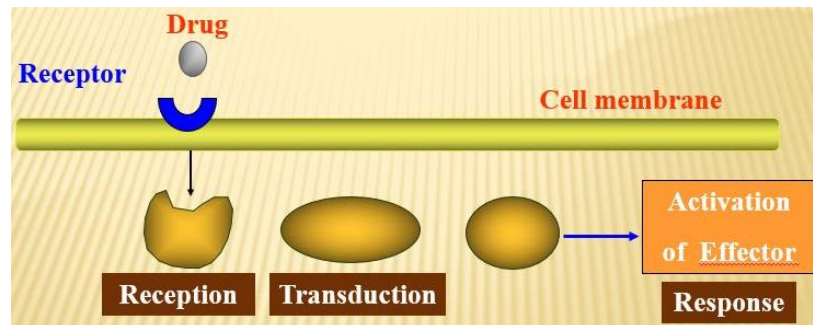


PHARMACODYNAMICS

A) Mechanism of drug action

a. **Receptor-mediated actions:** the drug interacts with cellular receptors. The action occurs in 2 steps:

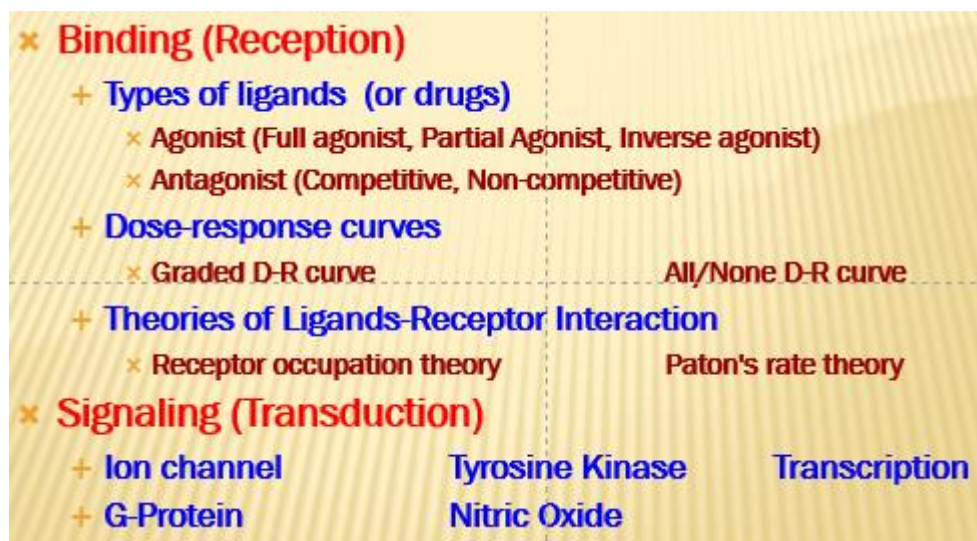
- Binding (Reception):** it is the attachment of the drug to the receptors.
- Signaling (Transduction):** is post-binding changes that induce drug action.



b. **Non receptor-mediated actions:**

- Actions on non-receptor targets:** the drug interacts with cellular molecules that serve biological functions other than drug reception.
- Chemical actions:** the drug acts by its chemical properties e.g. electric charge, basic nature ...etc.
- Physical actions:** the drug acts by its physical properties e.g. osmosis, adsorption... etc.

1. Receptor-mediated mechanisms

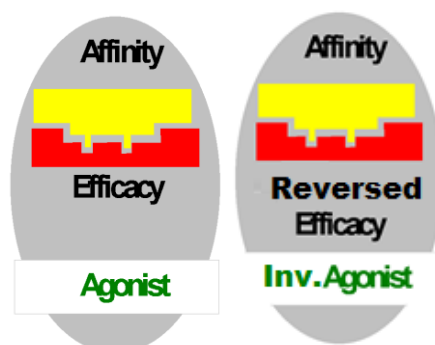


Receptors¹ are specific cellular macromolecules that interact with a ligand e.g. drug molecule (**BINDING**) to stimulate or block a cellular response (**SIGNALING**).

¹ The pharmacological actions mediated by the receptors are characterized by **3S**: **Sensitivity** (i.e. very small concentration of the ligand is enough to elicit the action), **Selectivity** (i.e. each receptor has the type of ligand that can interact with it) & **Specificity** (i.e. they elicit the same response each time they interact with the ligand).

Types of ligands:

1. **Agonist:** the drug is called an agonist if it has **affinity** (i.e. it interacts with the receptor) and **efficacy** (i.e. the interaction → pharmacologic effect). e.g. epinephrine at α & β receptors or morphine at μ & δ receptors, If the drug produced an opposite effect to the natural agonist, it is called inverse agonist e.g. β -carboline at BZD receptors or loratadine at H_1 receptors.



2. **Antagonist:** the drug is called antagonist if it has **affinity** but **no efficacy** (i.e. the interaction with the receptor → no pharmacologic effect) e.g. curare, naloxone². There are 2 types of **pharmacological antagonists**³: **competitive antagonists** where the antagonist competes with the agonist for the receptors e.g. atropine at M receptors or naloxone at μ receptors & **non-competitive antagonists** where the antagonist cannot compete with the agonist for the receptors⁴ e.g. phenoxybenzamine at α receptors.



3. **Partial agonist:** the drug is called partial agonist if it has **affinity** but **incomplete efficacy** (i.e. the interaction with the receptor → weak response) e.g. bromocriptine at D_2 receptors. It may be also called **agonist-antagonist**⁵ since it may replace the already bound agonist e.g. pindolol at β receptors.

² However, if the receptor is pre-occupied with an agonist; the displacement of the agonist by the antagonist will terminate its action.

³ Sometimes, we can terminate the action of the agonists by drugs that do not interact with the receptors e.g. drugs which interacts with the agonist (**chemical antagonism** e.g. *protamine sulfate and heparin*) or interact with the other cellular components to produce an action opposite to that produced by the agonist (**physiological antagonism** e.g. *epinephrine and histamine*).

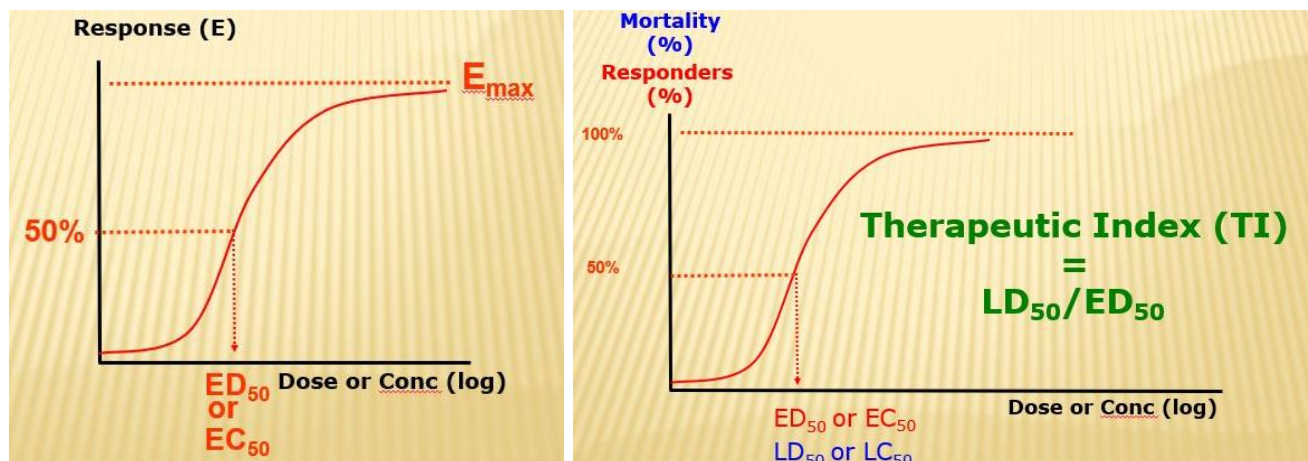
⁴ This occurs if the antagonist binds to the receptor by a covalent bond or it binds to a different allosteric site.

⁵ If it is given when the receptors in absence of the agonist it acts as a weak agonist while if it is given in presence of the agonist it will replace it giving a weaker agonistic effect (i.e. it acts as antagonist).

Dose (or Concentration)-response curves:

The dose-response relationship can be represented graphically by 2 types of curves: the qualitative (**All/None**) dose-response curve and the quantitative (**Graded**) dose-response curve.

I. Agonist Curves



1. **Graded dose-response** curve is obtained if the degree of response is depicted against log the dose e.g. the decrease of blood glucose against the dose of the antidiabetic drug.

Parameters inferred from the graded dose-response curve:

- 1) **Efficacy (Emax)**: is the maximal effect produced by the drug (= *the maximum value of the dose-response curve*)
- 2) **Potency** of the drug can be assessed from 2 parameters:
 - a. **ED₅₀**; it is dose that produces 50% of the maximal response. The lower the ED₅₀, the more potent the drug is.
 - b. **Slope**; of the middle linear portion of the curve = the effect of the drug produced by one unit of the dose (the steeper the curve, the more potent the drug is).

2. **All/None dose-response** curve is obtained if the percentage of patients who respond to the drug is depicted against log the dose e.g. the % of patients in whom the arrhythmia is terminated by different doses of an antiarrhythmic drug.

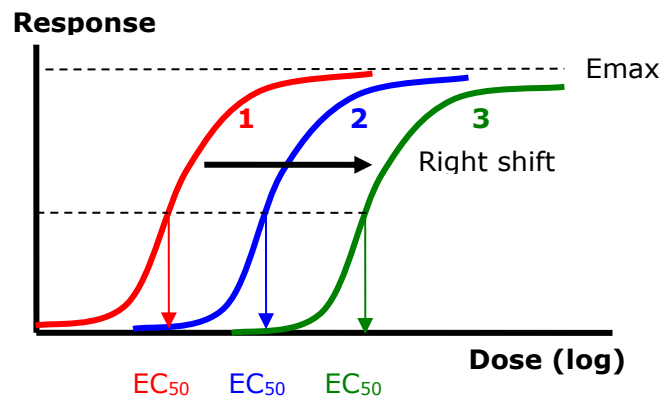
Parameters inferred from All/None curve:

- 1) **ED₅₀**: It the dose that cures 50% of cases. It is used for comparison between drugs e.g. the drug with lower ED₅₀ is more potent than that with higher ED₅₀.
- 2) **LD₅₀**: If we are concerned about the toxicity of the drug, we may draw the relation between the % mortality in animals treated by the drug against log of the dose. In such case the dose that kills 50% of animals is called LD₅₀. LD₅₀ gives an idea about the absolute toxicity of the drug (the lower the LD₅₀ the more toxic is). It is recommended that the dose should not exceed 10% of the estimated LD₅₀.
- 3) **Therapeutic index (TI)**: it is the ratio between ED₅₀ & LD₅₀ (i.e. $TI = LD_{50}/ED_{50}$). It gives an idea about the safety of the drug (the higher the TI, the safer drug is). Examples of drugs with narrow therapeutic margin (low TI) are aminoglycosides, theophylline, anticoagulants ... etc.

II. Agonist Curves in presence of an Antagonist

1. Competitive antagonists

1. The antagonist competes with the agonist to bind to the active site of the receptor.
2. The duration of action of the antagonist is directly proportional to its concentration.

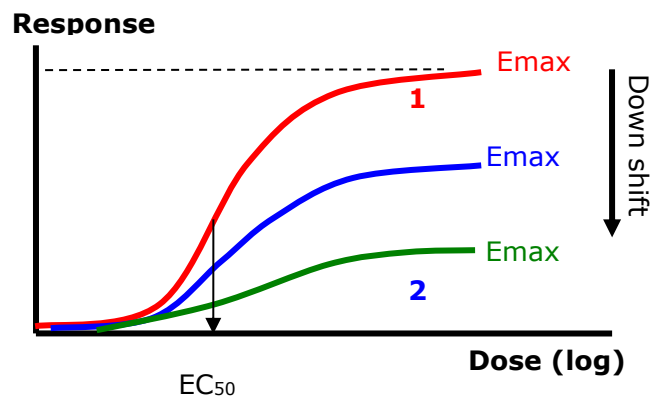


1: Agonist alone 2: Agonist + small dose Antagonist 3: Agonist + high dose Antagonist

3. Increasing the dose of the antagonist shifts the dose-response curve to the right →
 - E_{max} & the slope are not affected
 - EC_{50} is increased
4. Examples of competitive antagonists include atropine (M-receptors), curare (Nn receptors), naloxone (μ -receptors)

2. Non-competitive antagonists

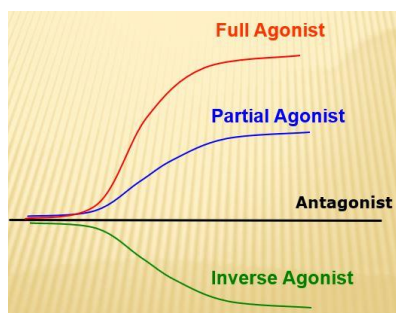
1. The antagonist either binds to the allosteric site of the receptor or irreversibly to the active site.
2. The duration of action of the antagonist is directly proportional to the rate of receptors turnover.



1: Agonist alone 2: Agonist + small dose Antagonist 3: Agonist + high dose Antagonist

3. Increasing the dose of the antagonist shifts the dose-response curve downward →
 - E_{max} & the slope are decreased
 - EC_{50} is not affected
4. The famous example of noncompetitive antagonists is phenoxybenzamine (α -receptors).

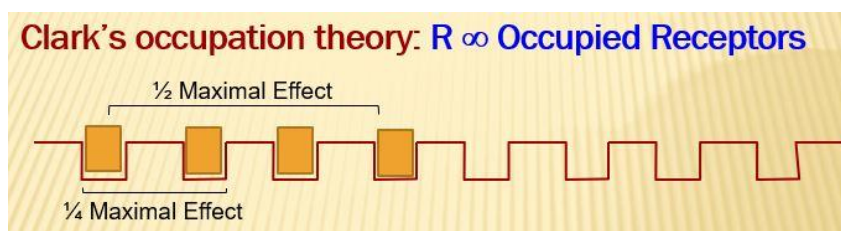
III. Inverse & Partial Agonist Curves



Theories for the relation between the dose & the response:

1. Receptor occupation theory:

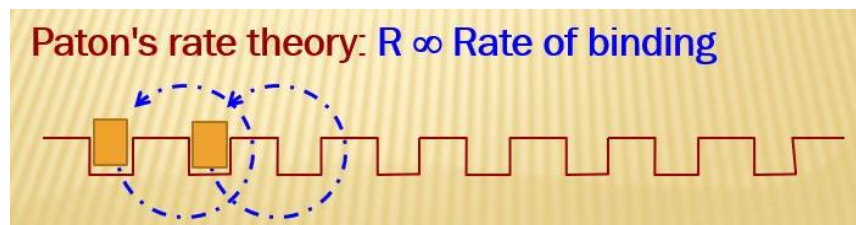
The drug effect is proportional to the fraction of receptors occupied ⁶



The maximum effect occurs when all receptors are occupied

2. Paton's rate theory:

The drug effect is proportional to the rate of association/dissociation between the receptors & the drug.



The maximum effect occurs with the highest association/dissociation rate.

3. "Two-states" model Theory:

The receptor is present in 2 states: the antagonist shifts equilibrium to R_i (inactive) state & the agonist shifts equilibrium to R_a (Active) state. Some suggest an additional constitutional state ($R^\#$) that is active in absence of a ligand (three states model theory).

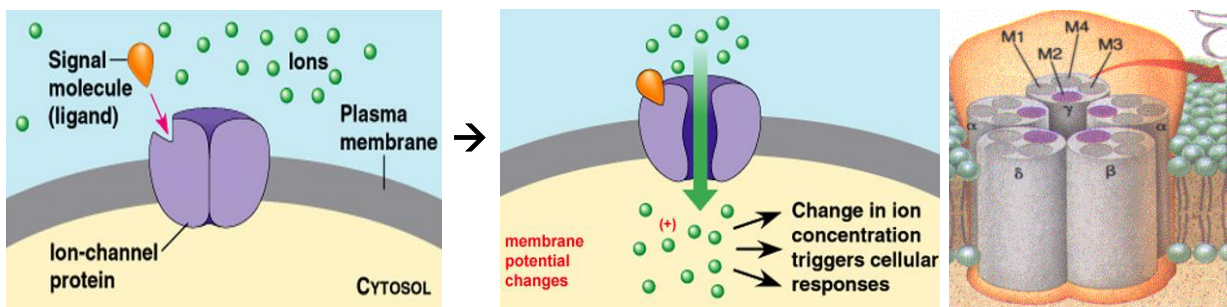
⁶: The number of the receptors is not constant: Binding of the agonist \rightarrow increases receptor internalization \rightarrow \downarrow the number of recruited receptors [down regulation] while binding of the antagonist \rightarrow \uparrow the number of recruited receptors [up regulation]. It is to be noticed that only a small number of the cell receptors are recruited while the remaining is spare.

CELLULAR SIGNALING or TRANSDUCTION

Conformation change in the receptors after drug binding initiates changes in other intracellular molecules → changes in other cellular components. The most important function of transduction is amplification of the response *e.g. binding of one molecule of epinephrine to β_2 -adrenergic receptors → activates 100 G-proteins → activates 10000 adenylyl cyclase enzyme → activates 1000000 glycogen phosphorylase enzymes → stimulate glycogenolysis → release of 100000000 molecules of glucose.*

1. Ion channel Receptors

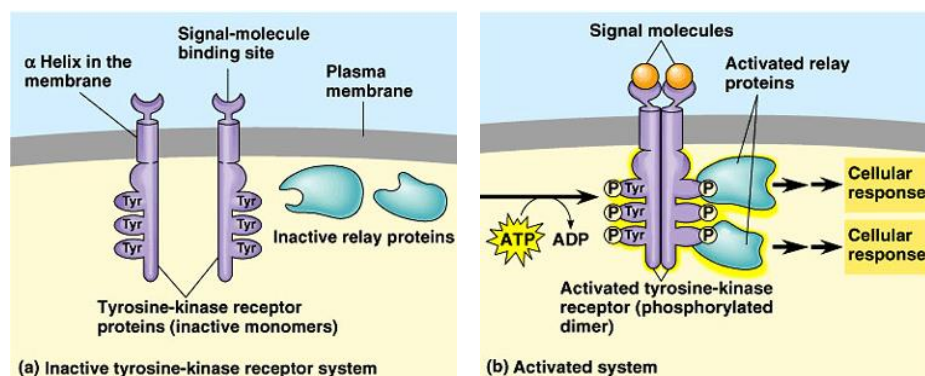
The ion channel receptor is a protein pore in the cell membrane. It opens in response to binding a signal molecule *e.g.* a neurotransmitter as Ach or GABA. Ions flood through the opened channel, changing the membrane potential & triggering very rapid response in the cell.



The nicotinic Ach receptor is the classic example. It is a pentamer made of 5 homologous polypeptide subunits: $\alpha_1 \beta \delta \alpha_2 \gamma$. Each subunit is made of 4 membrane spanning regions (M1-M4). Ach binds to the α subunit and the adjacent subunit while the pore is formed by the 5 M2 subunits. Opening of this mixed Na^+/K^+ channel leads to entry of Na^+ into and escape of K^+ from the cell. This leads to induction of end plate potential (in skeletal muscles) or fast excitatory postsynaptic potential in the autonomic ganglia.

2. Receptors linked to Tyrosine Kinase (RTKs)

These are receptor proteins that have tyrosine kinase activity (i.e. they can phosphorylate tyrosine). Ligands *e.g.* insulin cause 2 single tyrosine-kinases receptors to aggregate into a dimer. Each unit of the dimer phosphorylates the other unit tyrosine residues. Then, the activated-phosphorylated dimer binds to relay proteins, activating them, which in turn can activate up to 10 others ... etc. These relay proteins trigger the cellular response through either production of a second messenger or turning on gene expression.

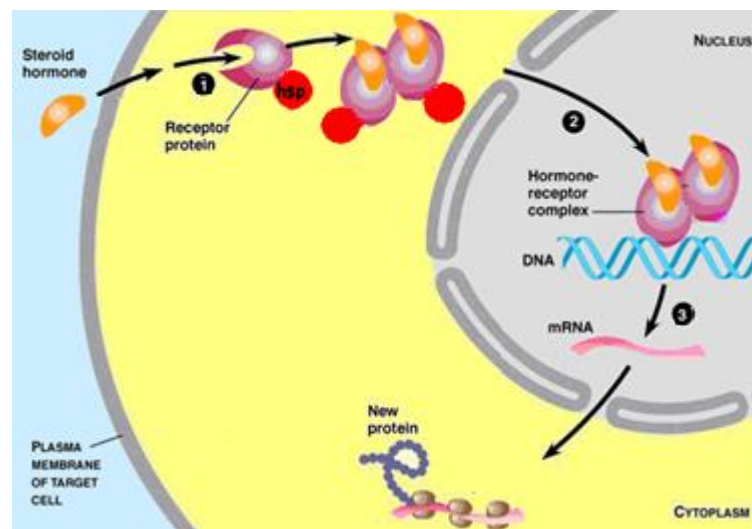


The insulin is the classic example of these receptors. It leads to phosphorylation of relay proteins called insulin receptors substrates (IRS) e.g. IRS-1 & IRS-2. These IRSs mediate the actions of insulin through phosphorylation of other cellular components e.g. glycogen synthase (→ activates glycogen deposition in the liver) or hormone sensitive lipase (→ inhibits fat cell lipolysis) ...etc.

JAK Tyrosine Kinase Enzyme receptors for cytokines is very similar.

3. Non-membrane bound Steroid Receptors

These receptors are located intracellularly (cytoplasmic or nuclear) i.e. the drugs which act by this mechanism should be lipophilic. The action occurs in 3 steps:

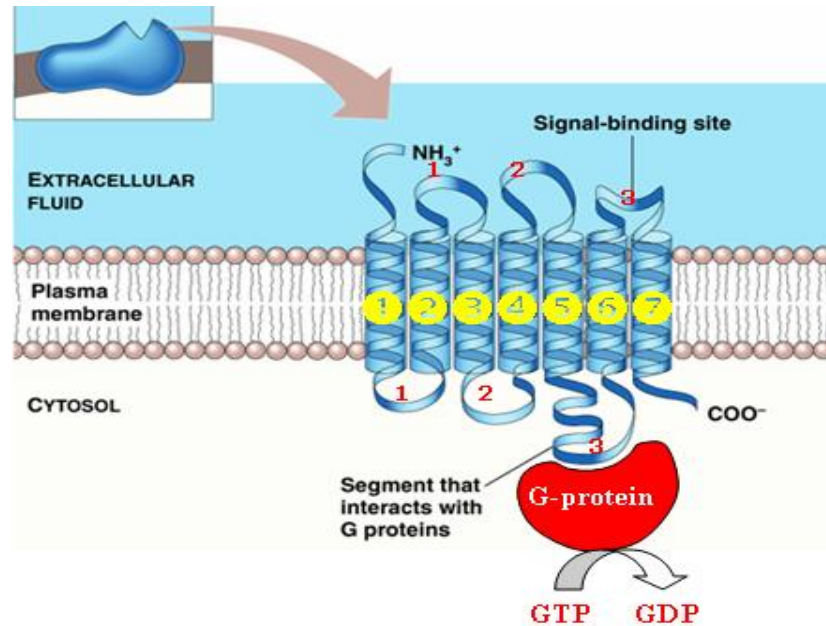


1. **Drug binding** to the drug-binding domain of the receptor → ligand-receptor complex (However, this complex is inactive since heat shock proteins (hsp) are bound to the DNA-binding site). Dissociation of hsp is followed by dimerization → active homodimer which translocates to the nucleus.
2. **DNA binding** e.g. glucocorticoid receptors dimers bind to glucocorticoid responsive elements on the nuclear DNA
3. **DNA activation** is triggered → initiates gene transcription → mRNA synthesis. The mRNA passes to the ribosomes to initiate new protein⁷ synthesis which mediates the actions of the steroid ligand.

4. G-Protein Receptors

The G-protein receptor is a peptide made of 7 transmembrane domains; with 6 loops connecting the transmembrane segments (3 extracellular & 3 intracellular). The G-protein binds to the 3rd cytoplasmic loop while the ligand binds to a site surrounded by 7 transmembrane domains. N-terminal end of the peptide is the extracellular tail and the C-terminal end of the peptide is the cytoplasmic tail. The G protein binds with GDP (inactive form). Ligand binding → conversion of GDP into GTP (active form).

⁷: In case of cortisol; it is called lipomodulin or lipocortin since it activates phospholipase A2 enzyme to release arachidonic acid



The G proteins are heterotrimers (i.e., made of 3 different subunits: $G\alpha$, $G\beta$ & $G\gamma$). There are at least 20 different kinds of $G\alpha$ molecules; the most famous of these are:

1. **G_s** : It is linked to activation of adenylyl cyclase enzyme $\rightarrow \uparrow$ c-AMP. It is associated with the receptors for many hormones e.g. β -adrenergic receptors for adrenaline.
2. **G_i** : It is linked to inhibition of adenylyl cyclase enzyme $\rightarrow \downarrow$ c-AMP. It is associated with the receptors for α_2 adrenergic receptors for adrenaline, $M_{2,4}$ receptors for acetylcholine.
3. **G_q (G_p)**: It is linked to activation of phospholipase C enzyme $\rightarrow \uparrow$ IP_3 & DAG ($IP_3 \rightarrow Ca^{++}$ release & DAG \rightarrow PKC activation). It is associated with the receptors for α_1 -adrenoceptors for adrenaline and $M_{1,3,5}$ muscarinic receptors for acetylcholine.

5. Nitric oxide “NO” receptors

Nitric oxide induces formation of c-GMP which lead to calcium efflux. C-GMP is metabolized by PDE enzyme. PDE inhibitors as sildenafil mimics the action of NO,

Non receptor-mediated mechanisms

1. NON-RECEPTOR PROTEINS:

Examples of drugs acting through **ENZYMES**:

- Aspirin inhibits cyclooxygenase enzyme (COX)
- omeprazole inhibits K^+ -H⁺ ATPase enzyme

Examples of drugs acting through **CELL wall /& CELL membrane**:

- Penicillin antibiotic binds to penicillin binding protein of the cell wall
- Nystatin binds to ergosterol of the cell membrane

Examples of drugs acting through **MICROTUBULES**:

- Colchicine (anti-inflammatory drug used in gout) binds to tubulin protein to inhibit neutrophil migration

Examples of drugs acting through **RIBOSOMES**:

- Tetracycline & aminoglycosides (antibiotics) bind to 30s r-RNA

Examples of drugs acting through **MITOCHONDRIA**:

- Niclosamide (anthelmintic drug) uncouples oxidation & phosphorylation

2. DRUGS CAN ACT BY PHYSICAL MEANS

1. **Emollients & Demulcents**: e.g. olive oil is used for soothing dry skin & mucous membranes.
2. **Adsorbents** e.g. kaolin & pectin are used in diarrhea
3. **Lubricants** e.g. mineral oil is used in constipation
4. **Osmotics** e.g. Mannitol is used as an osmotic diuretic.

3. DRUGS CAN ACT BY CHEMICAL ACTION:

1. **Antacids** neutralize HCL in peptic ulcer
2. **Protamine sulfate** neutralizes heparin in treatment of heparin overdose
3. **Citrates** interact with calcium to inhibit blood coagulation in test tubes

4. **Chelation**:

This means the capacity of organic compounds to form complexes with metals → “chelates” which are more water soluble → easily excreted.

Examples:

- Penicillamine (copper)
- Desferrioxamine (iron).

Therapeutic effects of drugs

Types:

1. **Curative** i.e. get rid of the disease process e.g. Chloramphenicol
2. **Symptomatic** i.e. improve the symptoms while the disease process is not affected e.g. morphine
3. **Prophylactic** i.e. used in case of anticipation of a disease to prevent its occurrence e.g. chloroquin in malarial prophylaxis
4. **Replacement** i.e. replace a deficient element in the body e.g. vitamins & hormones.

Factors affecting the therapeutic response:

[1] Age:

Younger patients cannot tolerate the adult dose; accordingly, the dose of the drug for the children should be reduced. Various methods & formulas are used for calculating the child dose depending on the **age**, the **surface area**, or the **body weight** e.g.

$$\text{Child dose} = \text{Adult dose} \times \text{Child Weight} / \text{Adult weight}$$

[2] Sex:

- Young females: certain drugs act specifically on the female organs e.g. sex hormones estrogen & progesterone.
- Pregnant & lactating female: → some drugs can cause teratogenicity e.g. antithyroid drugs or pass to milk e.g. phenobarbitone.

[3] Pathological factors:

The presence of certain disease may make the patient more sensitive to certain drugs e.g.

- In bronchial asthma: β -blockers → asthmatic attack.
- In myasthenia gravis: skeletal muscle relaxants → myasthenic attack

[4] Psychological factors:

Some patients may respond to a **PLACEBO** (an inert substance that closely resembles the active drug) the same way they respond to the active drug.

The placebo may be used for psychological therapy and in control studies to differentiate the true effect of the drug from that due to psychological factors

[5] Pharmacological factors:

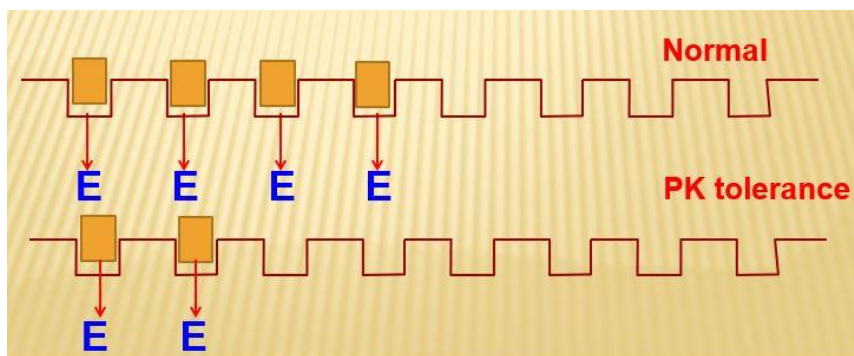
[A] TOLERANCE:

Definition:

It is reduced responsiveness to the drug on repeated administration so that higher doses are needed to produce the same effect.

Mechanisms:

Pharmacokinetic tolerance: it is tolerance due to decrease drug level that reach the receptors e.g.



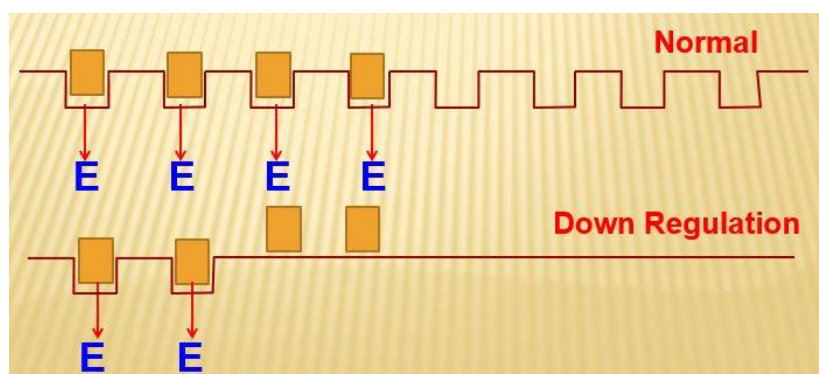
Diminished absorption e.g. furosemide tolerance due to gut edema in heart failure

Diminished distribution to the site of action e.g. furosemide tolerance due to hypoalbuminemia in nephrotic syndrome or ascites

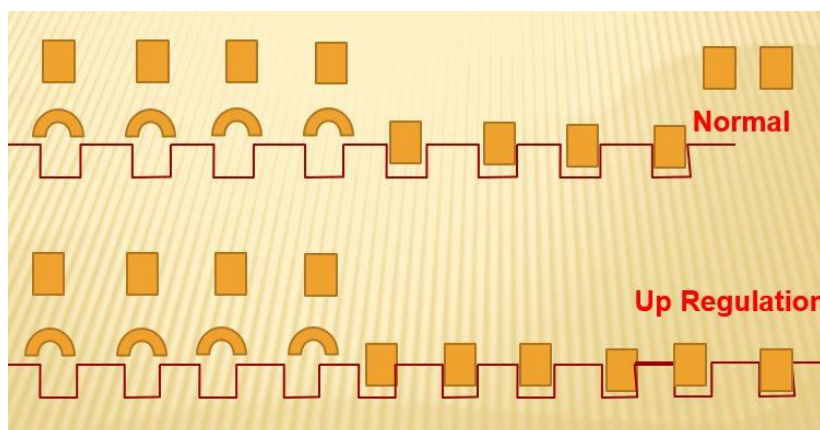
Increased elimination e.g. increased metabolism due to enzyme induction with phenobarbitone

Pharmacodynamic tolerance: it is tolerance without decrease of drug level e.g.

Down regulation [Decreased number of receptors with agonists] e.g. β_2 -agonists as salbutamol



Up regulation [Increased number of receptors with antagonists] e.g. H_2 -receptor antagonists as famotidine



Activation of counter regulatory mechanism e.g. salt and water retention with some antihypertensive drugs

Special types of tolerance:

- a. **Tachyphylaxis:** It is acute tolerance but you cannot get the same effect by \uparrow the dose e.g. tolerance due to depletion of norepinephrine from few doses of ephedrine
- b. **Cross tolerance:** It is tolerance to related drugs e.g. cross tolerance between different members of opioids or xanthine bases.

[B] Drug interactions

It is the modulation of the pharmacologic activity of one drug (*the object drug*) by the prior or concomitant administration of another drug (*the precipitant drug*). The pharmacologic properties of the object drug and/or the precipitant drug can be either enhanced or diminished:

Pharmaceutical interaction: outside the body

e.g. penicillin & streptomycin

Pharmacokinetic interactions: inside the body

- Absorption interactions e.g. antacids \downarrow iron absorption
- Distribution interactions e.g. aspirin displaces warfarin
- Metabolism interactions e.g. enzyme induction/ inhibition
- Excretion interactions e.g. probenecid \downarrow penicillin excretion

Pharmacodynamic interactions: inside the body

- **Summation:** the combined effect “drug A and Drug B” = the effect of drug A + the effect of drug B (when used separately). e.g. *additional sedation induced by antihistaminics*

Effect of Drug A		Effect of Drug B		Effect of Both A & B
10	+	10	=	20

- **Potentiation:** Drug A has no effect but it increases the effect of drug B e.g. *the antibacterial action of clavulanic acid & amoxycillin*

Effect of Drug A		Effect of Drug B		Effect of Both A & B
0	+	10	<	15

- **Synergism:** the combined effect “drug A and Drug B” > the effect of drug A + the effect of drug B (when used separately) e.g. *the antihypertensive effect of vasodilators & diuretics*

Effect of Drug A		Effect of Drug B		Effect of Both A & B
10	+	10	<	25

- **Antagonism:** the combined effect “drug A and Drug B” < the effect of drug A + the effect of drug B (when used separately) e.g. *the aspirin decreases the diuretic effect of furosemide*

These are the harmful effects of the drugs. They are complicating 5 to 15 % of therapeutic drug courses. They are classified into:

A) Type A or Augmented action:

- i. **Intolerance** (may occur at doses < therapeutic dose): e.g. tinnitus after a single, small dose of aspirin due to a lower threshold to a normal pharmacologic action
- ii. **Side effect** (occurs at therapeutic dose) e.g.
 1. **Primary pharmacological action** e.g. dry mouth from antihistamines
 2. **Secondary pharmacological action** e.g. thrush while taking antibiotics
- iii. **Overdose** (occurs at doses slightly higher than therapeutic dose) e.g. seizure from excessive lidocaine or bleeding from heparin
- iv. **Toxic effect** (occurs at very high doses) e.g. hepatotoxicity from acetaminophen

B) Type B or Bizarre action:

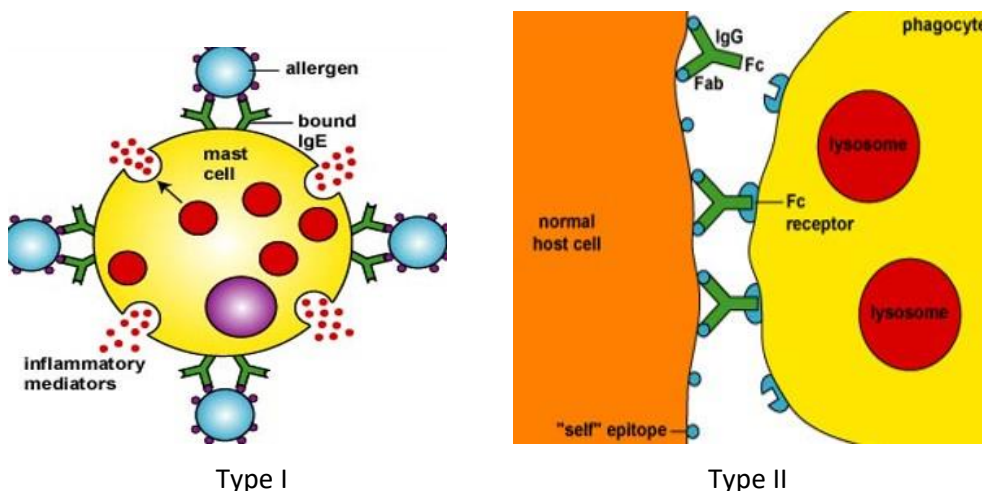
- i. **Allergic reactions:** are adverse effects mediated by immunologic mechanisms. They are classified into:

Type I (immediate) hypersensitivity: This is the most common type of hypersensitivity, seen in about 20% of the population.

Mechanism: IgE is made in response to an allergen e.g. penicillin. In allergic individuals, the levels of IgE may be thousands of times higher than in those without allergies. It binds to mast cell → trigger histamine release when it binds the antigen → anaphylactic reaction.

Type II (cytotoxic) hypersensitivity:

Mechanism: specific IgG/IgM antibodies directed at drug-hapten coated cells. This leads to host cell lysis e.g. hemolytic anemia induced by alpha methyl dopa



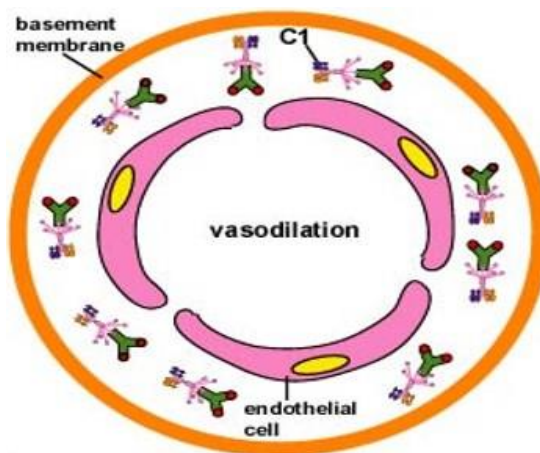
⁸ : If the adverse drug reaction takes the form of well known disease, it is called iatrogenic disease (drug-induced diseases) e.g. drug-induced bronchial asthma, peptic ulcer or Parkinsonism.

Type III (immune complex) hypersensitivity:

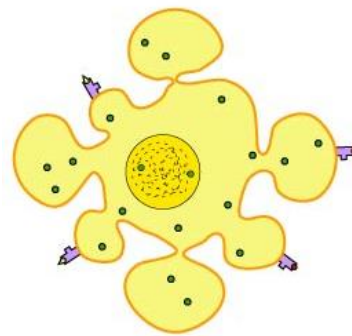
Mechanism: soluble antigen-antibody (IgG/ IgM) complexes, fix complement in the vascular space → inducing vasculitis e.g. with methimazole

Type IV (delayed, cell-mediated) hypersensitivity):

Mechanism: T-helper cells (CD4+) recognize foreign antigen on the surface of macrophage → releases of cytokines → activate T-cytotoxic cells (CD8+) which destroy the target cell & the macrophage are converted into multinucleated giant cell → granuloma formation e.g. neomycin-induced contact dermatitis



Type III



Type IV

- ii. **Pharmacogenetic (Idiosyncratic) reactions:** genetically-mediated adverse effects e.g.

Slow acetylators are liable to:

- INH-induced neurotoxicity & hepatitis
- Hydralazine-induced SLE

Atypical pseudocholine esterase enzyme →

- Succinylcholine apnoea

G-6-PD deficiency →

- Oxidant drugs induce hemolytic anemia

Mutation in calcium release channel of SR →

- Malignant hyperthermia with halothane+succinylcholine

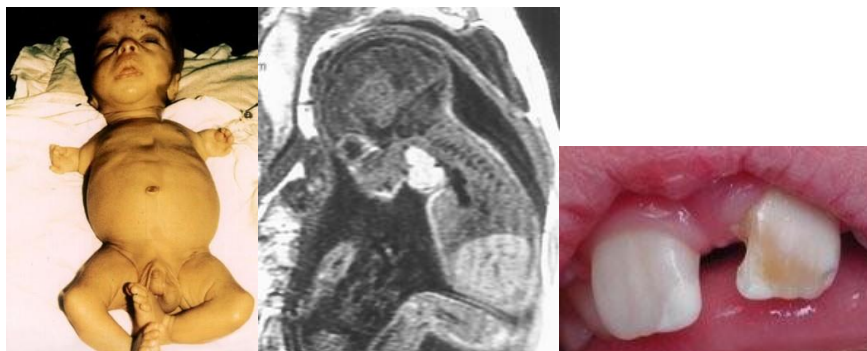
C) Type C or Continuous type:

This adverse effect occurs only with prolonged use of the drug e.g. interstitial nephritis occurs with acetaminophen-aspirin combination for several years

D) Type D or Delayed type: This adverse effect may occur even after drug cessation:

- i. **Teratogenicity**⁹: It is drug-induced fetal malformations. It is caused by drugs given early in pregnancy when the organs are being formed (organogenesis). The most vulnerable period lies between the 3rd and the 10th week of intrauterine life.

Major teratogens: Thalidomide (phocomelia), I¹³¹ (fetal goiter), tetracyclines (dental enamel hypoplasia).



Drugs during pregnancy are assigned letters according to their safety in the first trimester of pregnancy:

A: Controlled human studies show no risk
B: No evidence of risk but there is no controlled studies
C: Risk cannot be ruled out
D: Positive evidence of risk but benefits may be acceptable
X: Contraindicated in pregnancy

- ii. **Mutagenicity:** It is drug-induced gene abnormalities e.g. with metronidazole
- iii. **Carcinogenicity:** It is drug-induced neoplasm e.g. with IM iron or radioactive drugs

E) Type E or End of dose adverse effects:

These are adverse effects that occur after cessation of therapy:

Withdrawal syndrome with morphine

Addisonian crisis with chronic corticosteroid therapy

Ischemic Heart Disease after abrupt cessation of β -blockers

Hypertension after clonidine withdrawal

Thromboembolism after withdrawal of oral anticoagulants

Tardive dyskinesia after cessation of phenothiazines

⁹: Teratos = monster; genesis = production