
# Distribution

Manas Bhowmik

# Introduction

- After entry into the systemic circulation, either by intravascular injection or by absorption from any of the various extravascular sites, the drug is subjected to a number of processes called as disposition processes.
- Disposition is defined as the processes that tend to lower the plasma concentration of drug. The two major drug disposition processes are –
    1. Distribution which involves reversible transfer of a drug between compartments.
    2. Elimination which causes irreversible loss of drug from the body.
- Elimination is further divided into two processes –

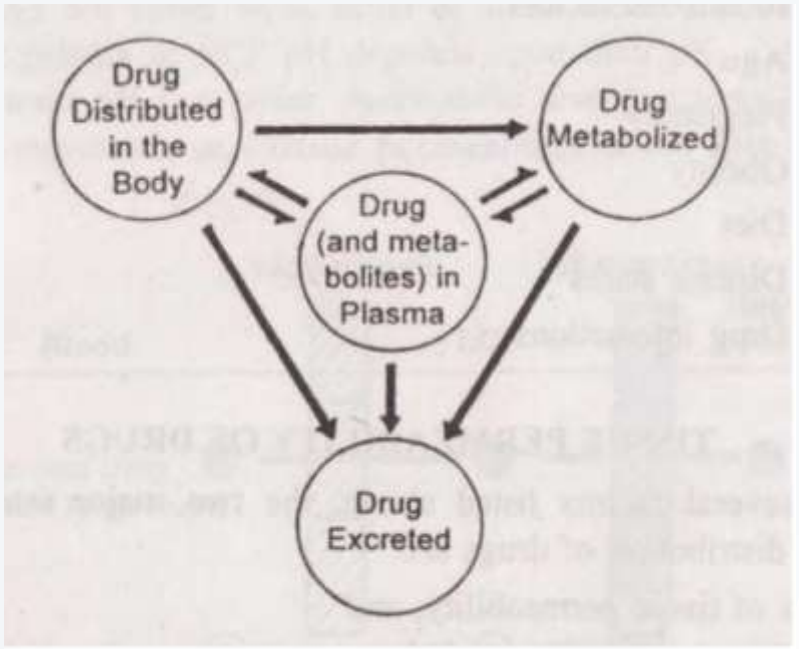
  (a) Biotransformation (metabolism)

  (b) Excretion.

# Contd.

Distribution is defined as the reversible transfer of a drug between one compartment and another. Since the process is carried out by the circulation of blood, one of the compartments is always the blood or the plasma and the other represents extravascular fluids and other body tissues.

In other words, distribution is reversible transfer of a drug between the blood and the extravascular fluids and tissues.




nterrelationship between different processes of drug disposition

# Steps in Drug Distribution

Permeation of free or unbound drug present in the blood through the capillary wall (occurs rapidly) and entry into the interstitial/extracellular fluid

Permeation of drug present in the ECF through the membrane of tissue cells and into the intracellular fluid. This step is rate-limiting and depends upon two major factors –

(a) Rate of perfusion to the extracellular fluid

(b) Membrane permeability of the drug

# Factors Affecting Distribution of Drugs

**1. Tissue permeability of the drug:**

- a. Physicochemical properties of the drug like molecular size, pKa and o/w partition coefficient
- b. Physiological barriers to diffusion of drugs

**2. Organ/tissue size and perfusion rate**

**3. Binding of drugs to tissue components:**

- a. Binding of drugs to blood components
- b. Binding of drugs to extravascular tissue proteins

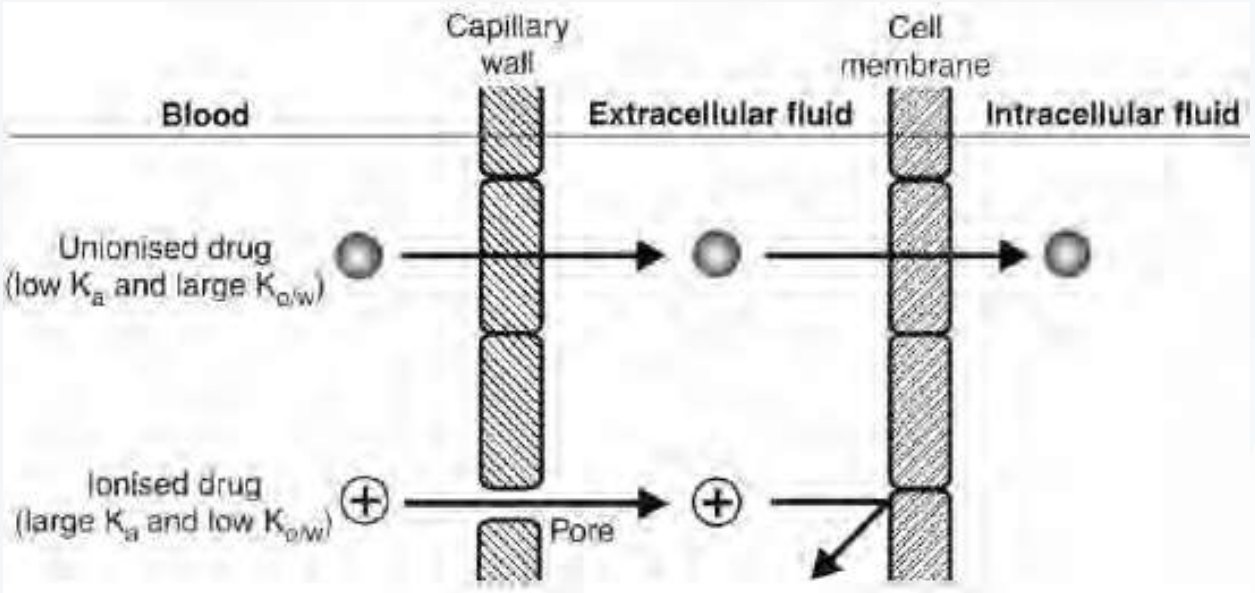
**4. Miscellaneous factors:**

- a. Age
- b. Pregnancy
- c. Obesity
- d. Diet
- e. Disease states
- f. Drug interactions.

# Contd.

Of the several factors listed above, the two major rate-determining steps in the distribution of drugs are -

1. Rate of tissue permeation, and
2. Rate of blood perfusion.




**Physicochemical Properties of the Drug**

- ✓ Molecular size
- ✓ pKa and
- ✓ o/w partition coefficient

# Contd.

*All drugs that ionise at plasma pH (i.e. polar, hydrophilic drugs), cannot penetrate the lipoidal cell membrane and* ***tissue permeability is*** **the rate-limiting step** ***in the distribution of such drugs.***

*In case of polar drugs where permeability is the rate-limiting step in the distribution, the driving force is the* ***effective partition coefficient of drug. It is calculated by the following*** formula:

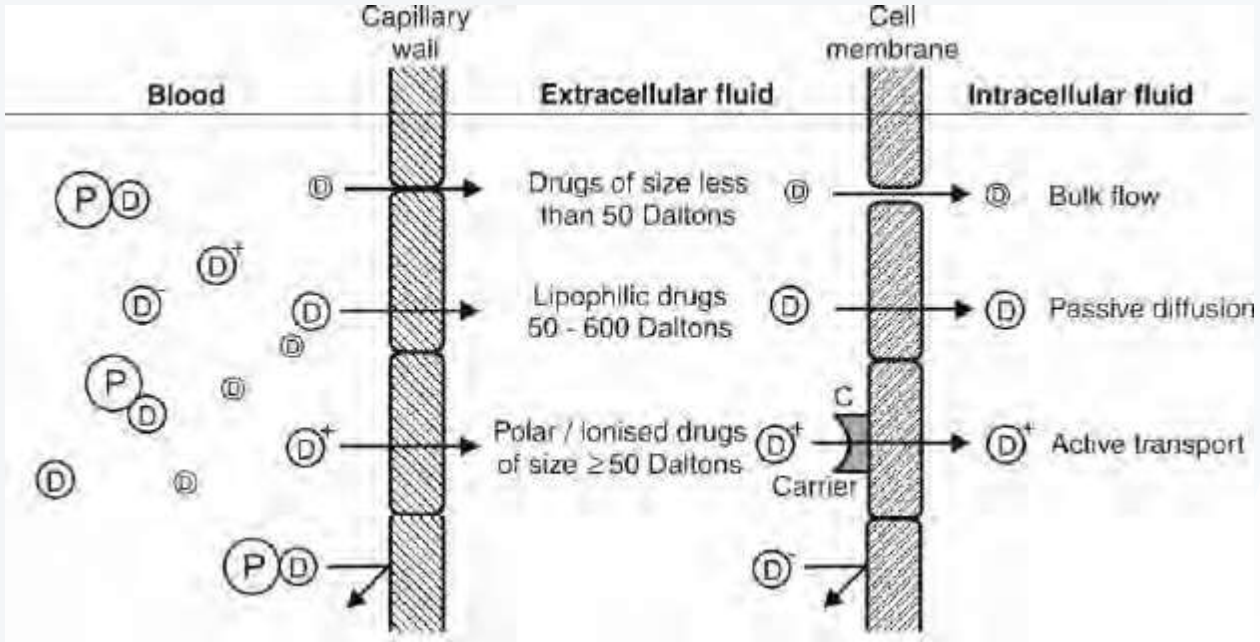
Effective $K_{o/w}$ = (Fraction unionised at pH 7.4) × ($K_{o/w}$ of unionised drug)

# Contd.

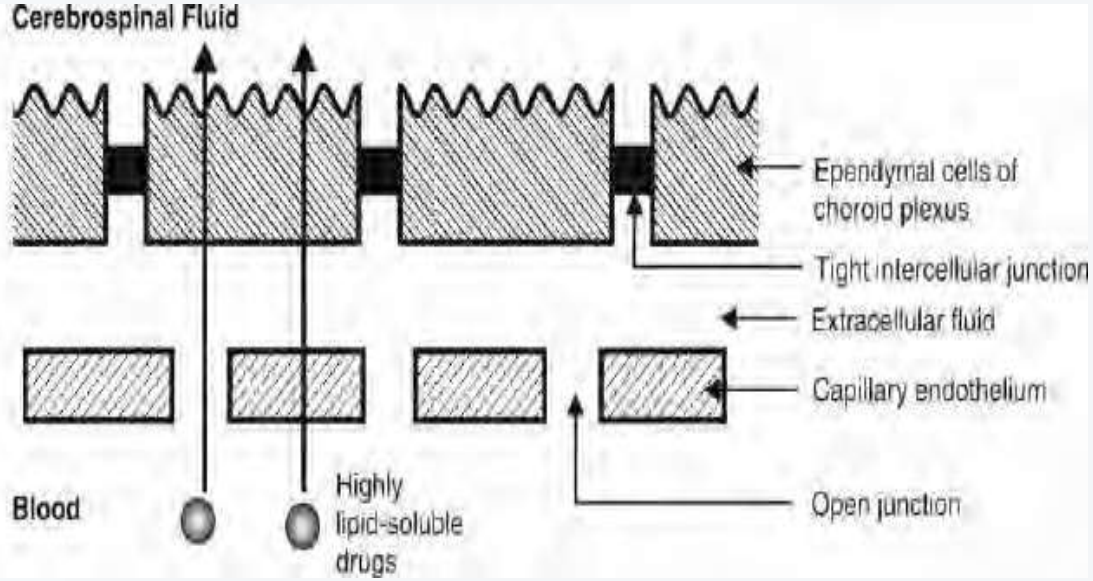
**Physiological Barriers to Distribution of Drugs**

A membrane (or a barrier) with special structural features can be a permeability restriction to distribution of drugs to some tissues. Some of the important simple and specialized physiological barriers are:

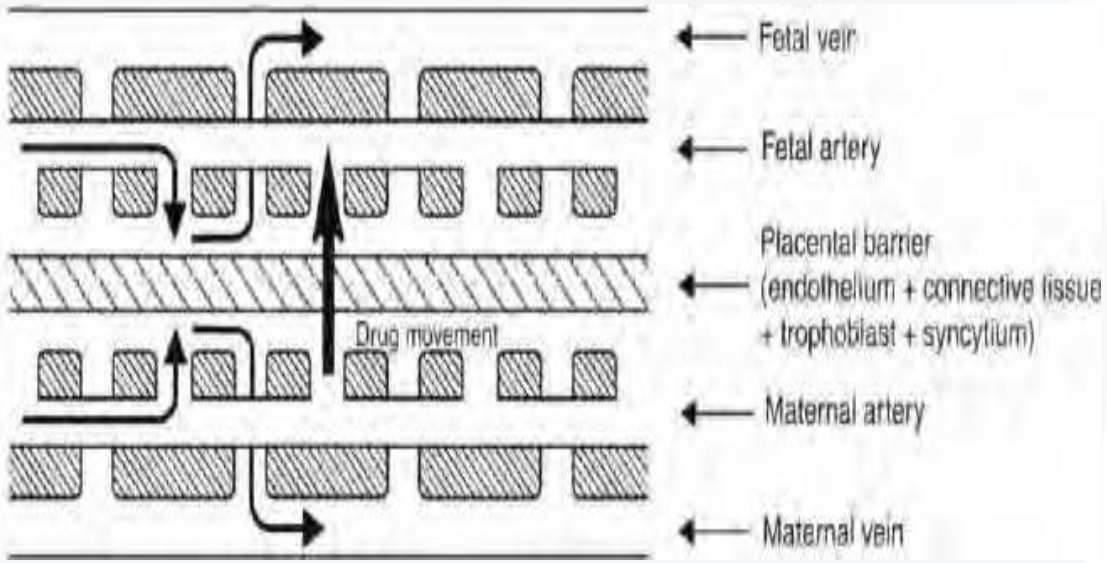
1. Simple capillary endothelial barrier
2. Simple cell membrane barrier
3. Blood-brain barrier
4. Blood-CSF barrier
5. Blood- placental barrier
6. Blood-testis barrier.



# Contd.



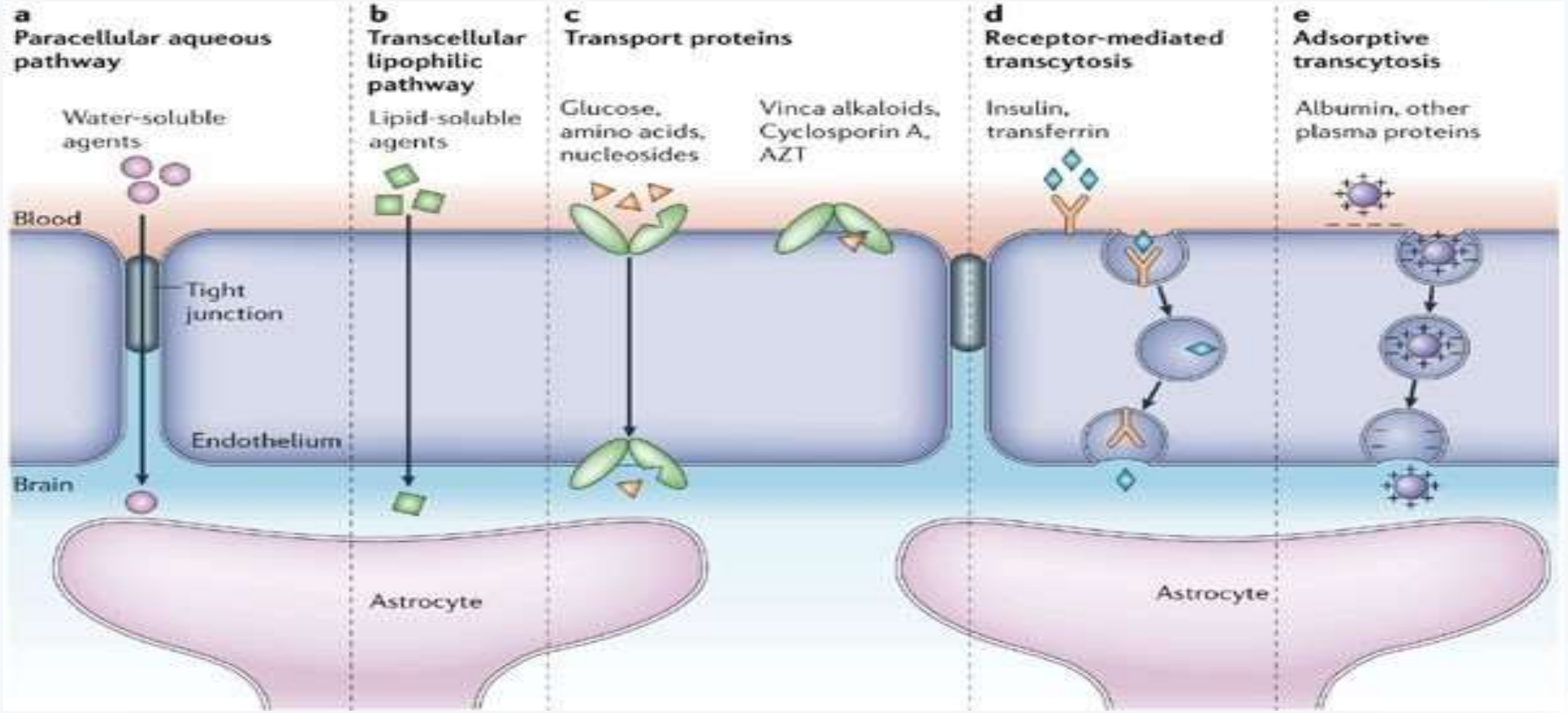

The blood-CSF barrier




Placental barrier and blood flow across it

***Schematic representation of various barriers***

# Contd.




Blood brain barrier

# Contd.

**Organ/tissue size and perfusion rate**

Distribution is **permeability rate-limited in the following cases:**

a. When the drug under consideration is ionic, polar or water-soluble.

b. Where the highly selective physiologic barriers restrict the diffusion of such drugs to the inside of the cell.

In contrast, distribution will be **perfusion rate-limited when**

i. The drug is highly lipophilic.

ii. The membrane across which the drug is supposed to diffuse is highly permeable

such as those of the capillaries and the muscles.

# Contd.

**Perfusion rate** *is defined as the volume of blood that flows per unit time per unit volume of the tissue.*

*It is expressed in ml/min/ml of the tissue.*

If Kt/b is the tissue/blood partition coefficient of drug then the first-order distribution rate constant,

Ktb is given by following equation:

$$K_t = \frac{Perfusion\ rate}{K_{t/b}}$$

The tissue distribution half-life is given by equation:

$$\text{Distribution half life} = \frac{0.693}{K_t} = \frac{0.693K_{t/b}}{Perfusion\ rate}$$

# Contd.

**Binding of drugs to tissue components**

A drug in the body can bind to several components such as the plasma proteins, blood cells and haemoglobin (i.e. blood components) and extravascular proteins and other tissues.

**Miscellaneous factors affecting drug distribution**

**Age:** Differences in distribution pattern of a drug in different age groups are due to differences in—

a. *Total body water (both intracellular and extracellular) — is much greater in* infants

b. *Fat content — is also higher in infants and elderly*

c. *Skeletal muscles — are lesser in infants and in elderly*

d. *Organ composition — the BBB is poorly developed in infants, the myelin content* is low and cerebral blood flow is high, hence greater penetration of drugs in the brain

e. *Plasma protein content — low albumin content in both infants and in elderly*

# Contd.

**Pregnancy:** During pregnancy, the growth of uterus, placenta and foetus increases the volume available for distribution of drugs. The foetus represents a separate compartment in which a drug can distribute. The plasma and the ECF volume also increase but there is a fall in albumin content.

**Obesity:** In obese persons, the high adipose tissue content can take up a large fraction of lipophilic drugs despite the fact that perfusion through it is low. The high fatty acid levels in obese persons alter the binding characteristics of acidic drugs.

# Contd.

**Diet:** A diet high in fats will increase the free fatty acid levels in circulation thereby affecting binding of acidic drugs such as NSAIDs to albumin.

**Disease States:** A number of mechanisms may be involved in the alteration of drug distribution characteristics in disease states:

a. Altered albumin and other drug-binding protein concentration.

b. Altered or reduced perfusion to organs or tissues.

c. Altered tissue pH.

**Drug Interactions:** Drug interactions that affect distribution are mainly due to differences in plasma protein or tissue binding of drugs.

# Volume of Distribution

At distribution equilibrium, different organs and tissues contain varying concentrations of drug which can be determined by the volume of tissues in which the drug is present. If the concentration of drug in plasma, C, and the amount of drug in the body, X.

$$X \alpha C$$

$$\text{or, } X = Vd\ C$$

Where Vd = proportionality constant having the unit of volume and popularly called as **apparent volume of distribution.**

*It is defined as the hypothetical volume of body fluid into which a drug is dissolved or distributed. It is called as* ***apparent volume because all parts of*** the body equilibrated with the drug do not have equal concentration.

# Contd.

The **plasma volume (3L) can be determined by use of** substances of high molecular weight or substances that are totally bound to plasma albumin, for e.g. high molecular weight dyes such as Evans blue, indocyanine green, I-131 and albumin. When given i.v., these remain confined to the plasma. The total blood volume can also be determined if the haematocrit (% volume of erythrocyte in blood; 2L) is known. Blood volume is 6L.

The **extracellular fluid (ECF) volume (15L) can** be determined by substances that easily penetrates the capillary membrane and rapidly distribute throughout the ECF but do not cross the cell membranes, for e.g. the Na+, Cl-, Br–,SCN– and SO42– ions and inulin, mannitol and raffinose.

# Contd.

The **total body water (TBW) volume (42) can be determined by use of** substances that distribute equally in all water compartments of the body (both intra- and extracellular), for e.g. heavy water (D2O), tritiated water (HTO) and lipid soluble substances such as antipyrine. The **intracellular fluid volume is determined as the difference between** the TBW and ECF volume. The intracellular fluid volume including those of blood cells is approximately 27 litres.

# Contd.

factors that produce an alteration in binding of drug to blood components, result in an *increase in Vd and those that influence drug binding to extravascular components result in* a *decrease in Vd. Other factors that may influence Vd are changes in tissue perfusion and* permeability, changes in the physicochemical characteristics of the drug e.g. ionisation, changes in the body weight and age and several disease states.

Apparent volume of distribution is expressed in litres and sometimes in litres/Kg body weight. The Vd of various drugs ranges from as low as 3 litres (plasma volume) to as high as 40,000 litres (much above the total body size).

# Protein Binding

A drug in the body can interact with several tissue components of which the two major categories are –

1. Blood, and

2. Extravascular tissues.

The interacting molecules are generally the macromolecules such as proteins, DNA or adipose.

The proteins are particularly responsible for such an interaction. *The phenomenon of complex formation with proteins is called as* ***protein binding of drugs.***

# Contd.

Protein binding may be divided into –

1. **Intracellular binding –** where the drug is bound to a **cell protein** which may be the drug receptor; if so, binding elicits a pharmacological response. *These receptors with which drug interact to show response are called as* ***primary receptors.***

2. **Extracellular binding –** where the drug binds to an **extracellular protein** but the binding does not usually elicit a pharmacological response. These receptors are called ***secondary or silent receptors.***

# Mechanism of Drug- Protein Binding

Binding of drugs to proteins is generally *reversible which suggests that it generally involves* weak chemical bonds such as –

1. Hydrogen bonds
2. Hydrophobic bonds
3. Ionic bonds, or
4. *van der Waal's forces.*

Irreversible drug binding, though rare, arises as a result of covalent binding and is often a reason for the carcinogenicity or tissue toxicity of the drug; for example, covalent binding of chloroform and paracetamol metabolites to liver results in hepatotoxicity.

# Contd.

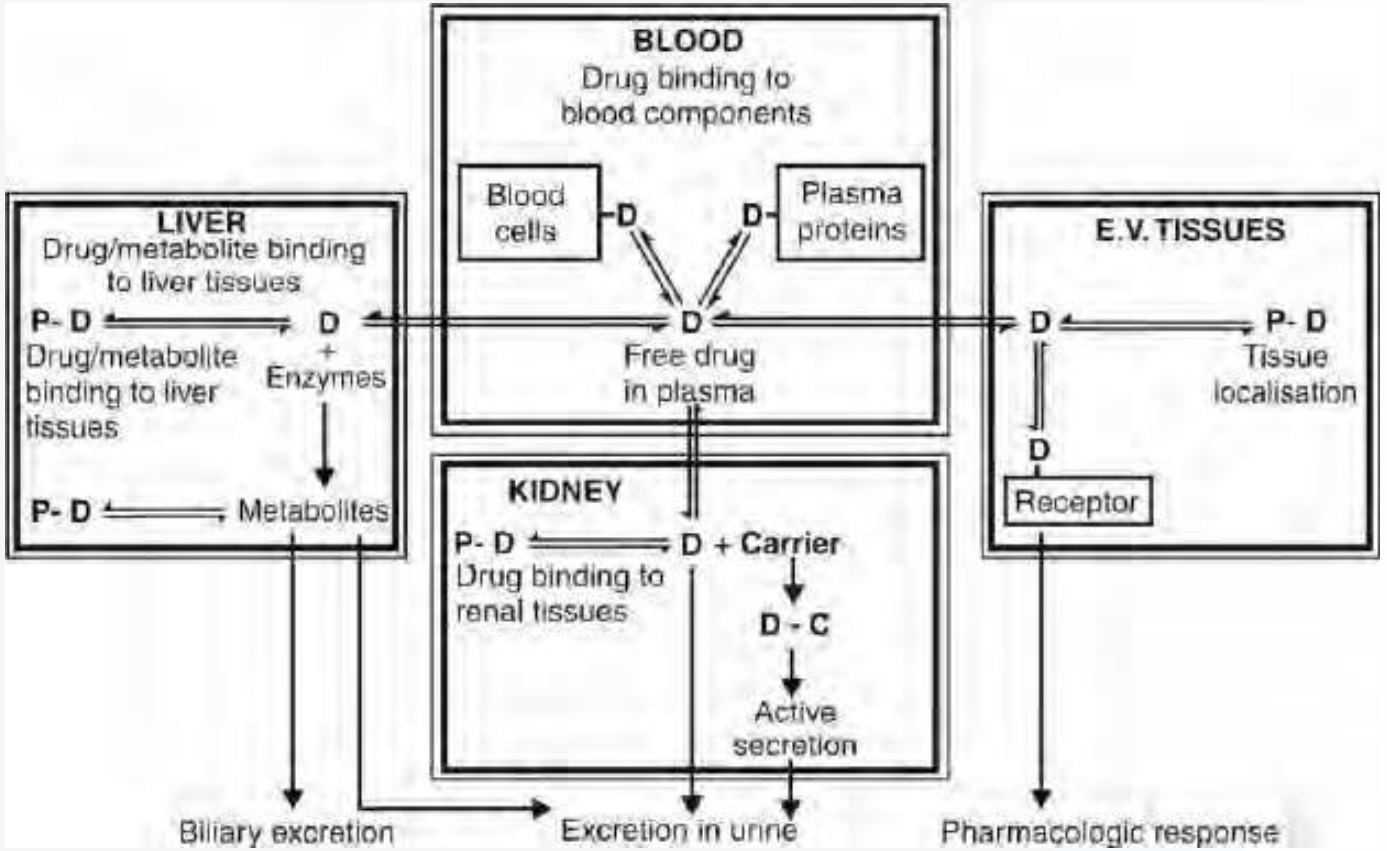
Binding of drugs falls into 2 classes:

1. Binding of drugs to blood components like—

a. Plasma proteins

b. Blood cells

2. Binding of drugs to extravascular tissue proteins, fats, bones, etc.



# Binding of Drugs to Blood Components

**Plasma Protein-Drug Binding**

Following entry of a drug into the systemic circulation, the first things with which it can interact are blood components like plasma proteins, blood cells and. The main interaction of drug in the blood compartment is with the plasma proteins which are present in abundant amounts and in large variety. The binding of drugs to plasma proteins is reversible. The extent or order of binding of drugs to various plasma proteins is:

*Abumin > 1-Acid Glycoprotein > Lipoproteins > Globulins.*

# Contd.

**Binding of Drugs to Human Serum Albumin**

The human serum albumin (HSA), having a molecular weight of 65,000, is the most abundant plasma protein (59% of total plasma and 3.5 to 5.0 g%) with a large drug binding capacity. The therapeutic doses of most drugs are relatively much smaller and their plasma concentration do not normally reach equimolar concentration with HSA. The HSA can bind several compounds having varied structures. Both endogenous compounds such as fatty acids, bilirubin and tryptophan as well as drugs bind to HSA. A large variety of drugs ranging from weak acids, neutral compounds to weak bases bind to HSA.

# Contd.

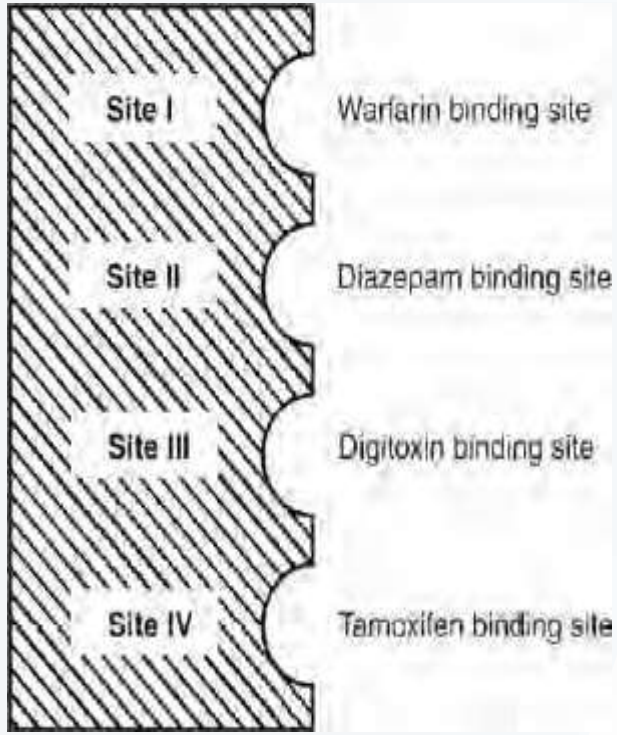
4 different sites on HSA for drug-binding-

**Site I (warfarin and azapropazone binding site):** Large number of drugs are bound, e.g. several NSAIDs (phenylbutazone, naproxen, indomethacin), sulphonamides (sulphadimethoxine, sulphamethizole), phenytoin, sodium valproate and bilirubin.

**Site II (the diazepam binding site):** Drugs which bind to this region include benzodiazepines, medium chain fatty acids, ibuprofen, ketoprofen, tryptophan, cloxacillin, probenicid, etc. Site I and site II are responsible for the binding of most drugs.

**Site III: is also called as digitoxin binding site.**

**Site IV: is also called as tamoxifen binding site.**



# Contd.

**Binding of Drugs to 1-Acid Glycoprotein ( 1-AGP or AAG):** Also called as the **orosomucoid, it has a molecular weight of 44,000 and a plasma** concentration range of 0.04 to 0.1 g%. It binds to a number of basic drugs like imipramine, amitriptyline, nortriptyline, lidocaine, propranolol, quinidine and disopyramide.

**Binding of Drugs to Lipoproteins:** Binding of drugs to HSA and AAG involve hydrophobic bonds. Since only lipophilic drugs can undergo hydrophobic bonding, lipoproteins can also bind to such drugs because of their high lipid content. However, the plasma concentration of lipoproteins is much less in comparison to HSA and AAG.

# Contd.

A drug that binds to lipoproteins does so by dissolving in the lipid core of the protein and thus its capacity to bind depends upon its lipid content. The molecular weight of lipoproteins varies from 2 lakhs to 34 lakhs depending on their chemical composition. They are classified on the basis of their density into 4 categories –

1. Chylomicrons (least dense and largest in size).
2. Very low density lipoproteins (VLDL).
3. Low-density lipoproteins (LDL) (predominant in humans).
4. High-density lipoproteins (HDL) (most dense and smallest in size).

# Contd.

**Binding of Drugs to Globulins:** Several plasma globulins have been identified and are labelled as 1-, 2-, 1-, 2- and - globulins.

1. **1-globulin: also called as transcortin or CBG (corticosteroid binding globulin),** it binds a number of steroidal drugs such as cortisone and prednisone. It also binds to thyroxine and cyanocobalamin.
2. **2-globulin: also called as ceruloplasmin, it binds vitamins A, D, E and K and** cupric ions.
3. **1-globulin: also called as transferrin, it binds to ferrous ions.**
4. **2-globulin: binds to carotinoids.**
5. **-globulin: binds specifically to antigens.**

# Contd.

**Binding of Drugs to Blood Cells:** More than 40% of the blood comprises of blood cells of which the major cell component is the RBC. The RBCs constitute 95% of the total blood cells. Thus, significant RBC drug binding is possible. The red cell is 500 times in diameter as the major plasma protein binding component, albumin.

# Contd.

The RBC comprises of 3 components each of which can bind to drugs:

1. **Haemoglobin:** It has a molecular weight of 64,500 (almost equal to that of HSA) but is 7 to 8 times the concentration of albumin in blood. Drugs like phenytoin, pentobarbital and phenothiazines bind to haemoglobin.

2. **Carbonic Anhydrase:** Drugs known to bind to it are acetazolamide and chlorthalidone (i.e. carbonic anhydrase inhibitors).

**3. Cell Membrane:** Imipramine and chlorpromazine are reported to bind with the RBC membrane.

# TISSUE BINDING OF DRUGS

The body tissues, apart from HSA, comprise 40% of the body weight which is 100 times that of HSA.

1. It increases the apparent volume of distribution of drugs in contrast to plasma protein binding which decreases it. This is because the parameter is related to the ratio of amount of drug in the body to the plasma concentration of free drug and the latter is decreased under conditions of extensive tissue binding of drugs.

2. Tissue-drug binding results in localization of a drug at a specific site in the body (with a subsequent increase in biological half-life). This is more so because a number of drugs bind *irreversibly with the tissues (contrast to plasma protein-drug binding); for* example, oxidation products of paracetamol, phenacetin, chloroform, carbon tetrachloride and bromobenzene bind covalently to hepatic tissues.

For majority of drugs that bind to extravascular tissues, the order of binding is:

***Liver > Kidney > Lung > Muscles***

# Contd.

Several examples of extravascular tissue-drug binding are:

1. **Liver:** As stated earlier, epoxides of a number of halogenated hydrocarbons and paracetamol bind irreversibly to liver tissues resulting in hepatotoxicity.

2. **Lungs:** Basic drugs like imipramine, chlorpromazine and antihistamines accumulate in lungs.

3. **Kidneys:** Metallothionin, a protein present in kidneys, binds to heavy metals such as lead, mercury, and cadmium and results in their renal accumulation and toxicity.

4. **Skin:** Chloroquine and phenothiazines accumulate in skin by interacting with melanin.

5. **Eyes:** The retinal pigments of the eye also contain melanin. Binding of chloroquine and phenothiazines to it is responsible for retinopathy.

# Contd.

6. **Hairs:** Arsenicals, chloroquine and phenothiazines are reported to deposit in hair shafts.

7. **Bones:** Tetracycline is a well-known example of a drug that binds to bones and teeth. Administration of this antibiotic to infants or children during odontogenesis results in permanent brown-yellow discoloration of teeth. Lead is known to replace calcium from bones and cause their brittleness.

8. **Fats:** Lipophilic drugs such as thiopental and the pesticide DDT accumulate in adipose tissues by partitioning into it. Highly lipophilic basic drugs like imipramine and chlorpromazine are not localized in fats.

9. **Nucleic Acids:** Molecular components of cells such as DNA interact strongly with drugs like chloroquine and quinacrine resulting in distortion of its double helical structure.

# FACTORS AFFECTING PROTEIN-DRUG BINDING

1. Drug related factors
   a. Physicochemical characteristics of the drug
   b. Concentration of drug in the body
   c. Affinity of a drug for a particular binding component
2. Protein/tissue related factors
   a. Physicochemical characteristics of the protein or binding agent
   b. Concentration of protein or binding component
   c. Number of binding sites on the binding agent
3. Drug interactions
   a. Competition between drugs for the binding site (displacement interactions)
   b. Competition between the drug and normal body constituents
   c. Allosteric changes in protein molecule
4. Patient related factors
   a. Age
   b. Intersubject variations
   c. Disease states

Thank you