drug bind receptor then it form complex and completely binding of drug with receptor is called Affinity.

* **efficacy:-** After formation of DR complex drug Produce some responce and the level of responce is called efficacy of drug.

* **Types of drug:-**
→ on the basis of Affinity and efficacy drug is of four type.

1. Agonist → A↑ E↑
2. Antagonist → A↑ E✗ zero
3. Partial Agonist → A↓ E↓
4. Inverse Agonist → A↑ E↓

Agonist:-
→ Agonist are those drug molecule which have similar structure and action to the natural drug their affinity and efficacy is 100%.

Antagonist:-

→ Those drug Molecule whose affinity is 100%. but efficacy is 0%, so they bind with the Receptor completely but no responce Produce.

Partial Agonist:-

→ Those drug Molecule which is not completely Bind with Receptor and Produce less no of Responce is called Partial Agonist. There affinity & efficacy is less than 100%.

Inverse Agonist:-

→ Those drug molecule which bind with Receptor and produce opposite responce. So there affinity is 100% and efficay is 100%. but Response opposite.

Types of Receptor:-

→ on the basis of structure and function Receptor four type

(a) Ionic Receptor / Legand gated Receptor / Ion channel Receptor.

(b) GPCR - G Protein coupled Receptor

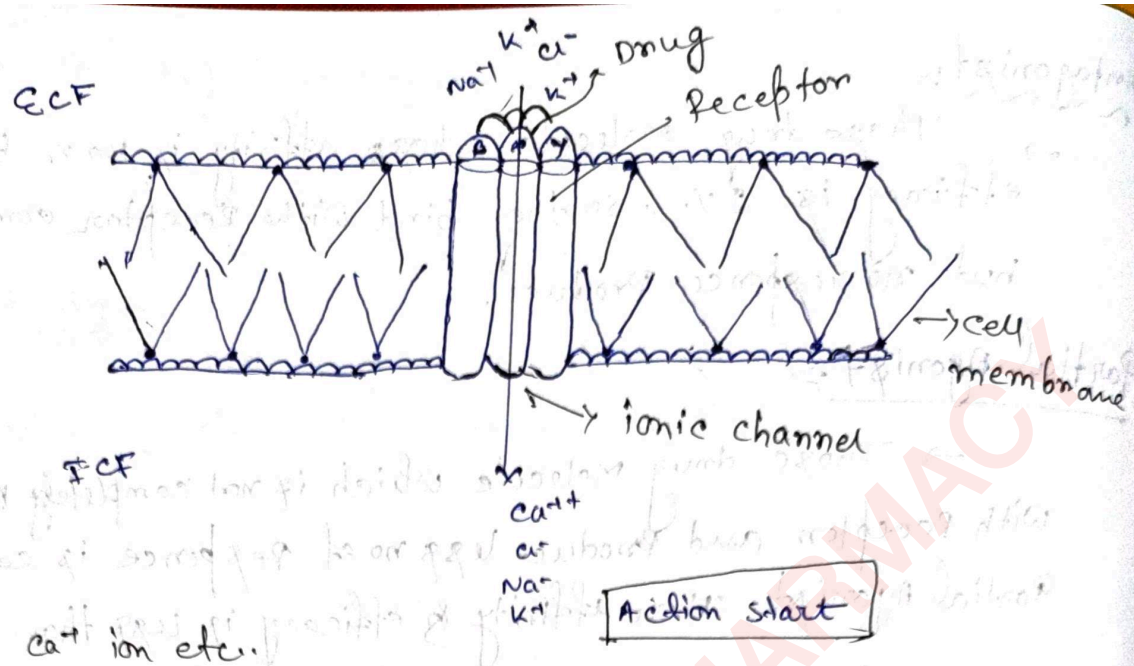
(c) Enzyme Linked Receptor. (JAK-STAT Receptor)

(d) Receptor Regulating gene expression.

Ionic Receptor:-

→ Ionic Receptor is present on the surface of cell membrane. This Receptor Produce the Action due to the movement of Respective ions like - Na^+ ion, K^+ ion, Cl^-

organ
↓ made up
Tissue
↓
cell
↓
cell membrane.



and Ca^{+} ion etc..

→ So it is called ionic Receptor ionic Receptor is present Armound the ionic channel. When the drug bind With Receptor the ionic channel is open and the movement of ions takes Place form Ecf to Icf and Action is generated.

eg:- Chlinergic, Adrenergic, dopaminergic Receptor are the ionic Receptor.

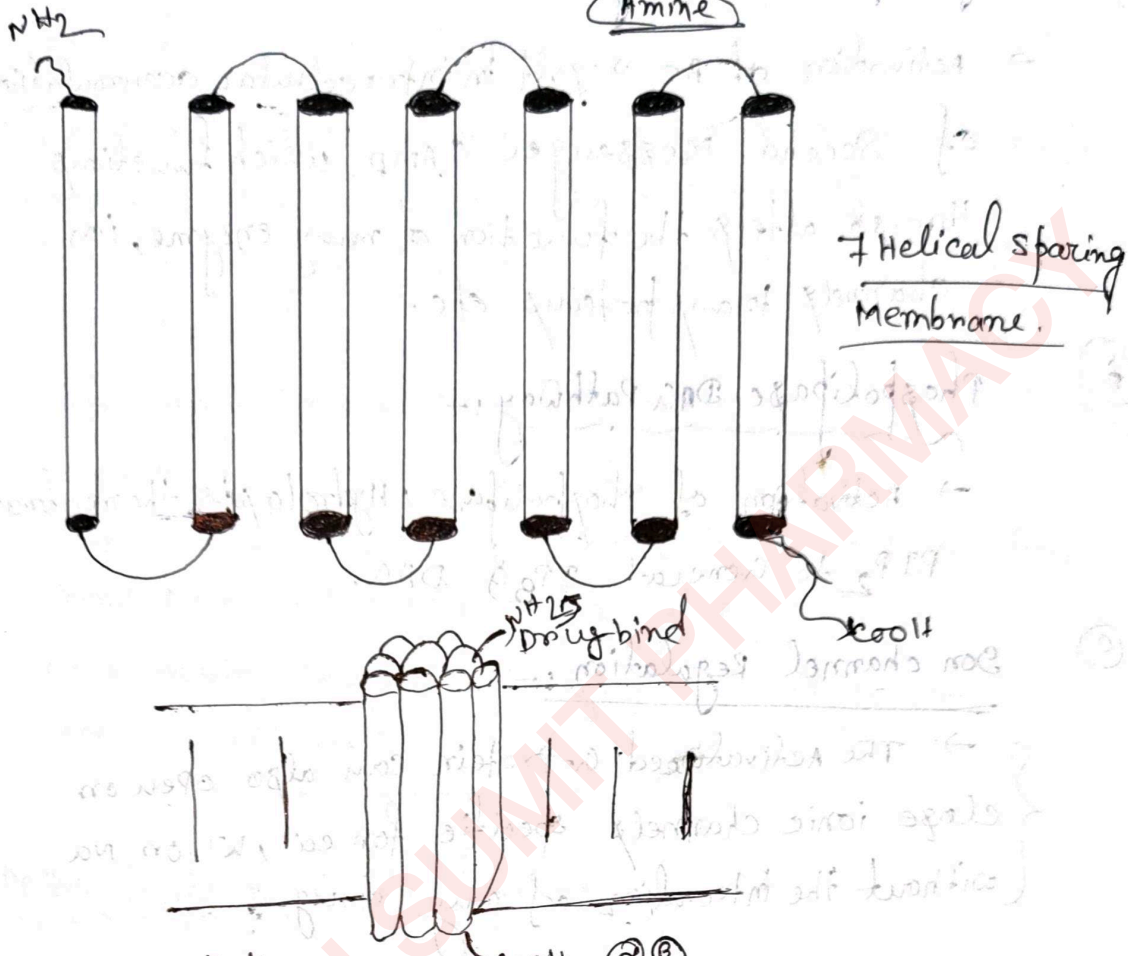
(x) G-Protein couple Receptor (GPCR) :-

→ GPCR Receptor is a family of cell membrane Receptor which is Activated by G-Protein this Seven Helical Sparing Membrane which are concted each other.

→ on this helical channel three Sigment three Sigment run in extra cellular and three run into cellular drug Agonist by is bind With Amino group of extra cellular then G-Protein is Activated and G-Protein bind the Receptor.

and Produce Action. ⊛ - $NH_2 - R - COOH$

Amine



→ The G-PCR Receptor Produce Action by following three Pathway

(a) Adenyl cyclase Pathway (cAMP)

(b) IP_3 Dag Pathway

(c) Ion channel Pathway

(a) Adenyl cyclase Pathway :-

→ Activation of AC result in intracellular accumulation of second messenger cAMP which functions through alters the function of many enzyme, ion channels trans proteins etc.

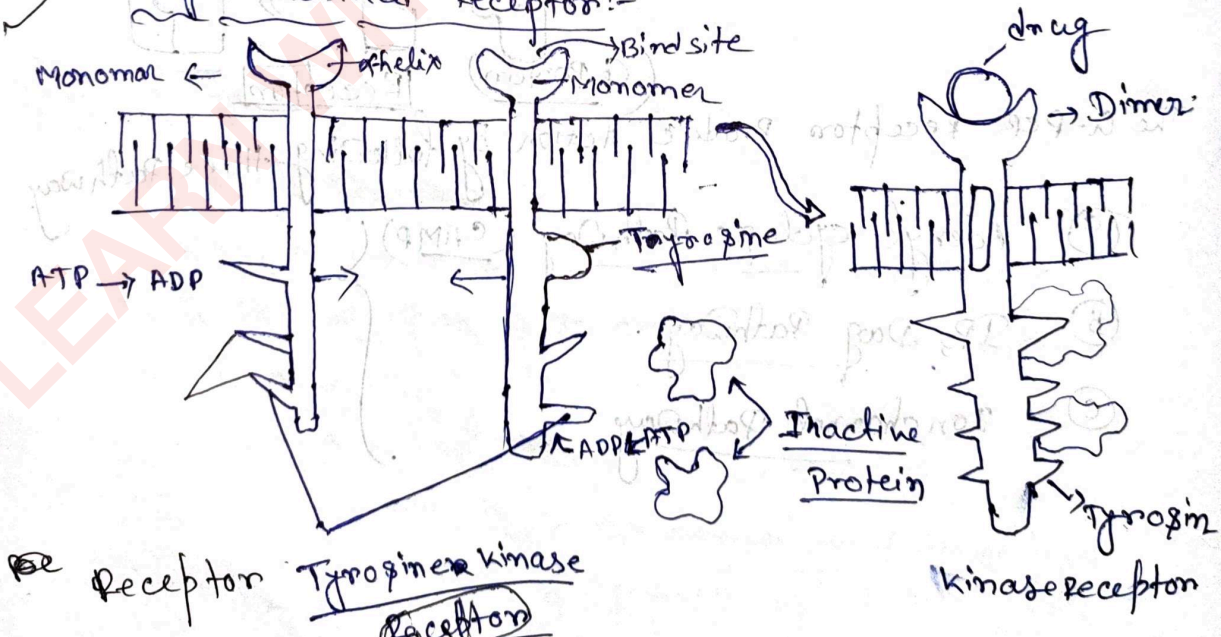
(b) Phospolipase DAG Pathway :-

→ Activation of phospholipase, Hydrolases the membrane PIP_2 to Generat IP_3 & DAG.

(c) Ion channel Regulation :-

→ The Activated G-Protein can also open or close ionic channels specific for cat, K^+ or Na without the intervation of any drug.

(*) Enzyme linked Receptor :-



Receptor Tyrosine kinase Receptor

RTKs

Note
→ Peptide hormone

→ This type of Receptor Activated by the enzyme tyrosine 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 bind with the binding site α-helix then it joined form dimer.

→ Some inactive Protein are present in Icf but when drug bind with the Receptor it becomes active.

→ Now Protein bind with the tyrosine receptor and Produce different Responce.

(*) Dose Responce Relationship:-

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

Responce:- Responce is the Pharmacological Action which is Produce after binding of the drug with receptor is called Responce.

→ In dose responce relation ship it depends upon two component:

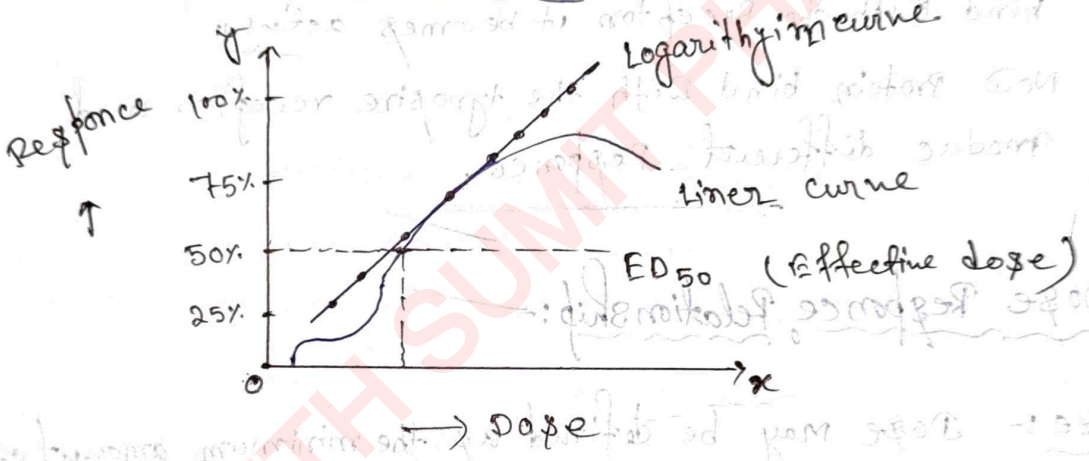
(i) Drug Plasma concentration Relationship
(ii) Plasma concentration Responce Relationship.

→ The Responce is quantitaively directly proportional to the Plasma concentration.

$$Pc \propto Responce$$

→ If the drug Plasma concentration level increase responce will be increase, if Plasma concentration level decreage Responce will also be decreage.

⑧ Dose Responce curve (DRC) :-



→ When we plot the relationship of dose & Responce on the graph then this graph is called dose-Responce curve.

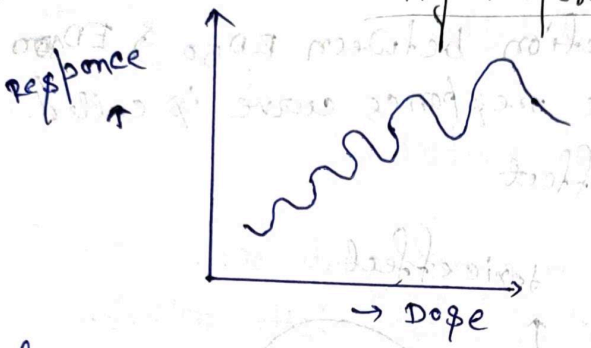
→ In dose responce curve dose is ploted on x-axis and Responce is ploted on y-axis.

⑨ Types of DRC (Dose Responce curve) :-

① Graded curve
② Quantal curve

⊛ Graded curve :-

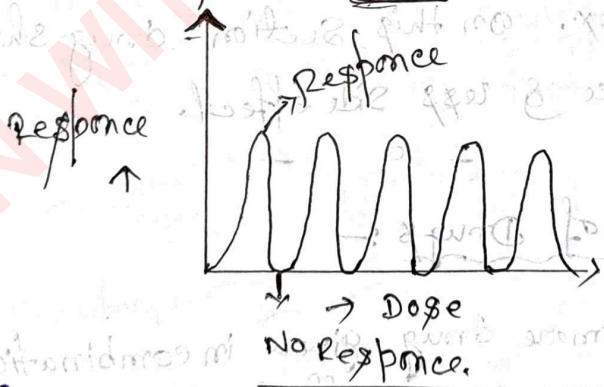
→ This type of curve is depends on the quantitative relationship as well as the dose of the ~~dose~~ drug is increased their responce will also be increase. this is quantitative directly Proportional relationship.



⊛ Quantal curve :-

→ The quantal curve is depends on the "all or none" principle.

→ It means after taking any toxic drug, either responce will be 100 % or Responce will be 0 %. their is no Chance of less or more.



⊛ Therapeutic Index :-

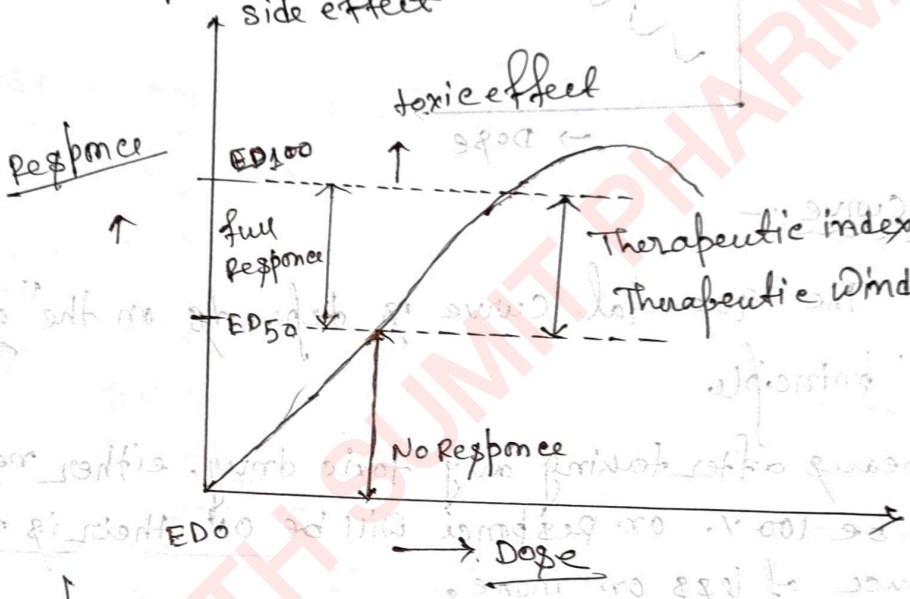
⊛ LD-50 (Lither Dose-50) :- on which dose the 50 % of animal ~~who~~ were killed that dose is called LD_{50} Dose.

(*) ED_{50} Dose (effective dose):-

→ on which dose the 50% of Animal were cure or alive that dose is called ED_{50} Dose.

Therapeutic Index:-

→ The section between ED_{50} & ED_{100} of any drug in dose responce curve is called



→ Therapeutic index. on this section drug shows maximum responce & less side effect.

- o -

(*) combined effect of Drugs:-

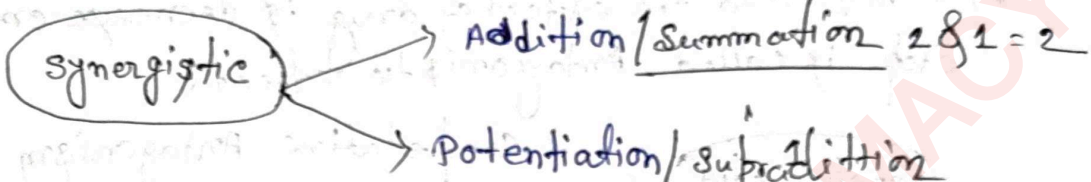
→ when two or more drug given in combination then they either increase the effect of drug or they decrease the effect of drug.

→ on the basis of their effect, effect is of combination is of two type—

(a) Synergistic
(b) Antagonistic

(*) Synergistic effect :-

→ When the two different drug, are given in combination then they enhance the Action of each other, and the effect of drug is increase, is called synergistic effect.



(1) Addition :-

when two drug given in combination then after addition their effect is increase two time.

→ for example Paracetamol and Aspirin both given in combination, then it increase effect two time for Analgesic and Antipyretic effect.

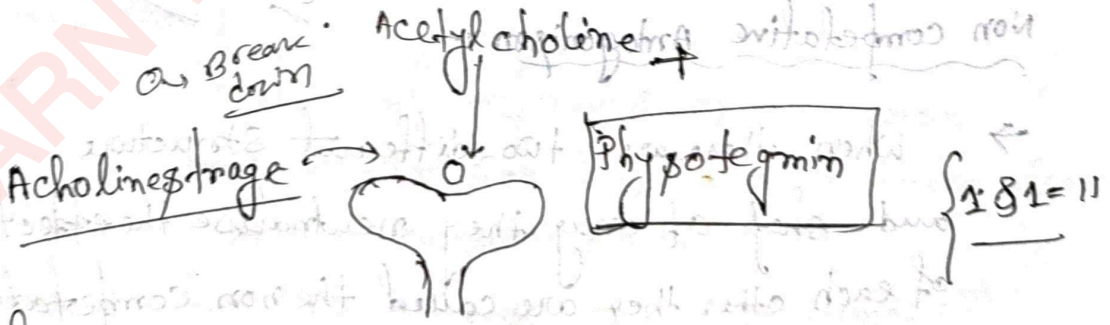
ex :- 1 + 1 = 2

(Paracetamol + Ibuprofen → combiflam)

(2) Potentiation :-

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

1 & 1 → 11



→ When Acetylcholine and Physotegmin drug are given then Physotegmin drug block the effect of acholinestrase enzyme so Acetylcholine can bind with the receptor And the effect can increase multiple number of time

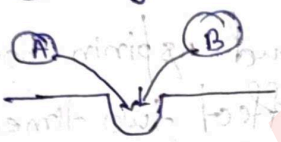
this is called potentiation effect.

(7) 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.

Antagonistic → Competative Antagonism
→ Non-competative Antagonism.

→ competative Antagonism :-



→ This is based upon the principle that an Antagonist or Antagonist can bind to the same recognition Site on the Recepton, and when Both are Present they can competed for such sites.

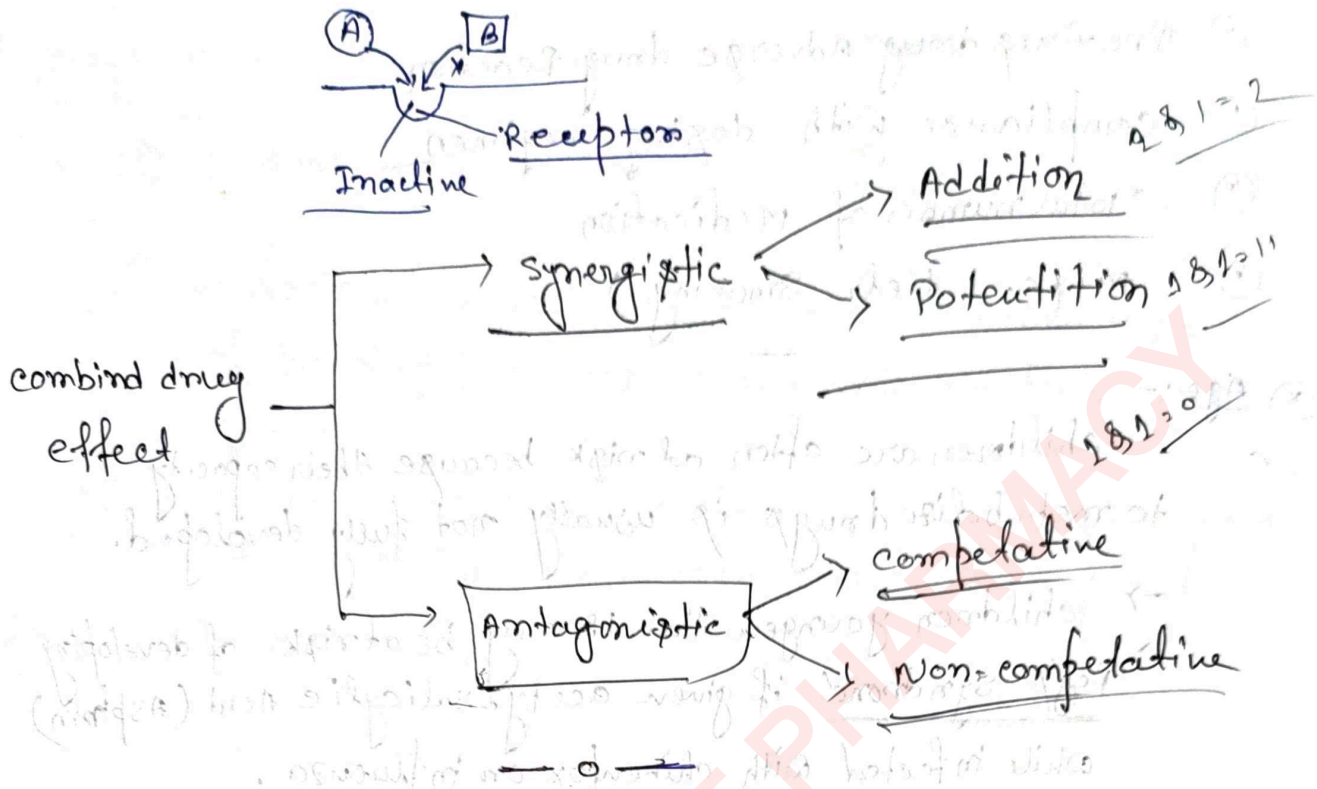
eg. Ach & Atropine

→ Non competative Antagonism :-

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

→ In this type of Antagonist the other drug inactive the receptor org an

eg:- Acetylcholine & Papperverine.



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ADVERSE DRUG REACTION:-

→ Any unwanted medical occurence that may present during treatment with medicine; but which may not have casual relationship with treatment. They are called ADRs.

common causes:-

- over dosing
- Allergics to chemical components of the medicine.
- Taking a medicine that was prescribed for someone else.
- combining the medicine with Alcohol.
- failing to take correct dose in correct time.

Factor affecting Adverse Drug Reaction :- (Patient Related)

- Age
- Sex
- Genetic influence
- concurrent diseas (renal, liver, cardia)

- Previous ~~drug~~ Adverse drug Reaction
- compliance With dosing regimen
- Total number of medication
- Misc. (diet, Smoking)

(*) **Age:-**

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

→ children youngen 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.

→ Reason for ADRs in the elderly.

1. concomitant use of several drug.
2. ~~Drugs~~ Decreased drug ADME Activity due to Age.

(*) **Breast feeding:-**

→ many drug can be Passed from mother to infant via breast milk.

→ Amantadine (antiviral)

→ cyclophosphamide (antineoplastic)

→ cocaine (schedule 2 FDA drug)

→ carisoprodol (Skeletal muscle relaxment)

Pregancy :—

1. Sulfonamids → Jaundice and brain damage in the fetus.
2. Warfarin → Birth defects, and increased risk of bleeding problems in ~~newborns~~ newborns and Mothers
3. Lithium → Defects of the heart, lethargy, reduced muscle tone, effect on thyroid gland.

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)

↑ Based on nature

→ Types Based on onset :—

⊙ onset of event —
- Acute → With 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.	Requir intensive treatment, life threating Permanent damage.	Directly/Indirectly contributes to the death of the Patient.

(A) Types-A Reactions or Augumented :—

→ This type of Adverse drug Reaction is Predetermind & Predefined.

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

Eg :- Benzo diazepines → Sedation
Furosemide → Water & electroly te imbalance.
Heparin, Waratin → Spontaneous bleeding
Insulid → Hypoglycemia

(B) Type-B Reactions or Bizare :-

→ The type-B 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

→ unknown form the drug's known Pharmacological actions.

eg:- → Hypersensitivity reactions
→ Stevens-Johnson's syndrome }

⑧ Type C Reaction on continuous:-

→ These type of Adverse drug Reaction which can appear in human body by taking continuous dose of Any drug for long duration is called C-type Adverse drug Reaction.

eg:- Ethambutol ⟶ Retinopathy.
NSAIDS ⟶ Nephrotoxicity.

⑨ Type-D Adverse drug Reaction or Delayed:-

→ This type of Adverse drug Reaction the Adverse effect of drug will be delayed after the Prolong use of any medication.

eg: carcionogenesis
Teratogenesis } by using Thalidomide drug.

⑩ Type E Adverse drug Reaction or Ending:-

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

eg:- clonidine → Rebound hypertension
Benzodiazipines → Rebound insomia }

Type F or Failure of efficiency :-

→ This type of Adverse drug Reaction ~~appear~~ after ~~increasing~~ of dose is certain and this is basically failure of efficacy

→ on this type of Reaction the drug can't shows their own Responce.

eg :- ① counterfit medicines
② Drug interactions

Drug interactions :-

→ Drug interection is defined as the Pharmacological ~~action~~ Activity of one drug is altered by the concominant use of another drug or by the presence of some other Substance.

Type of Drug interections :-

① Drug - Drug interections ★★
② Drug - food interections
③ chemical - Drug interections
④ Drug - Laboratory interections
⑤ Drug - Disease interections

Factor contributing to drug interections :-

① multiple Prescriberes
② multiple ~~Drugs~~ dosag therapy
③ Poor patient compliance
④ Multiple disease.
⑤ Advancing Age of Patient

① Multiple effect of Drug

Mechanism of Drug interactions :-

→ The three mechanism by which drug interactions can develop are -

- Pharmaceutical interaction
- Pharmacokinetic interaction
- Pharmacodynamic interaction

Pharmaceutical interaction :-

→ Pharmaceutical interaction also called as incompatibility. It is a physiochemical interaction that occurs when drugs are mixed in IV (intravenus).

eg:- Ampicillin, chlorpromazine & barbiturates interact with in dextron sol^{n} & from chemical compounds.

Pharmacokinetic interactions :-

→ These interaction are those in which ADME properties of the object drug is altered by precipitant and hence such interaction are also called of ADME interactions.

→ These are classified as —

- Absorption interactions
- Distribution "
- Metabolism "
- Excretion "

Absorption interaction :-

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

- Faster or slower drug absorption.
- More or less complete drug absorption.

→ Major mechanisms of absorption interections are -

① complexation
② Alteration in GI pH
③ Inhibitation of GI enzyme

↳ Digoxin interections with Antibiotics

eg:- Sulphonamides, Aspirin, Ferrous sulphate interect each other when Prespend Antacid.

(*) Distribution interections :-

→ Distribution interection are those where the distribution Pattern of the object drug is altered.

→ The major mechanism for distribution interaction is alternation in drug - Protein binding.

eg:- Tolbutamide interect with sulphonamide this is distribution interections.

(*) Metabolism interections :-

→ metabolic interection are those where the metabolism of the object drug is altered.

Mechanism :-

① enzyme induction :- Increased Rate of ~~Absorption~~ Metabolism
② enzyme inhibition :- Decreased rate of Metabolism

(*) enzyme induction :- corticosteroides, Phenytoin With Barbiturates.

(*) enzym induction :- Tyramine Rich food with MAO Inhibitons

⊛ excretion interections :-

→ excretion interection are those where the excretion pattern of object drug is altered.

→ Major mechanism of excretion interection are —

- ⊙ Alternation of urine pH.
- ⊙ Alternation in renal blood flow.

eg:- Lithium bicarbonate interect with NSAIDS

- NSAIDS
- → Ibuprofen
- → Aspirin.

NSAIDS :- Non-sterodical Anti-inflamatory drugs

⊛ Pharmacodynamics interections :-

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

→ There are two types — ⓐ Direct Pharmacodynamic
ⓑ Indirect "

ⓐ Direct Pharmaco dynamic interections :-

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

× Direct
- Antagonism
- Addition or Summation
- Synergism or Potentiation.

→ Antagonism :- The interacting drug have opposing Actions.

→ Acetylcholine & noradrenaline have opposing effect.

(iv) Addition or summation :-

→ The interacting drug have similar actions & resultant effect is the some individual drug response.

eg:- CNS depressants like sedatives and hypnotic

(v) Synergism or Potentiation :-

→ It is enhacement of action of one drug by another.

eg:- Alcohol enhance the analgesic activity of Aspirin.

(vi) Indirect Pharmacodynamic :-

→ In which both the objects and Precipitant have unrealated effects.

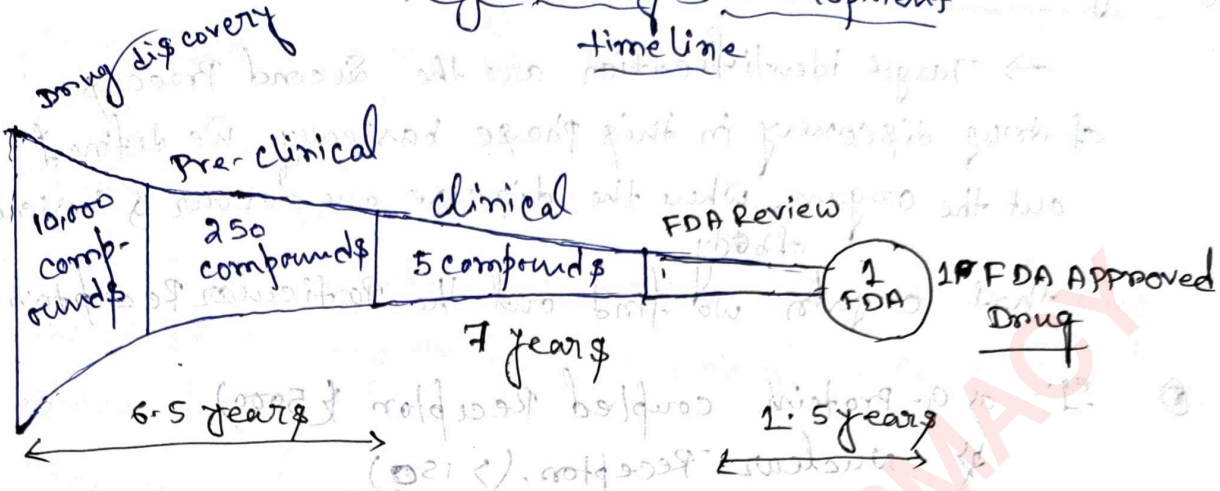
eg:- Salicylates decrease the ability of the Platlets.

(vii) Drug discovery :-

→ In the Past most drugs have been discovered either by identifying the Activity ingridient from remedies or by serendipitous discovery.

- ⊙ Basic Research
- ⊙ Programme
- ⊙ Non-clinical development
- ⊙ Clinical "

(1) Drug discovery & Development timeline



(2) Process of Drug discovery :-

- Pre-discovery
- Target identification
- Target validation
- Lead discovery
- Lead optimization
- Preclinical Testing
- clinical trial ⟹
  - Phase-0
  - Phase-I
  - Phase-II
  - Phase-III
  - Phase-V
- New drug

(3) Pre discovery :-

→ To find out the problems or disease before the discovery of disease this is called Pre discovery.

- This can be laboratory Method.

(*) Target identification :-

→ Target identification are the Second Process of drug discovery in this phase basically we defined out the organ, where the disease are occour & basically that organ of body we find out the Particular Receptor.

(*) eg :- a) G- Protein coupled Receptor (5000)
b) Nuclear Receptor. (> 150)

(*) Types of identification —

(a) Genomics
(b) Proteomics
(c) molecular biology
(d) Phenotype analysis
(e) Genetic association

(*) Target validation :-

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

(*) Lead discovery :-

→ Lead compounds are those molecule which are responsible for treatment of disease, which is letter known as drug.

- two types —
  a) Newer Techniques
  b) old Techniques

(*) Lead optimization :-

→ Increase the Potency of the compound on its target

- Increased its stability
- Increased its Metabolic stability

Pre-clinical testing :-

→ After the lead optimization & Lead finding the test of this drug into Animal is called Pre-clinical testing.

Time :- 1.5 years
usual no of compounds :- 20

⊛ clinical Trial :-

→ **Phase-1** :- First ~~stage~~ stage of testing in human Subject.

- 20-25 Healthy volunteers

- concerned with —
  - check the human toxicity
  - Tolerated Dosage Range
  - .

Phase-II :-
- Second stage
- 50-300 Patients

concerned With —
- Safety
- efficacy
- Drug toxicity

} .

Phase-III :

- Most. expensive & time consuming
- 250 - 1000 patients

→ concerned with —
- a) Safety
- b) efficacy

Phase-IV :-

- Post marketing surveillance
- Designed to detect rare & long term Adverse effects.

—

- Stimulation
- Depression
- Irritation
- Replacement
- cytotoxic
- modification of Immune System

JAK-STAT

Catalytic Domain :- The Region of an enzyme that interacts with its Substrate to cause the enzyme Reaction

→ cytokinase
growth hormone
Prolactin

ligands

Binding site

ECF

CM

JAK

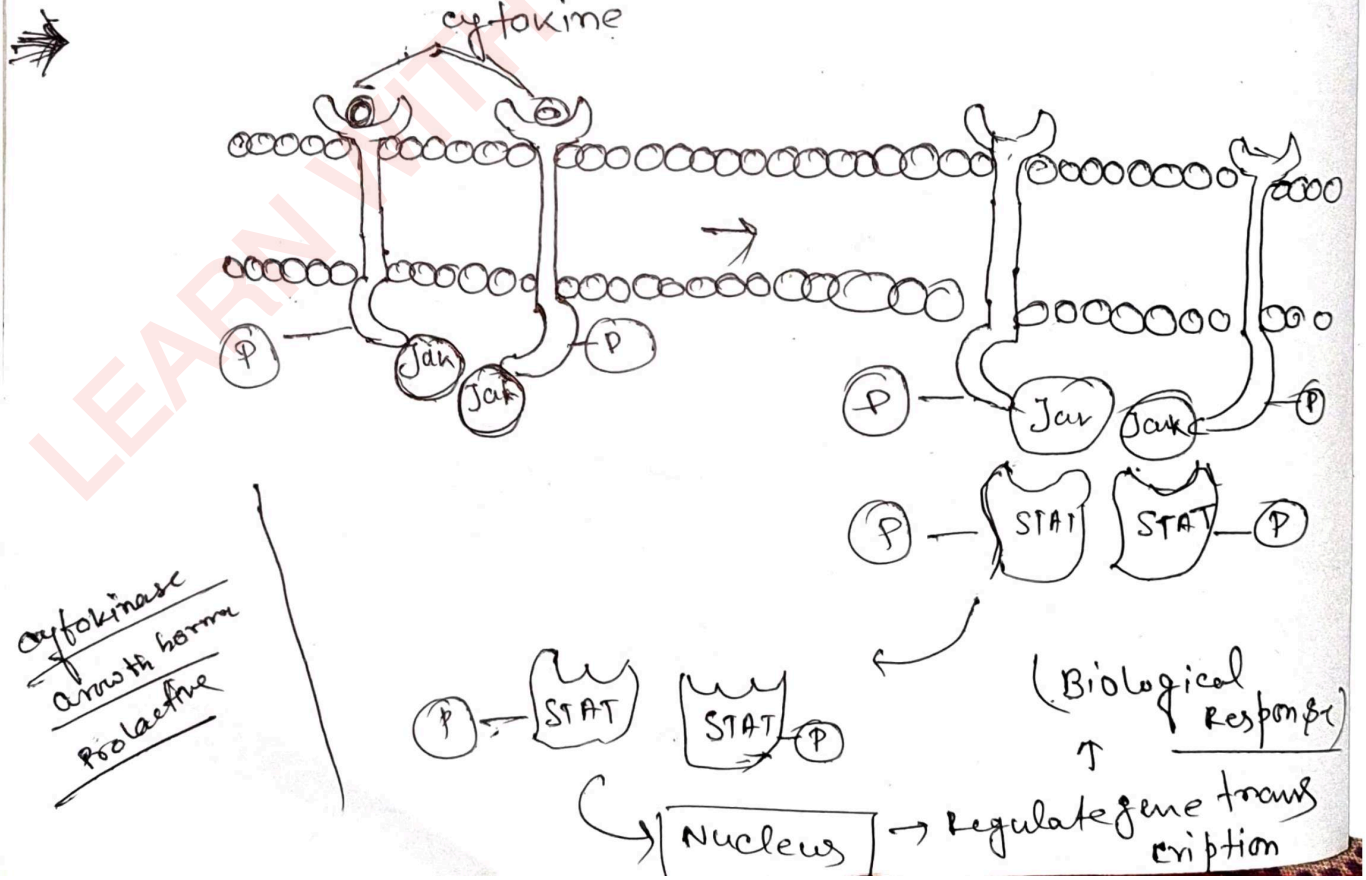
STAT

ICF

Janus Kinase

(Signal transducer & Activator of Transcription)

Receptor



cytokinase
Growth hormone
Prolactine

(Biological Response)

Nucleus → Regulate gene transcription

Mechanism

Agonist binds and induced dimerization

↓

which after the intracellular domain conformation to increase its affinity for a cytosolic tyrosine protein kinase JAK (Janus kinase)

↓

on binding, gets Activated and Phosphorylate tyrosine residuce of the Receptor.

↓

which now bind another free moving protein

STAT

↓

Pair of Phosphorylated STAT

dimerize

↓

Translocate to the nucleus to Regulate gene transcription

↓

Biological responces

Mechanism

GPCR

→ Drugs (Agonist) Bind with Receptor → currents flow through loops

↓

Activate of G-Protein

GTP Replace GDP ←

↓

Break down trimers → α GTP, β, γ

Dimers: β γ

α GTP → Activate

↓

Effector enzymes → Adenyl cyclase

→ Phospholipase C

→ ion channels Regulation

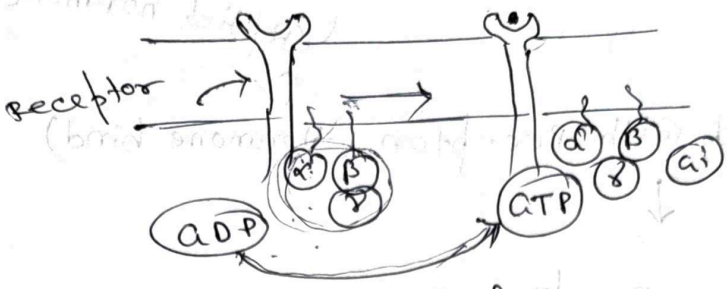
IP3 —

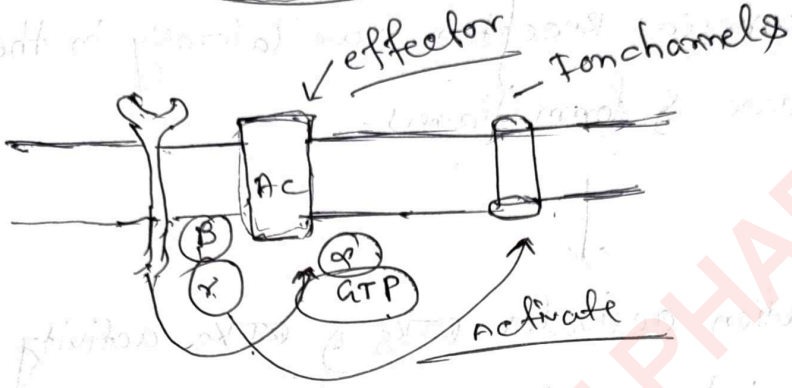
Adenyl cyclase Pathway:-

AC → ATP → cAMP → Protein kinase (PKA)

Phospholyase enzymes → effects

Secondary messenger





G_s → ↑ Adenylyl cyclase Action, Ca^{2+} channels open

G_i → Adenyl cyclase inhibitation.

G_o → Ca^{2+} channel inhibitation.

$G_{q/11}$ → Phospholipase activation

cAMP → (cyclic Adinine mono phosphate)

→ This system Works in → LAS H → Heart

Liver, Adipose tissue, Smooth muscle

Following organ