Pharmacology: It is a branch of science that deals with the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

A drug can be defined as any substance or product that makes changes in biologic function through its chemical actions. Usually, the drug molecule interacts with a specific molecule in the biological system that plays a regulatory role. This molecule is called a receptor.

Clinical pharmacology can be defined as the science that studies the clinical actions and applications of the drugs.

Pharmacology study can be divided into:

- Pharmacokinetics: represents what the body does to a drug.
- Pharmacodynamics: represents what the drug does to the body.

Pharmacokinetics: (ADME)

After administration of drugs through one of the routes of administration, the drugs are absorbed, distributed, metabolized, and finally eliminated.

1- Absorption:

- To enter the bloodstream, a drug must be absorbed from its site of administration (unless the drug has been injected directly into the vascular compartment).
- The rate and efficiency of absorption differ depending on [1]a drug's route of administration, [2]the chemical characteristic of the drug and [3]the environment where a drug is absorbed.
- The amount absorbed into the systemic circulation divided by the amount of drug administered constitutes the drug bioavailability by that route. So, bioavailability is defined as the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a medication is administered intravenously (IV), its bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability generally decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient.

Routes of drug administration:

- The route of administration of a drug is determined primarily by the properties of the drug (water or lipid soluble, ionized or non-ionized), and the aims of the treatment (rapid onset of action, or restriction of treatment to localized area).
- There are two major routes of drug administration, enteral and parenteral. In addition to other routes.

✓ Enteral include oral, sublingual buccal, rectal.
✓ Parenteral: intravenous, intramuscular, and subcutaneous injections.
✓ Other include inhalation, topical, intranasal, transdermal, intrathecal, eyedrops and others (figure 1).

ROUTE AND BIOAVAILABILTY (*F*)	ABSORPTION PATTERN	SPECIAL UTILITY	LIMITATIONS AND PRECAUTIONS
Intravenous	Absorption circumvented	Valuable for emergency use	Increased risk of adverse effects
$F = 1$ by definition	Potentially immediate effects	Permits titration of dosage	Must inject solutions *slowly* as a rule
	Suitable for large volumes and for irritating substances, or complex mixtures, when diluted	Usually required for high-molecular-weight protein and peptide drugs	Not suitable for oily solutions or poorly soluble substances
Subcutaneous $0.75 < F < 1$	Prompt from aqueous solution	Suitable for some poorly soluble suspensions and for instillation of slow-release implants	Not suitable for large volumes
	Slow and sustained from repository preparations		Possible pain or necrosis from irritating substances
Intramuscular $0.75 < F < 1$	Prompt from aqueous solution	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant therapy
	Slow and sustained from repository preparations	Appropriate for self-administration (e.g., insulin)	May interfere with interpretation of certain diagnostic tests (e.g., creatine kinase)
Oral ingestion $.05 < F < 1$	Variable, depends on many factors (see text)	Most convenient and economical; usually safer	Requires patient compliance
			Bioavailability potentially erratic and incomplete

Figure 1: Routes of drug administration (Goodman and Gilman 2018).

Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI (gastrointestinal) tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

A. Passive diffusion:

1. A drug moves from region of high concentration to one of lower concentration.
2. Passive diffusion does not involve a carrier
3. It doesn't require energy because the movement of drugs follows concentration gradient across cell membrane.
4. It is not saturable.
5. It shows a low structural specificity.
6. The vast majority of drugs gain access to the body by this mechanism.
7. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers (figure2).

B. Facilitated diffusion:

1. Other agents can enter the cell through specialized trans-membrane carrier proteins that facilitate the passage of large molecules.
2. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion.
3. It does not require energy.
4. It can be saturated.
5. It may be inhibited by compounds that compete for the carrier.

C. Active transport:

1. It also involves specific carrier proteins that span the membrane.
2. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins.
3. Energydependent active transport is driven by the hydrolysis of ATP (adenosine triphosphate).

4. It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration.
5. The process shows saturation kinetics for the carrier.
6. Active transport systems are selective and may be competitively inhibited by other co-transported substances.

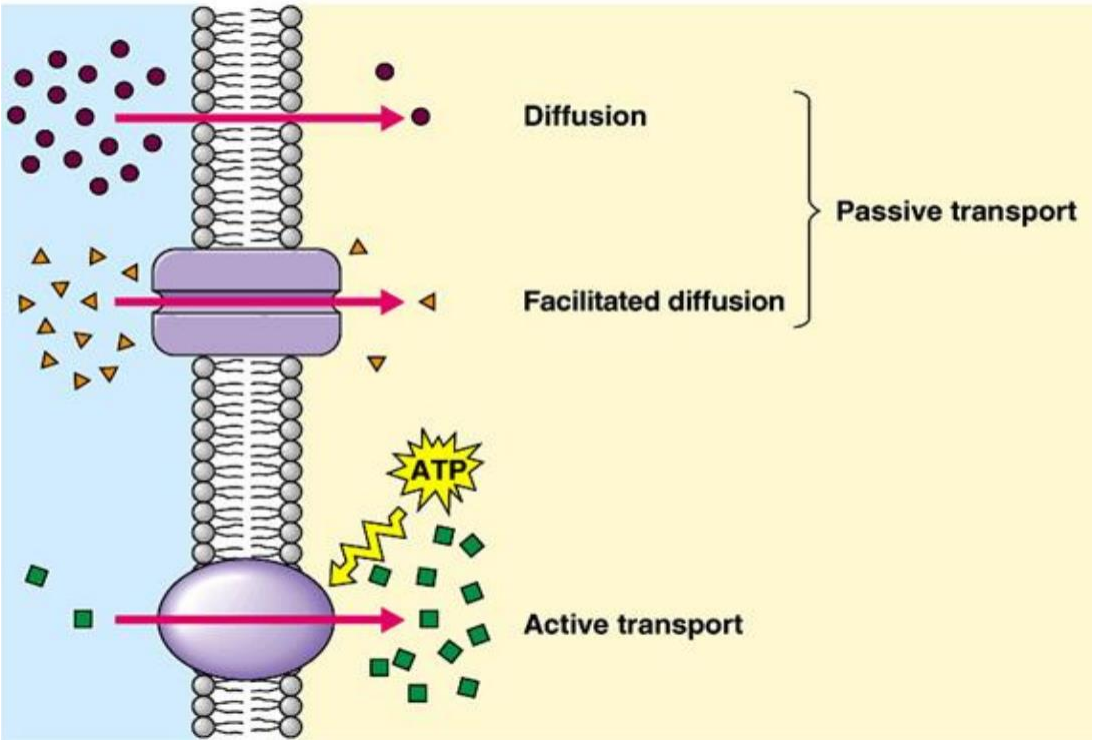

Figure 2: passive and active transport.

D. Endocytosis:

1. Endocytosis occurs through binding of the transported molecule to specialized components (receptors) on cell membranes, with subsequent internalization by in-folding of that area of the membrane. The contents of the resulting intracellular vesicle are subsequently released into the cytoplasm of the cell.
2. Endocytosis permits very large or very lipid-insoluble chemicals to enter cells. For example, large molecules such as proteins may cross cell membranes by endocytosis. Smaller, polar substances such as vitamin B12 and iron combine with special proteins (B12 with intrinsic factor and iron with transferrin), and the complexes enter cells by this mechanism.
3. Because the substance to be transported must combine with a membrane receptor, endocytotic transport can be quite selective.
4. Exocytosis is the reverse process, that is, the expulsion of material that is membrane encapsulated inside the cell from the cell. Most neurotransmitters are released by exocytosis (figure 3).

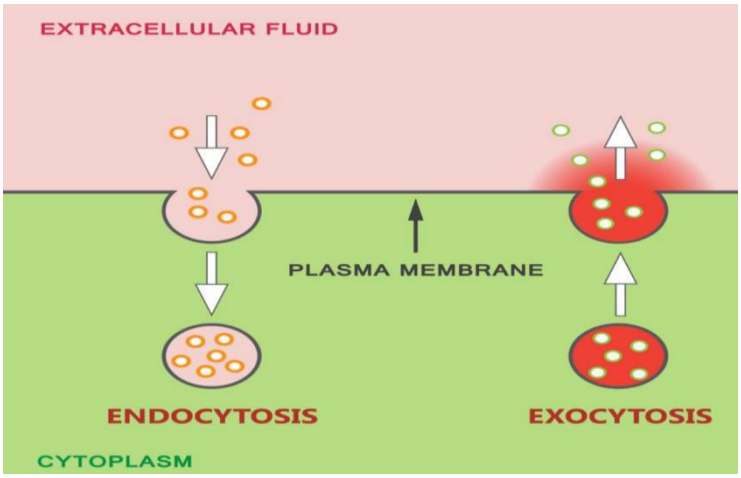

Figure 3: endo and exocytosis

Factors influencing absorption

1- Effect of the pH on drug absorption

Basically, the majority of drugs are either weak acids or weak bases.

Acidic drugs (HA) always release a proton (H+), causing a charged anion (A−) to form:

$HA \leftrightarrow H^{+} + A^{-}$

On the other hand, Weak bases (BH+) can also release an H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$BH^{+} \leftrightarrow H^{+} + B$

An uncharged form of a drug can pass through membranes more readily (Figure 4). For a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not.

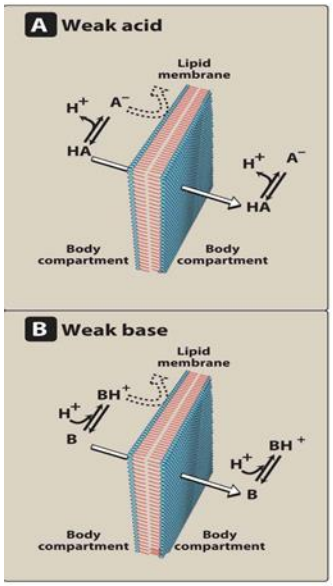

Figure 4: Diffusion of ionized and non-ionized drugs through cell membrane

2-Blood flow to the absorption site: Because blood flow to the intestine is much greater than the flow to the stomach, absorption from the intestine is favored over that from the stomach.

3-Total surface area available for absorption: the intestine has a surface area about 1000- fold that of the stomach, making absorption of the drug across the intestine more efficient.

4-Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

5-Expression of P-glycoprotein: P-glycoprotein is a multidrug trans-membrane transporter protein responsible for transporting various molecules, including drugs, from the intracellular space to the extracellular. P-glycoprotein reduces drug absorption.

Bioavailability (F or BA)

It refers to the degree and rate at which an administered drug is absorbed by the systemic circulation. For instance, if 100 mg of a drug is administered orally and 60 mg is absorbed unchanged, the bioavailability is 0.6 or 60%.

Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration. The bioavailability can be determined by the following equation:

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \text{X } 100$$

Where the AUC oral refers to the area under the blood concentration-time curve of orally administered drugs while the AUC injected represents the area under the blood concentrationtime curve of intravenous (IV) injected drugs (figure 5). The F value of the IV drugs usually equals to 100%; however, for a drug given orally, its bioavailability < 100%. This may be due to incomplete extent of absorption and first pass effect.

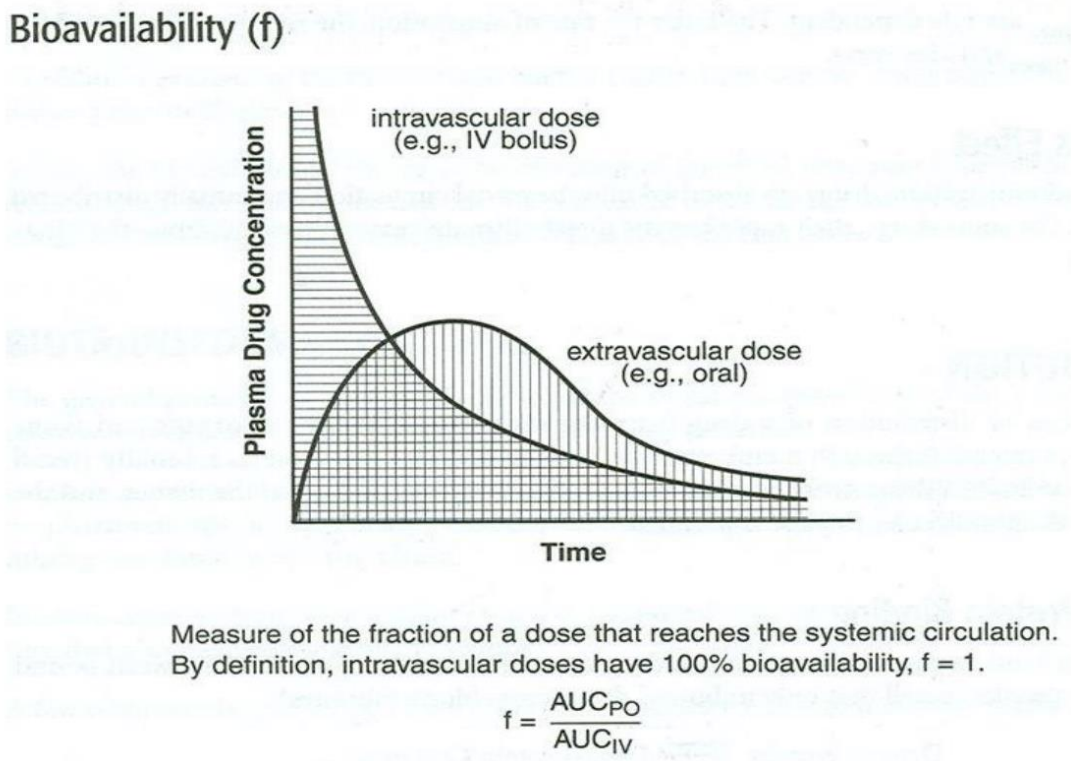

Figure 5: AUC for IV and oral route, and the calculation of bioavailability.

Factors that influence bioavailability:

After oral administration of drugs, the first-pass metabolism, the chemical and physical characteristics of the drug can play an important role in controlling the rate and extent of the drug fraction that reaches the systemic circulation as discussed below.

a- First-pass hepatic metabolism: After absorption of a drug from the GI tract, it will enter the portal circulation before entering the systemic circulation (figure 6). If the drug is rapidly metabolized in the liver or gut wall, a marked decrease in the amount of the unchanged drug will be recorded in the systemic circulation.

First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of nitroglycerin is cleared during first-pass metabolism. Therefore, it is primarily administered via the sublingual or transdermal route. So, drugs that extensively metabolized by liver or intestine should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

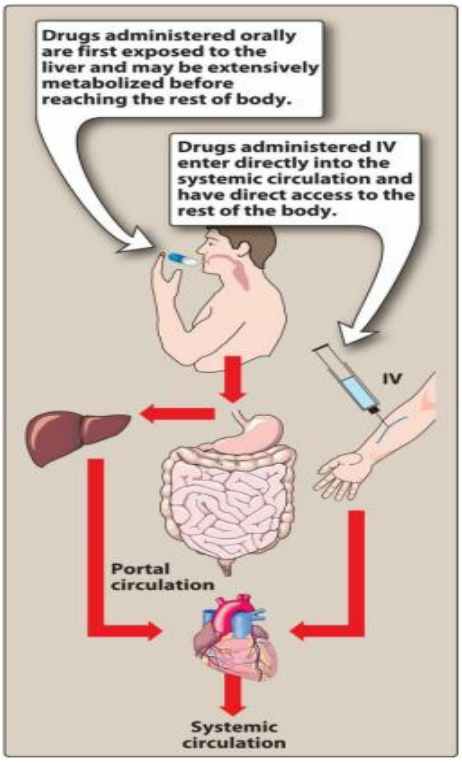

Figure 6: First pass metabolism.

b- Solubility of the drug:

- Very hydrophilic (water-soluble) drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes.
- Drugs that are extremely hydrophobic (lipophilic, lipid-soluble) are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells.
- For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

c- Chemical instability: Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes.

d- Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients, can influence the ease of dissolution and, therefore, alter the rate of absorption.

2- Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enter the interstitium (extracellular fluid) and then the cells of tissue. The delivery of a drug from the plasma to the interstitium primarily depends on blood flow, capillary permeability, the degree of binding of the drug to plasma and tissue proteins, and the relative hydrophobicity of the drug.

There are four main elements to this:

1- Distribution into body fluids mainly plasma, interstitial fluid and intracellular fluid.

2- Uptake into body tissues/organs. Some drugs are concentrated or accumulated in tissues or some organs of the body, which can lead to toxicity on chronic use. For example, tetracyclines—bones and teeth; thiopentone — adipose tissue; chloroquine—liver and retina; digoxin—heart, etc.

3- Extent of plasma protein binding. Plasma proteins such as albumin can bind drug molecules. This varies widely among drugs. Drugs bound to plasma proteins are pharmacologically inert. Some are highly bound (e.g. warfarin which is 99 per cent bound to plasma proteins). Some drugs can displace others from their binding sites on the plasma proteins e.g. phenylbutazone can displace warfarin from plasma proteins, which can lead to hemorrhage (bleeding).

4- Passage through barriers. The two main examples are the placenta and the blood brain barrier (BBB). Drugs must be highly lipid soluble to pass across these barriers. If not, they may not be able to reach their site of action.

3- Metabolism (Biotransformation)

Biotransformation of drugs is the process of metabolizing the parent drug compound and occurs mainly in the liver to different compounds called metabolites. The drug metabolite may have decreased, increased or undergone no change in pharmacological activity compared to the parent drug. Some drugs are what are termed pro-drugs that is the drug itself is pharmacologically inactive until it is metabolized by the liver to its active form. A good example is codeine, which is metabolized to the active form morphine by the body.

Metabolism of drugs can be divided into:

1- Phase I: reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or –NH2. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

2- Phase II: This phase consists of conjugation reactions. If the metabolite from phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic

acid, or an amino acid, results in polar, usually more water-soluble compounds that are often therapeutically inactive.

Metabolism of drugs can be altered through changes in hepatic enzymes as explained below:

Enzyme Induction: Repeated administration of certain drugs increases the synthesis of microsomal enzymes which results in accelerated substrate metabolism and usually in a decrease in the pharmacologic action of the inducer and also of co-administered drugs .This is known as enzyme induction. The drug is referred to as an enzyme inducer, e.g. rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, etc.

Enzyme Inhibition: Certain drugs inhibit the activity of drug-metabolizing enzymes and are known as enzyme inhibitors, e.g. chloramphenicol, ciprofloxacin, erythromycin, etc. Enzyme inhibition is a rapid process as compared to enzyme induction.

4- Elimination

- Removal of the drug and its metabolite from the body is known as drug excretion.
- The main channel of excretion of drugs is the kidney; others include lungs, bile, faeces, sweat, saliva, tears, milk, etc.
- Kidney: The processes involved in the excretion of drugs via kidney are glomerular filtration, passive tubular reabsorption and active tubular secretion. Glomerular filtration and active tubular secretion facilitate drug excretion whereas tubular reabsorption decreases drug excretion.
- Rate of renal excretion= (Rate of filtration + Rate of secretion)- Rate of reabsorption

a. **Glomerular filtration**: Drugs with smaller molecular size are more readily filtered. The extent of filtration is directly proportional to the glomerular filtration rate (GFR) and to the fraction of the unbound drug in plasma.

b. **Passive tubular reabsorption:** The main factor affecting the passive reabsorption is the pH of the renal tubular fluid and the degree of ionization. Strongly acidic and strongly basic drugs remain in ionized form at any pH of urine and hence are excreted in urine.

i. Weakly acidic drugs (e.g. salicylates, barbiturates) in acidic urine remain mainly in 'unionized' form; so they are reabsorbed into the circulation. If the pH of urine is made alkaline by sodium bicarbonate, the weakly acidic drugs get 'ionized' and are excreted easily.

ii. Similarly, weakly basic drugs (e.g. morphine, amphetamine, etc.) in alkaline urine remain in 'unionized' form, hence are reabsorbed. If the pH of urine is made acidic by vitamin C (ascorbic acid), the basic drugs get 'ionized' and are excreted easily.

c. **Active tubular secretion:** It is a carrier-mediated active transport that requires energy. Active secretion is unaffected by changes in the pH of urine and protein binding. Most of the acidic drugs (e.g. penicillin, diuretics, probenecid, sulphonamides, etc.) and basic drugs (e.g. quinine, procaine, morphine, etc.) are secreted by the renal tubules. The carrier system is relatively nonselective and therefore drugs having similar physicochemical properties compete for the same carrier system. For example, probenecid competitively inhibits the tubular secretion of penicillins/cephalosporins, thereby increases the duration of action as well as the plasma half-life and effectiveness of penicillins in the treatment of diseases such as gonococcal infections.

Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body.

The effect of the drugs can be one of the following:

1. Stimulatory: Some drugs act by increasing the activity of specialized cells, e.g. adrenaline stimulates the heart resulting in an increase in heart rate and force of contraction.
2. Depressive: Some drugs act by decreasing the activity of specialized cells, e.g. alcohol, barbiturates, general anaesthetics, etc. depress the central nervous system.
3. Irritant: Certain agents on topical application can cause irritation of the skin and adjacent tissues.

4. Replacement: When there is a deficiency of endogenous substances, they can be replaced by drugs, e.g. insulin in diabetes mellitus, thyroxine in cretinism and myxedema, etc.
5. Cytotoxic: Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/ anticancer drugs.

Mechanism of action of drugs

Although the majority of drugs work through interaction with specialized biological molecules called receptors, there are few groups of drugs that do not relay on receptors to mediate their effect. For example, medication that **depend on physical properties** (osmosis, adsorption, radioactivity), **chemical properties** (antacids, chelating agents).

Drug with receptors mediated mechanisms

Cells have different types of receptors, each of which is specific for a particular ligand. The term "ligand" refers to a small molecule that binds to a site on a receptor protein and produces a unique response.
Drug + Receptor ⟷ Drug–receptor complex → Biologic effect
The receptors may be divided into four families:
A) Ligand-gated ion channels,
B) G protein–coupled receptors,
C) Enzyme–linked receptors,
D) Intracellular receptors (figure 7).

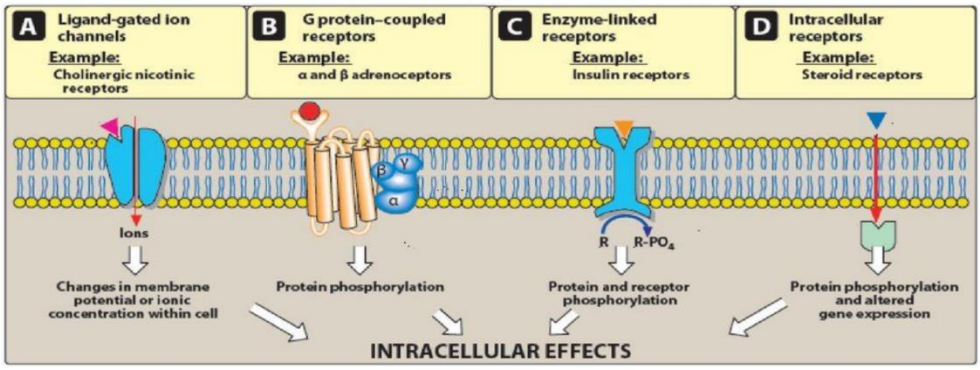

Figure 7: types of receptors.

According to the intrinsic activity of the drugs, they are classified into agonist and antagonist drugs.
An agonist drug can be defined as a chemical that binds to and activates the receptor to produce a biological response.
Agonist drugs has been sub-classified into:
1- **Full agonist:** If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist.
2- **Partial agonists:** drugs that bind to and activate a given receptor but have only partial efficacy at the receptor relative to a full agonist.
3- **Inverse agonist:** is a ligand that binds to the same receptor-binding site as an agonist; however, it produces an opposite effect by suppressing spontaneous receptor signaling (when present). (Figure 8)

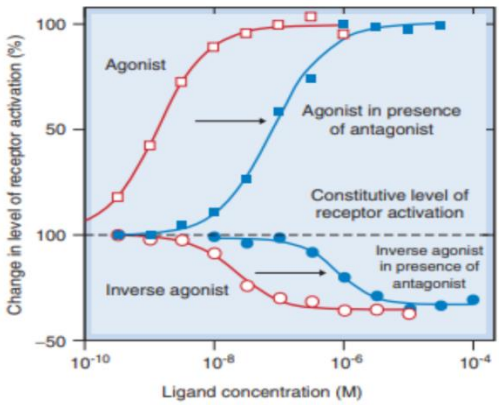

Figure 8: inverse agonist

4- **Agonists that Inhibit their binding molecules**: Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, acetylcholine esterase inhibitors, by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the actions of cholinoceptor agonist molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors. Because they amplify the effects of physiologically released agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

The antagonists are type of receptor ligands or drugs that block a biological response by binding to and blocking the receptors rather than activating them like an agonist. They are sometimes called blockers. Different types of antagonist drugs were recognized, which are:

1- **Competitive antagonists** can be defined as the drugs that bind to receptors at the same binding site as the endogenous ligand or agonist, but without activating the receptor. Agonists and antagonists "compete" for the same binding site on the receptor. Once bound, an antagonist will block agonist binding.

2- **Irreversible antagonists** can be defined as the drugs that bind to the receptors or targets molecule in a manner which makes them impossible to reverse the binding (bind by covalent bond). No amount of agonist will overcome this sort of bond.

3- And finally, **the functional antagonisms or physiological antagonism,** which can be observed when an antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. Take for example the glucocorticoids which increase the blood sugar while the insulin lowers it, but the two drugs act by completely different pathways.

Duration of Drug Action Termination of drug action is a result of one of several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, and dissociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has dissociated because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized.

Therapeutic index: The concept of therapeutic index aims to provide a measure of the margin of safety of a drug, by drawing attention to the relationship between the effective and toxic doses (Figure 9)

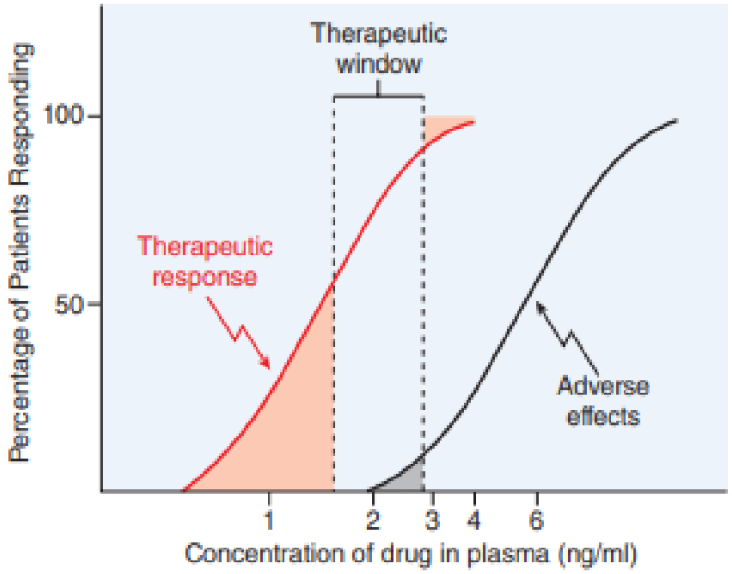

Figure 9: therapeutic index