Pharmacology: General concepts

Pharmacology is the branch of science that studies the drug properties and its actions when binds with the specified biological receptors. Depending on a drug dose, different effects can be observed in living body, which either a desirable effect (the therapeutic effect) or an undesirable effect (the side effects of the drug).

A **drug** can be defined as a natural or synthetic substance that can affect a function or a structure of living body. It can be used in diagnosing, treating and/or preventing a disease or discomfort situations. Usually, the activation process of the drug inside the living body occurred by interacting with a receptor which is a specialised target macromolecule present on the cell surface or within the cell.

Clinical pharmacology can be defined as the science that studies the clinical actions and applications of the drugs, by exploring:

1- The drug **pharmacokinetics** (represents what the body dose to a drug).
2- The drug **pharmacodynamics** (represents what the drug dose to the body) of the drugs.

Pharmacokinetics is represented by four process which are absorption, distribution, metabolism and elimination.

Route of drug administrations: The common routes of a drug administration were summarised in the figure 1.

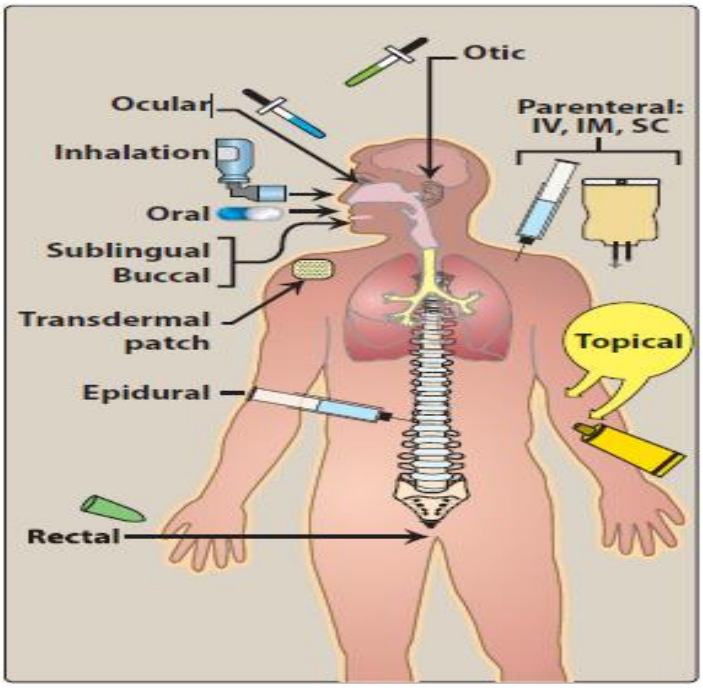


Figure 1: Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

Drug pharmacokinetics

As was mentioned above the drug pharmacokinetics studies what the living body does to a drug i.e. how will it be absorbed, distributed, metabolised and excreted outside the body.

Absorption

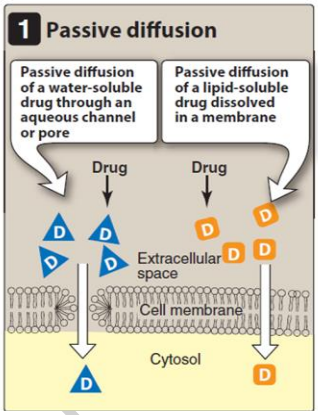
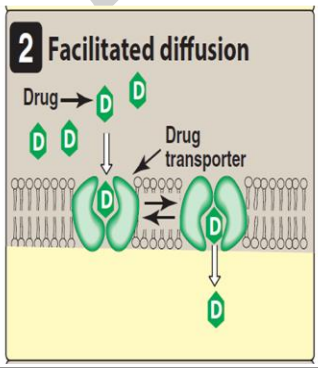
Absorption is the transfer of a drug from the site of administration to bloodstream. The rate and extent of absorption depend on

1- The environment where a drug is absorbed.
2- Chemical characteristics of a drug.
3- The route of administration (which influences bioavailability).

A. Mechanisms of absorption of drugs from the GI tract (GIT)

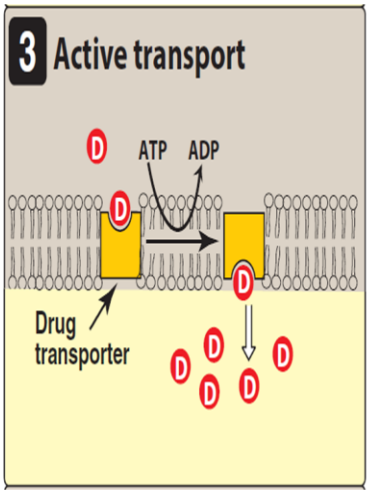
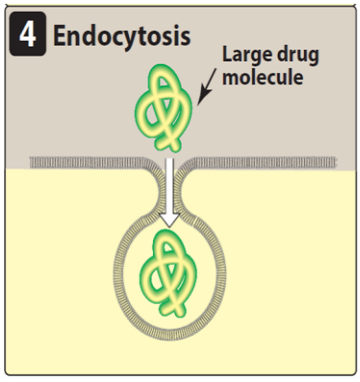
A drug absorption usually followed one of the process that demonstrated in table 1 and 2. These tables shows a brief explanation about each absorption mechanism

Table 1: Schematic representation of drugs crossing a cell membrane by passive diffusion and facilitated transport. with brief explanation about these absorption mechanisms.

Absorption process	Features
	1. A drug moves from region of high concentration to one of lower concentration. 2. Does not require a carrier and not saturable. 3. Lipid soluble drugs have freely movement through the biological membrane than that of the water- soluble drugs as the former has high solubility in the membrane lipid bilayers. 4. The vast majority of the drugs is absorbed into bloodstream using this mechanism.
	1. A drug moves from region of high concentration to one of lower concentration. 2. Requires a carrier and it is saturable; however, this mechanism does not require energy to transport a drug molecule. 3. It can be inhibited by a compound that competes for the carrier.

The other two mechanisms of absorption are the active transport and the endocytosis, which were explained briefly in table 2.

Table 2: Schematic representation of drugs crossing a cell membrane by active transport and endocytosis mechanisms with brief explanation about these absorption mechanisms. (ATP = adenosine triphosphate; ADP = adenosine diphosphate).

Absorption process	Features
	1- It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. 2- Requires a carrier and saturable; however, it does require energy by hydrolysing the ATP. 3- Drugs transport by this process has to be structurally similar to the naturally occurring metabolites. 4- Active transport systems are selective and may be competitively inhibited by other cotransported substances.
	1- For transporting of large size molecules across the cell membrane. 2- Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug filled vesicle. (e.g. Vitamin B 12) 3- Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation like releasing of norepinephrine from the nerve terminal.

B- Factors influencing absorption

1- Effect of the pH (pH of the medium) 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:

$$HA \rightleftharpoons H^+ + A^-$$

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):

$$BH^+ \rightleftharpoons H^+ + B$$

An uncharged form of a drug can pass through membranes more readily as demonstrated in figure 2; hence, 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.

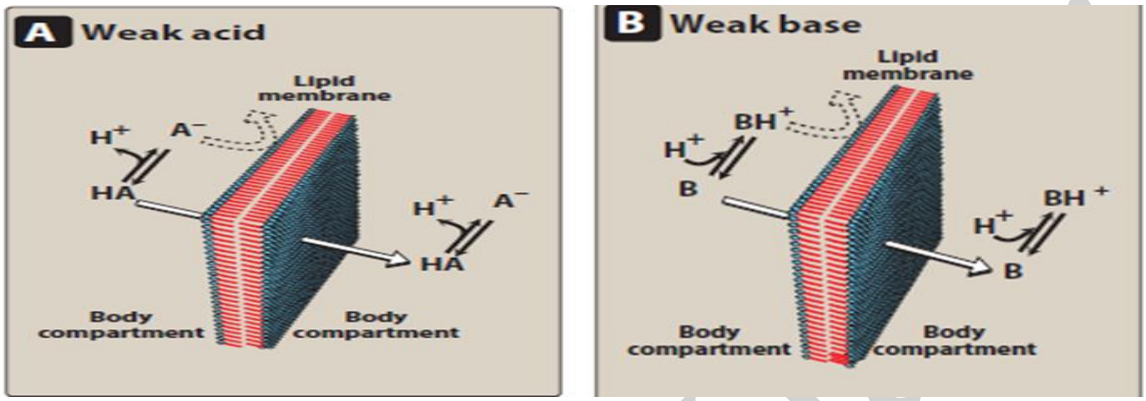


Figure 2: A. Diffusion of the nonionized form of a weak acid through a lipid membrane. B. Diffusion of the nonionized form of a weak base through a lipid membrane.

The ratio between the protonated and deprotonated forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pKa. The pKa is a measure of the strength of the interaction of a compound with a proton.

The lower the pKa of a drug, the more acidic it is. Conversely, the higher the pKa, the more basic is the drug. The relationship between pH and pKa can be summarised in three cases:

1. **pH = pKa, [HA] = [A–] and [BH+] = [B].**
2. **pH < pKa the protonated forms HA and BH^+ predominate**
3. **pH > pKa the deprotonated forms A^- and B predominate.**

2- Blood flow to the absorption site: The blood flow to a drug absorption site can significantly affect the drug absorption as the higher blood flow leads to higher drug absorption rate. This explains why a drug absorption rate is higher in intestine than in the stomach as the former has higher blood flow.

3- Total surface area available for absorption: With a surface rich in brush borders containing microvilli, 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 diarrhoea, 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 take for the example, presences of food inside the stomach can dilute the drug and slow the gastric emptying time.

5- **Expression of P-glycoprotein:** P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, from tissues to blood. Thus, in areas of high expression, P-glycoprotein reduces drug absorption.

C- 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:

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

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 concentration-time curve of intravenous (IV) injected drugs (figure 3). 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.

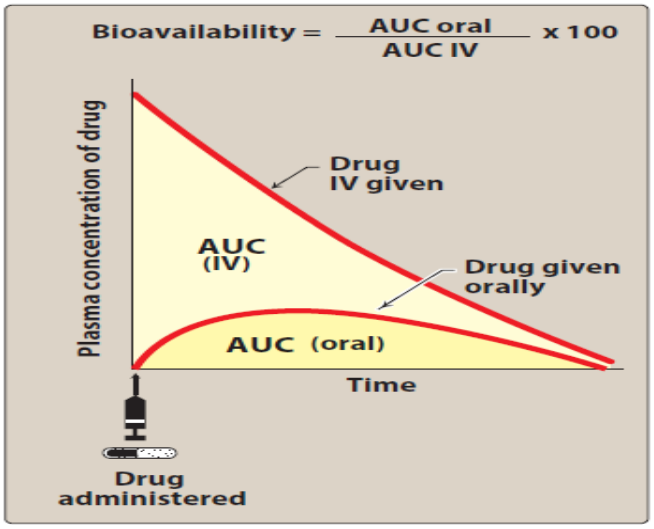


Figure 3: The difference between the bioavailability of a drug administered by IV and oral route.

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

4). 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 metabolise by liver or intestine should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

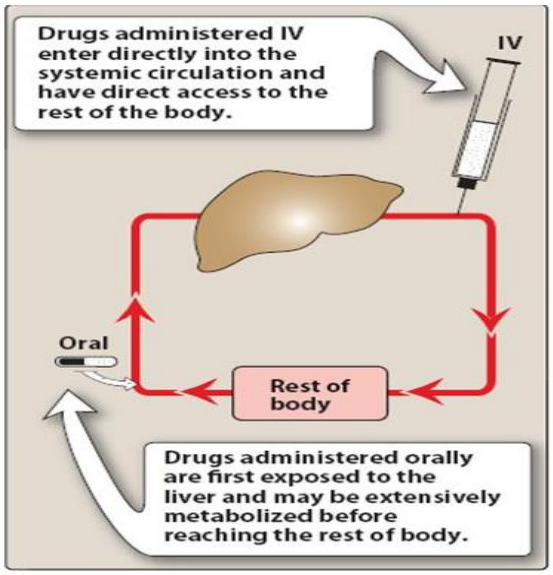


Figure 4: First- pass metabolism for orally administered drugs.

b- Solubility of the drugs: To get a high bioavailability for a drug, the drug itself has to be largely lipophilic, yet have some solubility in aqueous solutions. Because if the drug is very hydrophilic, this will inhibit the crossing through the lipid-rich cell membranes. On the other hand, if the drug is extremely hydrophobic, this will make it insoluble in aqueous body fluids, hence, cannot gain access to the surface of the cell.

c- Chemical instability: If the drug is chemically unstable this will reduce its bioavailability for example: *penicillin G,* are unstable in the pH of the gastric contents while the 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 related to the physical properties of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients as these factors can influence the ease of dissolution and, therefore, alter the rate of absorption.

Distribution

Drug distribution can be defined as the post absorptive transfer of drug from one location in the body to another. Different factors can affect the distribution process which are:

1- Cardiac output and local blood flow.
2- Capillary permeability.
3- The degree of binding of the drugs to plasma and tissue proteins.
4- The relative lipophilicity of the drugs.

To characterise the drug distribution, the volume of distribution (V) is used, which can be defined as the primary pharmacokinetics parameter that relates drug concentration measured in plasma or blood to the amount of drug in the body. It can be calculated using the following equation:

$$V = \frac{Amount\ of\ drug\ in\ the\ body}{The\ plasma\ \boldsymbol{concentration}\ of\ drug\ at\ time\ zero}$$

Metabolism (Biotransformation)

Drug metabolism may be defined as the biochemical modification of one chemical form to another, occurring usually through specialised enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body.

Drug metabolism involves two phases, which are phase I and Phase II (figure 5). 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. Mainly, the family of enzymes associated with these metabolic reactions is the cytochrome P450 family. The cytochrome P450s can be induced or inhibited by some drugs for example they can be induced by rifampin and inhibited by ketoconazole.

Phase II consists of conjugation reactions. If the metabolite from phase I metabolism is sufficiently polar, it can be directly 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 or acetic acid results in polar, usually more water-soluble compounds that are often therapeutically inactive. **A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine*.** Glucuronidation is the most common and the most important conjugation reaction. The highly polar drug conjugates are then excreted by the kidney or in a bile.

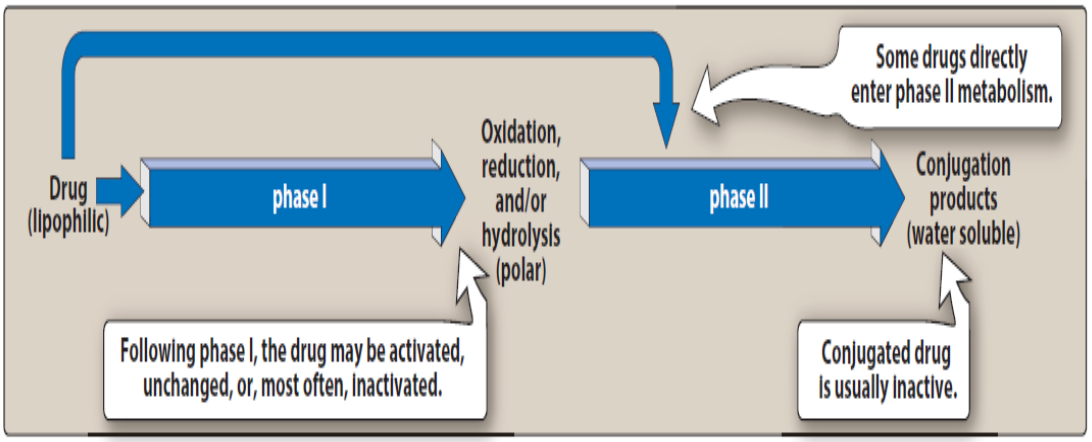


Figure 5: The biotransformation of drugs.

Factors influencing metabolism:

Factors that influence the drug metabolism process were summarised in figure 6, in which some examples were demonstrated regarding each factor.

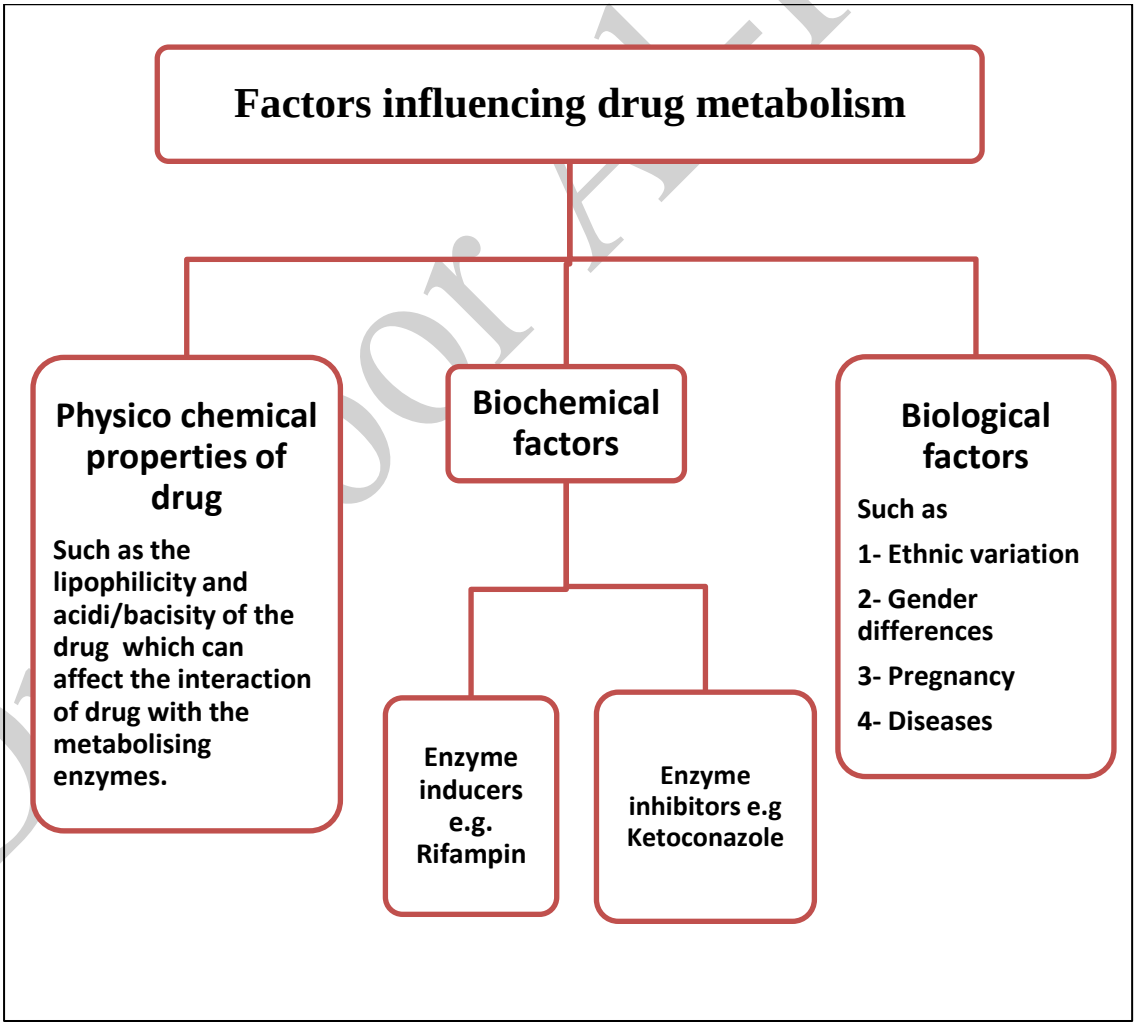


Figure 6: Summary of factors that influence the drug metabolism.

It is noteworthy to mention that the biotransformation process is not confined to transferring the active form of the drug to its metabolites to be excreted outside the living bodies, as it can also help to activate some drugs to their pharmacologically active forms. These types of drugs are called prodrugs. One of the best examples of transferring the drug from its inactive form to its active form is the **Levodopa**, which is metabolised to Dopamine.

Excretion (elimination)

Excretion is the removal of drugs and their metabolites from the living bodies. There are several routes for drug elimination from the body; however, the main one is the renal system or the hepatic system as most of the drugs are eliminated by pathways that involve the kidneys or the liver.

Renal excretion plays an important role in eliminating unchanged drugs or their metabolites into urine. A major characteristic of compounds excreted in urine is that they are polarised (i.e., charged) and water-soluble.

On the other hand, drugs that are lipid soluble are not readily removed by the kidneys and require hepatic metabolism (e.g., phase I and phase II biotransformation reactions) to increase their water solubility for possible urinary excretion. Drugs entering the hepatic circulation may also enter the bile and be excreted into the duodenum, small intestines and then in feces.

In some cases, drugs may also be excreted from the body through the lungs, milk, sweat, tears, skin, hair, or saliva. These are considered secondary processes for drug excretion.

Factors influencing drugs excretion

Different factors can affect a drug excretion which are:

1- Physico chemical properties of drugs such as:
    a. Molecular weight
    b. Lipid solubility
    c. Binding character
    d. Volume of distribution
    e. Degree of ionisation
2- Urine pH.
3- Blood flow to the organs like kidneys and liver.
4- Biological factors e.g. age.
5- Diseases state.

Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors. Pharmacology defines a receptor as any biologic molecule to which a ligand binds and produces a measurable response. The ligands can be defined as a molecule that binds to a site on a receptor protein and produces a unique response. The richest sources of therapeutically relevant pharmacologic receptors are proteins that transduce extracellular signals into intracellular responses.

Receptors may be divided into four families: 1) ligand-gated ion channels, 2) G protein–coupled receptors, 3) enzyme-linked receptors, and 4) intracellular receptors (figure 7). The type of receptor a ligand interacts with depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface (figures 7 A, B, C). In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside the cells (figure 7D).

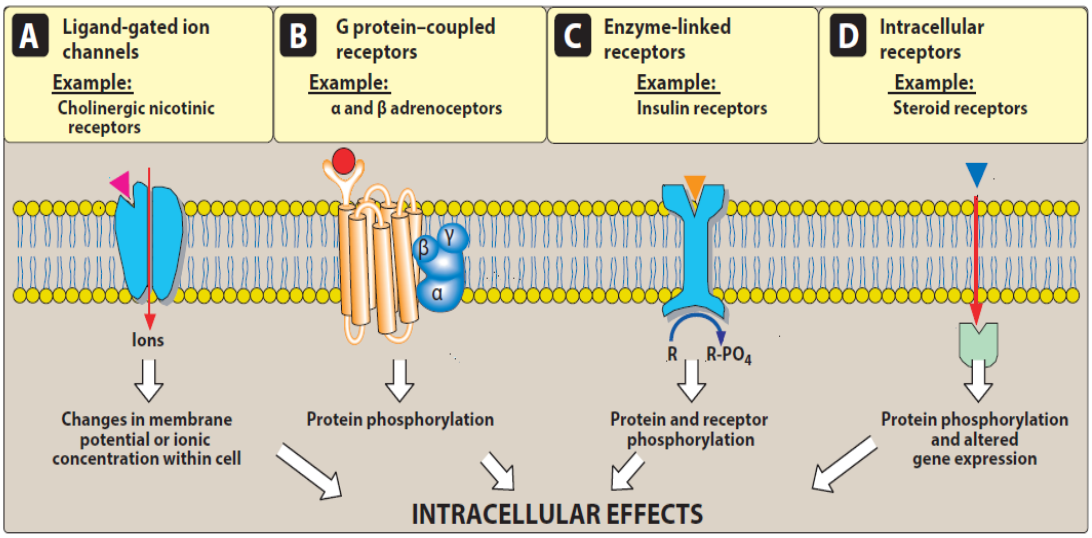


Figure 7: Transmembrane signalling mechanisms. A. Ligand binds to the extracellular domain of a ligand-gated channel. B. Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. D. Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

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- P**artial 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 signalling (when present).

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 recognised, 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.