DISTRIBUTION OF DRUGS

(Unit Objective: Student able to Understand the Mechanism of Drug Distribution)

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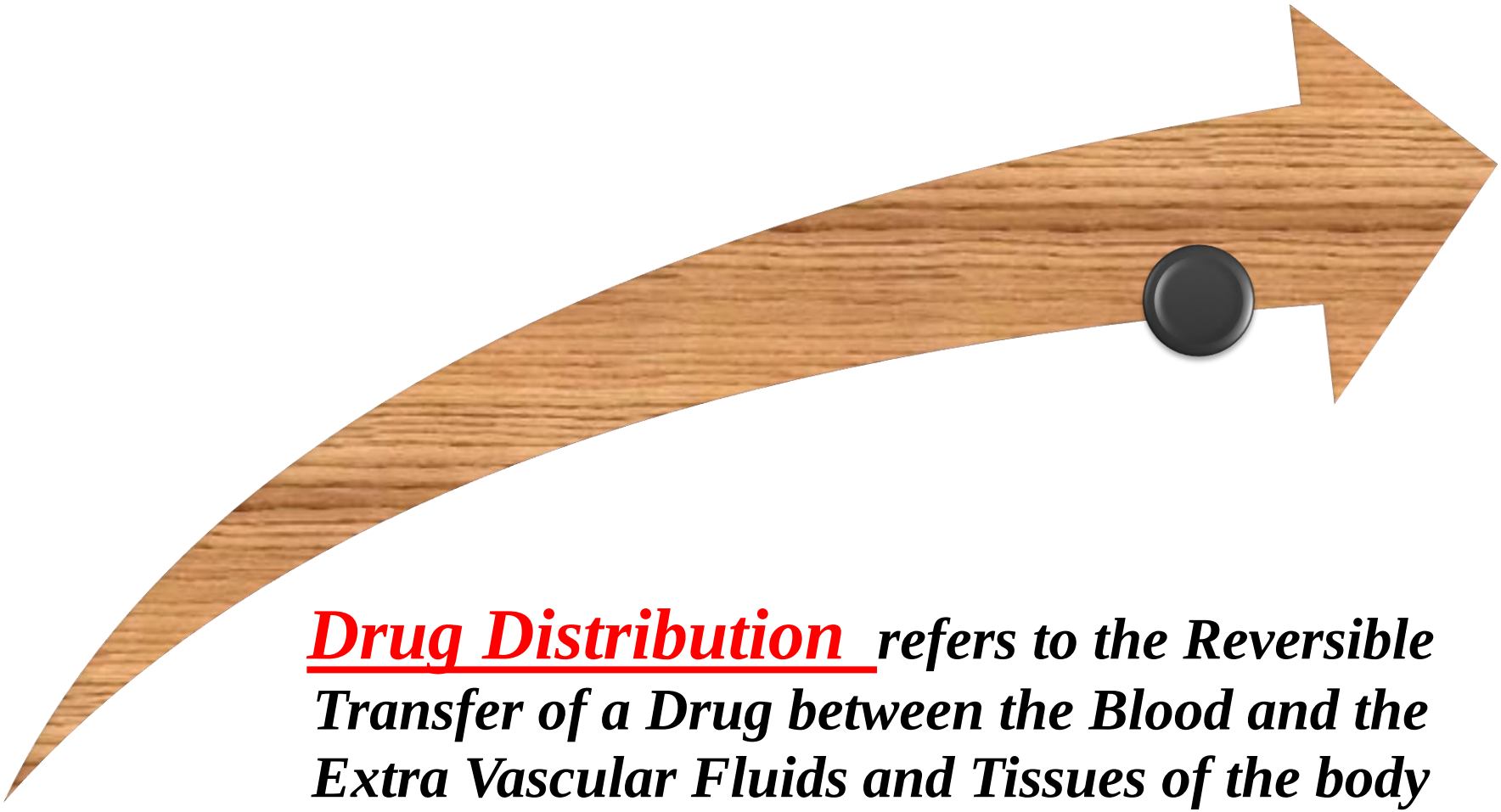
Introduction

Once a drug has gained excess to the blood stream, the drug is subjected to a number of processes called as Disposition Processes that tend to lower the plasma concentration.

1. Distribution which involves reversible transfer of a drug between compartments.

2. Elimination which involves irreversible loss of drug from the body. It comprises of biotransformation and excretion.



Drug Distribution ***refers to the Reversible Transfer of a Drug between the Blood and the Extra Vascular Fluids and Tissues of the body (for example, fat, muscle, and brain tissue).***

Distribution is a **Passive Process**,

for which the

driving force is the Conc. Gradient between the blood and Extravascular Tissues

- The Process occurs by the Diffusion of Free Drug until equilibrium is established.

As the Pharmacological action of a drug depends upon its concentration at the site of action Distribution plays a significant role in the Onset, Intensity, and Duration of Action.

Distribution of a drug is not Uniform throughout the body because different tissues receive the drug from plasma at different rates and to different extents.

Volume of Distribution

The **Volume of distribution** (V_D), also known as **Apparent volume of distribution**, is used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing.

It is called as Apparent Volume because all parts of the body equilibrated with the drug do not have equal concentration.

It is defined as the volume in which the amount of drug would be uniformly distributed to produce the observed blood concentration.

Redistribution

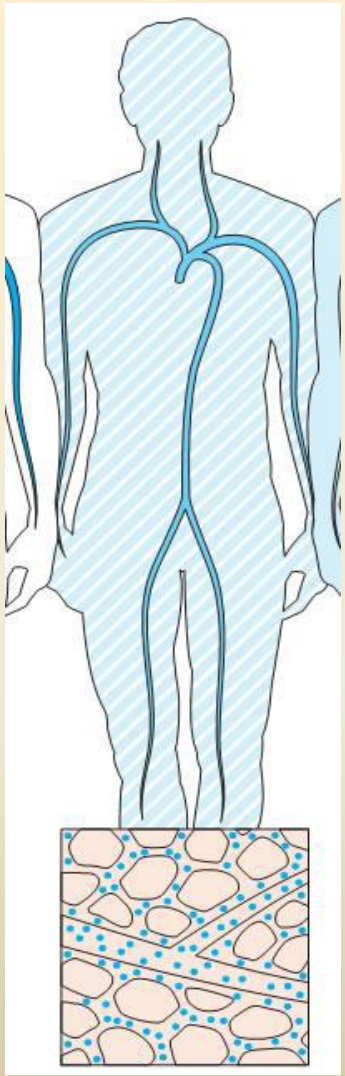
✓ Highly lipid soluble drugs when given by i.v. or by inhalation initially get distributed to organs with high blood flow, e.g. brain, heart, kidney etc.

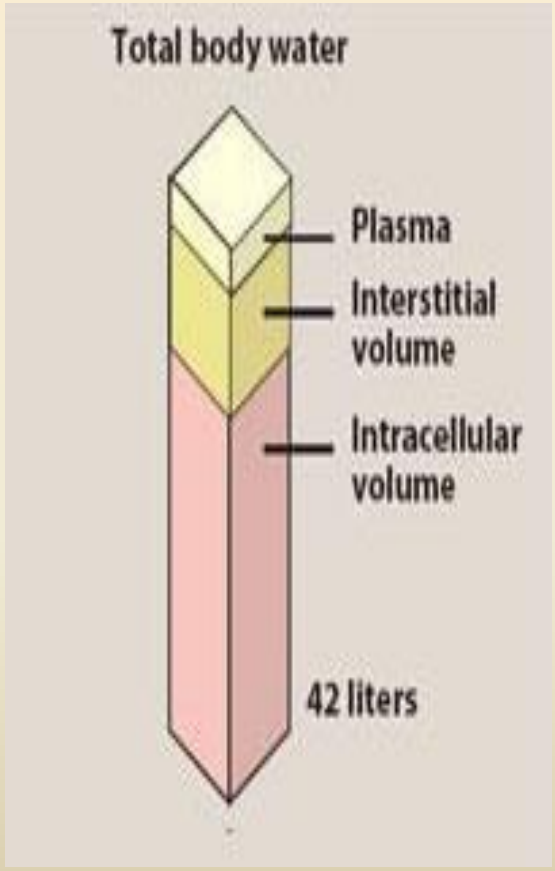
✓ Later, less vascular but more bulky tissues (muscles,fat) take up the drug and plasma concentration falls and drug is withdrawn from these sites.

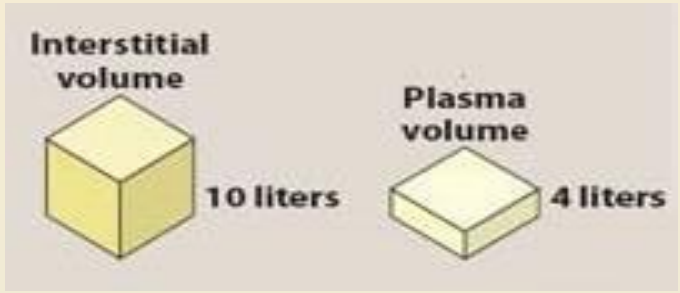
✓ If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of the drug action.

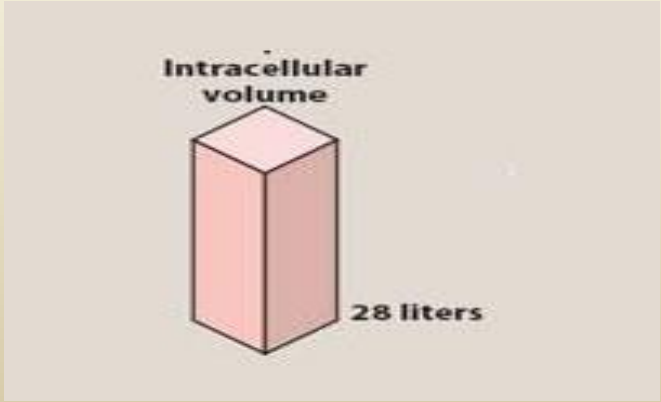
✓ Greater the lipid solubility of the drug, faster is its redistribution.

The real volume of distribution has physiological meaning and is related to the Body Water.









The volume of each of these compartments can be determined by use of specific markers or tracers.

Physiological Fluid Compartments the	Markers Used	Approximate volume (liters)
Plasma	Evans Blue, Indocyanine Green	4
Extracellular fluid	Inulin, Raffinose, Mannitol	14
Total Body Water	D_2O, Antipyrine	42

The intracellular fluid volume can be determined as the difference between total body water and extracellular fluid.

Drugs which bind selectively to Plasma proteins e.g. Warfarin have Apparent volume of distribution smaller than their Real volume of distribution.

The Vd of such drugs lies between blood volume and total body water i.e. b/w 6 to 42 liters.

Drugs which bind selectively to Extravascular Tissues e.g. Chloroquine have Apparent volume of distribution larger than their Real volume of distribution.

The Vd of such drugs is always greater than 42 liters.

Differences In Drug Distribution Among Various Tissues Arises Due To a Number of Factors:

- Tissue Permeability of the Drug
  - a. Physiochemical Properties of the drug like Molecular size, pKa and o/w Partition coefficient.
  - b. Physiological Barriers to Diffusion of Drugs.
- Organ / Tissue Size and Perfusion Rate
- Binding of Drugs to Tissue Components

  (Blood components and Extravascular Tissue Proteins)
- Miscellaneous Factors

  Age, Pregnancy, Obesity, Diet, Disease states, and Drug Interactions…

Tissue Permeability of the Drugs depend upon:

1. Rate of Tissue Permeability, and
2. Rate of Blood Perfusion.

The Rate of Tissue Permeability, depends upon Physiochemical Properties of the drug as well as Physiological Barriers that restrict the diffusion of drug into tissues.

Physiochemical Properties that influence drug distribution are:

i. Molecular size,
ii. pKa, and
iii. o/w Partition coefficient.

- **Drugs having molecular wt. less than 400 daltons easily cross the Capillary Membrane to diffuse into the Extracellular Interstitial Fluids.**
- **Now, the penetration of drug from the Extracellular fluid (ECF) is a function of :-**
  - ***Molecular Size:***

    Small ions of size < 50 daltons enter the cell through Aq. filled channels where as larger size ions are restricted unless a specialized transport system exists for them.
  - ***Ionisation:***

    A drug that remains unionized at pH values of blood and ECF can permeate the cells more rapidly.

    Blood and ECF pH normally remains constant at 7.4, unless altered in conditions like Systemic alkalosis/acidosis.

➢ ***Lipophilicity:***

Only unionized drugs that are lipophilic rapidly crosses the cell membrane.

e.g. Thiopental, a lipophilic drug, largely unionized at Blood and ECF pH readily diffuses the brain where as Penicillins which are polar and ionized at plasma pH do not cross BBB.

Effective Partition Coefficient for a drug is given by:

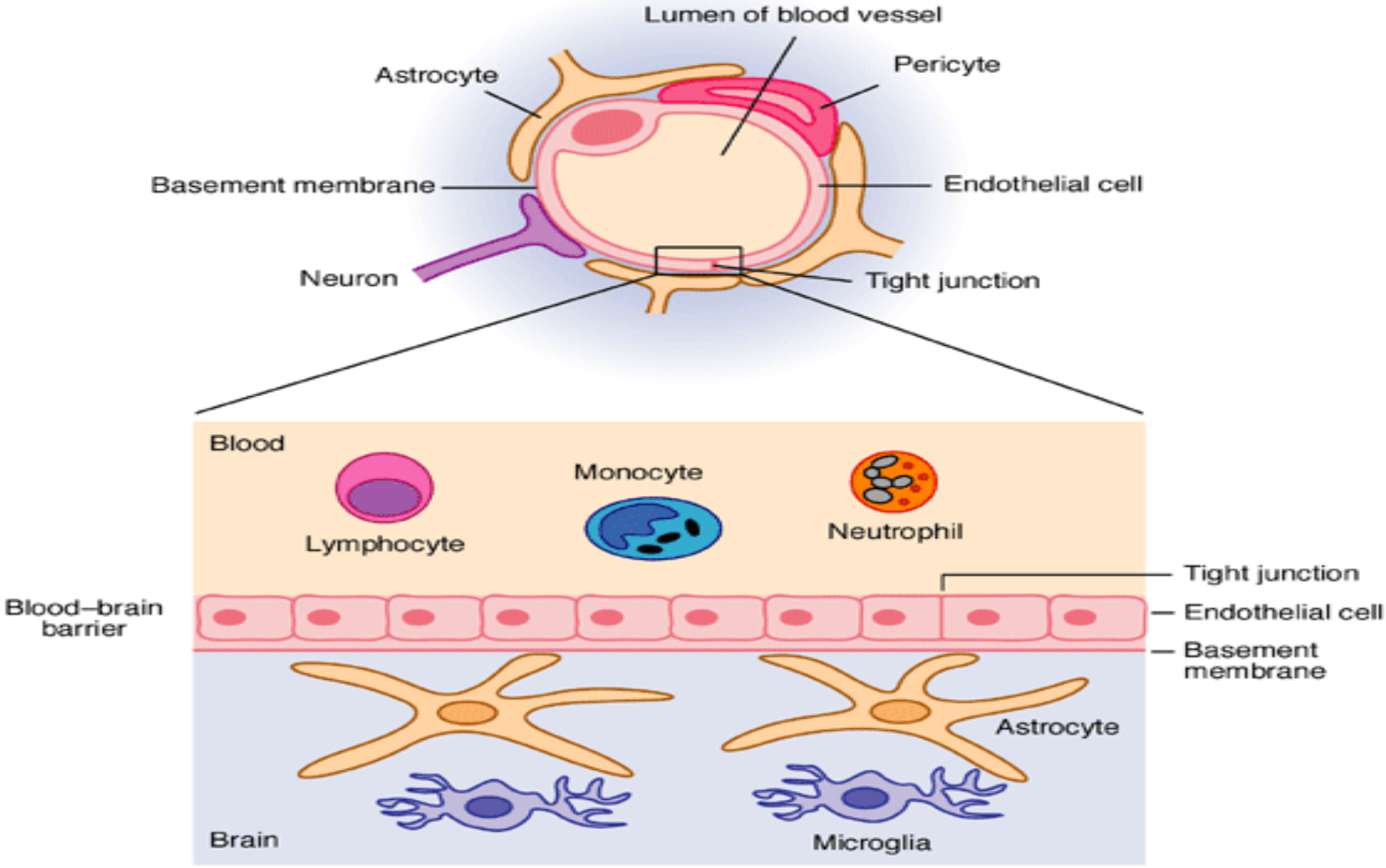
Effective K o/w = **Fraction unionized at pH 7.4** X **K o/w of unionized drug**

PENETRATION OF DRUGS THROUGH BLOOD BRAIN BARRIER

- A stealth of endothelial cells lining the capillaries.
- It has tight junctions and lack large intra cellular pores.
- Further, neural tissue covers the capillaries.
- Together , they constitute the BLOOD BRAIN BARRIER.

- Astrocytes : Special cells / elements of supporting tissue are found at the base of endothelial membrane.

- The blood-brain barrier (BBB) is a separation of circulating blood and cerebrospinal fluid (CSF) maintained by the choroid plexus in the central nervous system (CNS).



The blood–brain barrier (BBB)

Since BBB is a lipoidal barrier,

It allows only the drugs having high o/w partition coefficient to diffuse passively where as moderately lipid soluble and partially ionized molecules penetrate at a slow rate.

Endothelial cells restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophillic molecules into the CSF, while allowing the diffusion of small hydrophobic molecules (O_2, CO_2, hormones).

Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins.

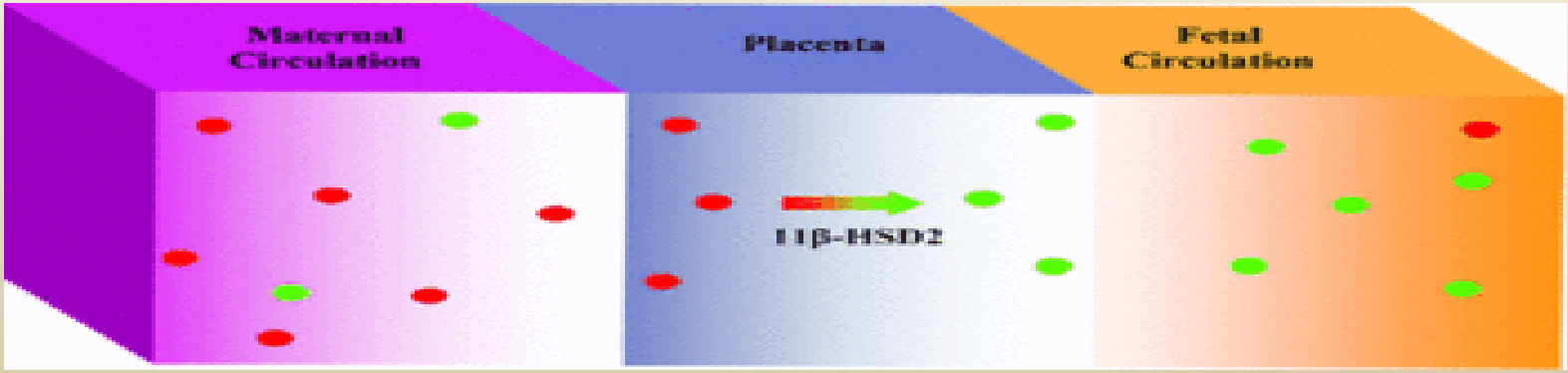
Various approaches to promote crossing BBB:

- Use of Permeation enhancers such as Dimethyl Sulfoxide.
- Osmotic disruption of the BBB by infusing internal carotid artery with Mannitol.
- Use of Dihydropyridine Redox system as drug carriers to the brain (the lipid soluble dihydropyridine is linked as a carrier to the polar drug to form a prodrug that rapidly crosses the BBB)

PENETRATION OF DRUGS THROUGH PLACENTAL BARRIER

- *Placenta is the membrane separating Fetal blood from the Maternal blood.*

- It is made up of Fetal Trophoblast Basement Membrane and the Endothelium.
- Mean thickness in early pregnancy is (25 µ) which reduces to (2 µ) at full term.

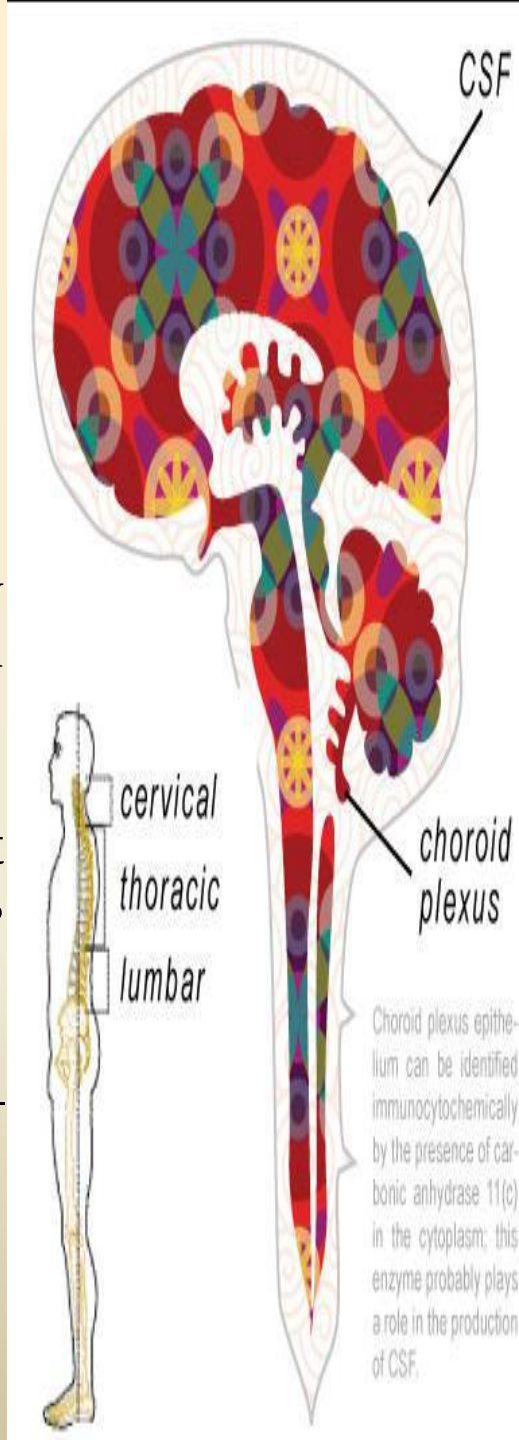


- Many drugs having mol. wt. < 1000 Daltons and moderate to high lipid solubility e.g. ethanol, sulfonamides, barbiturates, steroids, anticonvulsants and some antibiotics cross the barrier by simple diffusion quite rapidly .

- Nutrients essential for fetal growth are transported by carrier mediated processes.

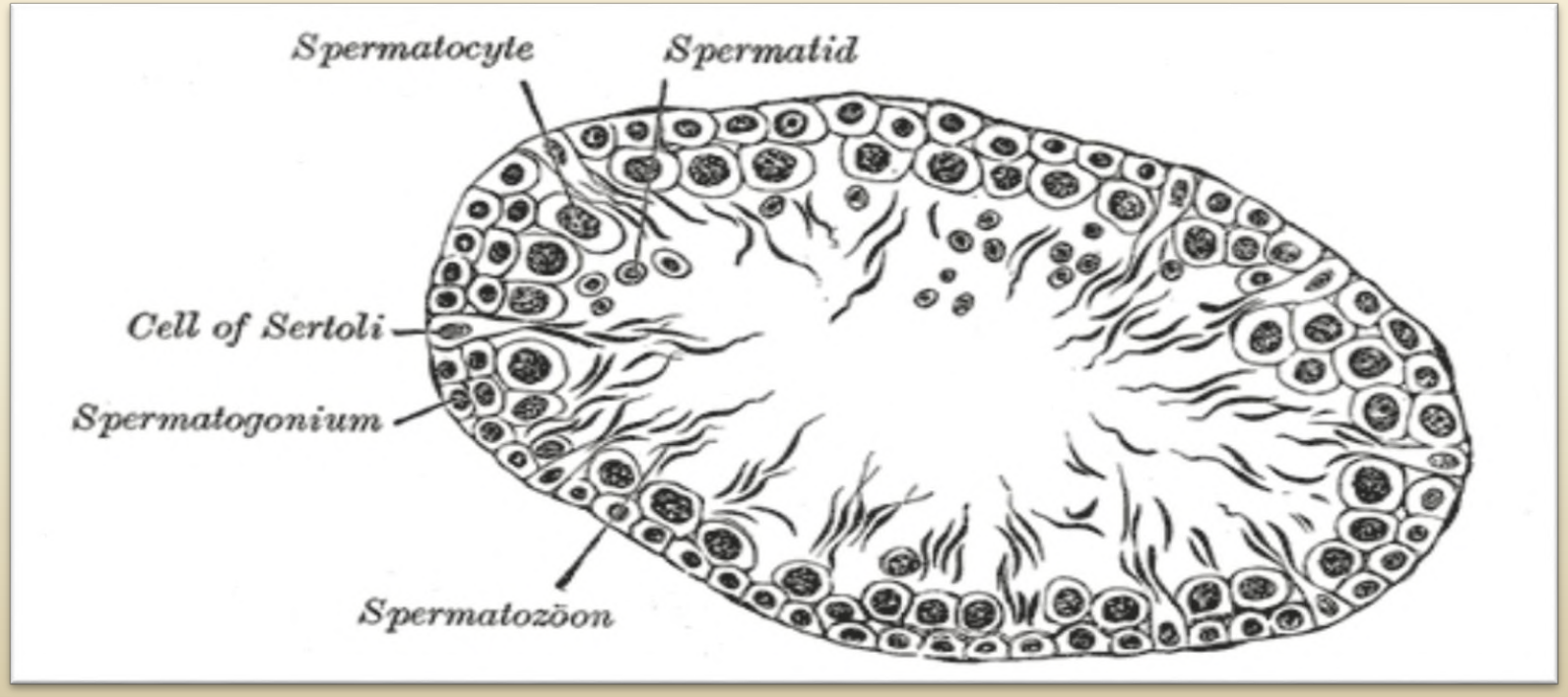
Blood – Cerebrospinal Fluid Barrier:

- The Cerebrospinal Fluid (CSF) is formed mainly by the Choroid Plexus of lateral, third and fourth ventricles.
- The choroidal cells are joined to each other by tight junctions forming the Blood – CSF barrier which has permeability characteristics similar to that of BBB.
- Only high lipid soluble drugs can cross the Blood – CSF barrier.



Blood – Testis Barrier:

- It has tight junctions between the neighboring cells of sertoli which restricts the passage of drugs to spermatocytes and spermatids.



Organ / Tissue Size and Perfusion Rate

- Perfusion Rate is defined as the volume of blood that flows per unit time per unit volume of the tissue.

- Greater the blood flow, faster the distribution.

- Highly perfused tissues such as lungs, kidneys, liver, heart and brain are rapidly equilibrated with lipid soluble drugs.

- The extent to which a drug is distributed in a particular tissue or organ depends upon the size of the tissue i.e. tissue volume.

Miscellaneous Factors

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.

Obesity: In Obese persons, high adipose tissue content can take up a large fraction of lipophilic drugs.

Pregnancy: During pregnancy the growth of the uterus, placenta and fetus increases the volume available for distribution of drugs.

Disease States: Altered albumin or drug – binding protein conc.
Altered or Reduced perfusion to organs /tissues
Altered Tissue pH

Factor affecting Drug-Protein binding, Significant, Kinetics of Drug-Protein binding

PLASMA PROTEIN- DRUG BINDING

BIND TO BLOOD PROTEIN

Protein	Molecular Weight (Da)	concentration (g/L)	Drug that bind
Albumin	65,000	3.5–5.0	Large variety of drug
α1- acid glycoprotein	44,000	0.04 – 0.1	Basic drug - propranolol, imipramine , and lidocaine . Globulins (-, -, -globulins corticosteroids.
Lipoproteins	200,000–3,400,000	.003-.007	Basic lipophilic drug Eg- chlorpromazine
α1 globulin α2 globulin	59000 13400	.015-.06	Steroid , thyroxine Cynocobalamine Vit. –A,D,E,K

Binding of drug to globulin

α1 globulin bind to a number of steroidal drug cortisone , prednisolone $ thyroxine , cynocobalamine

α2 globulin

(ceruloplasmin) bind to Vit. A D E K

γ- globulin

bind to antigen

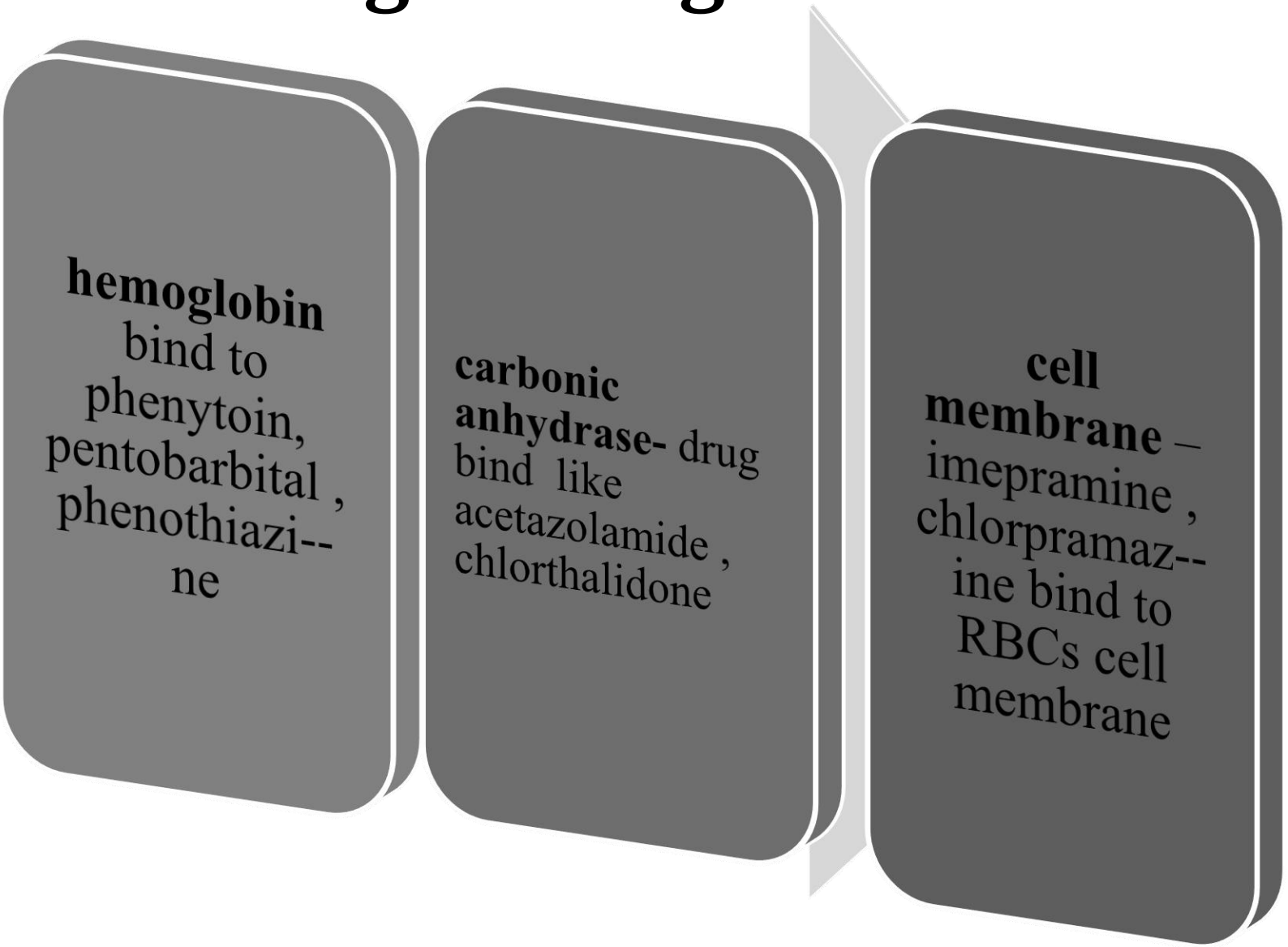
β1-globulin

(transferrin) bind to ferrous ion

β2-globulin

bind to carotinoid

Binding of drug to blood cells



Tissue binding of drug

majority of drug bind to extravascular tissue- the order of binding -: liver > kidney > lung > muscle

liver – epoxide of number of halogenated hydrocorban ,paracetanol

lung – basic drug imepramine , chlorpramazine , antihistaminis ,

kidney – metallothionin bind to heavy metel , lead, Hg , Cd ,

skin – chloroquine $ phenothizine

eye - chloroquine $ phenothizine

Hairs- arsenicals , chloroquine, $ PTZ bind to hair shaft .

Bone – tetracycline

Fats – thiopental , pesticide- DDT

Factor affecting drug protein binding

- 1. factor relating to the drug

a) Physicochemical characteristic of drug
b) Concentration of drug in the body
c) Affinity of drug for a particular componant

- 2. factor relating to the protein and other binding componant

a) Physicochemical characteristic of the protein or binding componant
b) Concentration of protein or binding componant
c) Num. Of binding site on the binding site

- 3. drug interation
- 4. patient related factor

Drug related factor

- **Physicochemical characteristics of drug**

➢ Protein binding is directly relategd to lipophilicity

lipophilicity ↑ = the extent of binding ↑

✓ e.g. The slow absorption of cloxacilin in compression to ampicillin after i.m. Injection is attributes to its higher lipophilicity it binding 95% letter binding 20% to protein

✓ Highly lipophilic thiopental tend to lacalized in adipose tissue .

✓ Anionic or acidic drug like . Penicillin , sulfonamide bind more to HSA

✓ Cationic or basic drug like . Imepramine alprenolol bind to AAG

CONCENTRATION OF DRUG IN THE BODY

- The extent of drug- protein binding can change with both change in drug and protein concentration
- The con. Of drug that binding HSA does not have much of an influence as the thereuptic concentration of any drug is insufficient to saturate it

Eg. Thereuptic concentration of lidocaine can saturate AAG with which it binding as the con. Of AAG is much less in compression to that of HSA in blood

DRUG PROTEIN / TISSUE AFFINITY

- Lidocaine have greater affinity for AAG than HSA
- Digixin have greater affinity for protein of cardiac muscle than skeleton muscles or plasma

Protein or tissue related factor

Physicochemical properity of protein / binding componant – lipoprotein or adipose tissue tend to bind lipophilic drug by dissolving them to lipid core .

- The physiological pH determine the presence of anionic or cationic group on the albumin molecule to bind a verity of drug

Concentration of protein / binding componant

- Mostly all drug bind to albumin b/c it present a higher concentration than other protein

number of binding sites on the protein

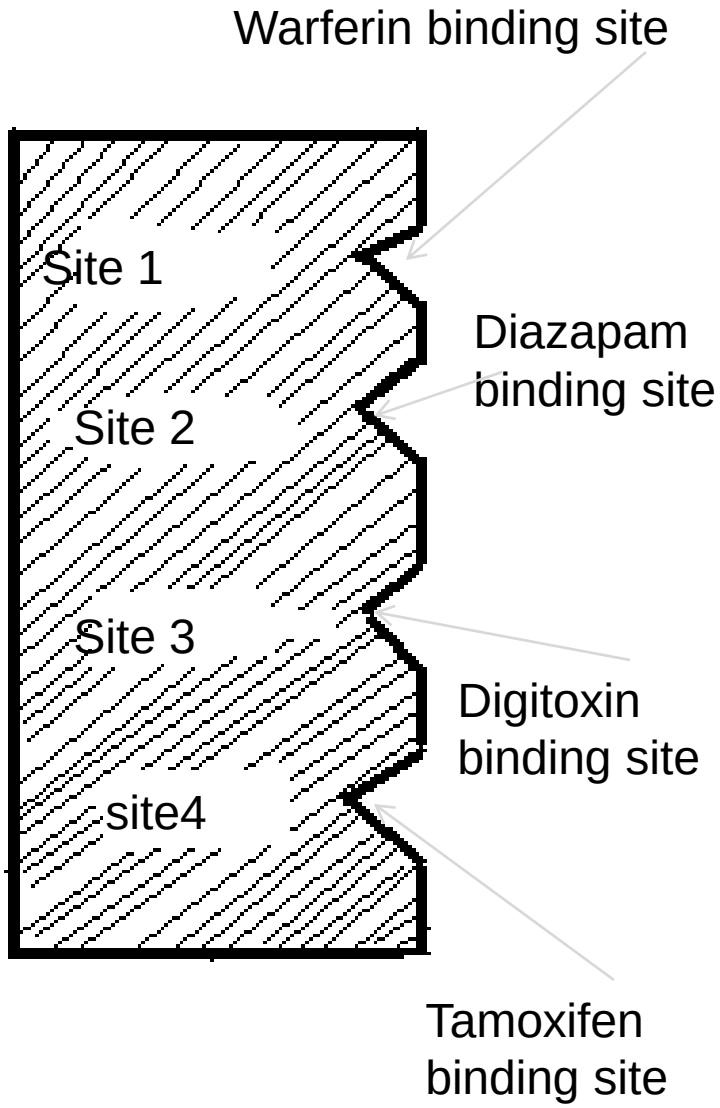
Albumin has a large number of binding site as compare to other protein and is a high capacity binding component

- Several drug capable to binding at more than one binding site

e.g.- flucoxacillin , flurbiprofen , ketoprofen , tamoxifen and dicoumarol bind to both pri . And secondary site of albumin

Indomethacin is bind to three different site

AAG is a protein with limited binding capacity b/c of it low -conc. And mol^{n}. Size . The AAG has only one binding site for lidocaine , in presence of HAS two binding site have been reported due to direct interaction b/w them



Drug binding site on HSA

Drug interaction

Competition b/w drug for binding site (displacement interaction)

When two or more drug present to the same site , competition b/w them for interaction with same binding site .

If one of the drug (A) is bound to such a site , then administration of the another drug (B) having high affinity for same binding site result in displacement of drugs (A) from its binding site . This type of interaction is known as displacement interaction .

Wher drug (A) here is called as the **displaced drug** and drug (B) as the **displacer .**

Eg. Phenylbutazone displace warferin and sulfonamide fron its binding site

Competition b/w drug and normal body constituent

- The free fatty acids are interact to with a number of drug that bind primarily to HSA . When free fatty acid level is increase in several condition – fasting , - pathologic – diabeties , myocardial infraction , alcohol abstinence – the fatty acid which also bind to albumin influence binding of several drug

  ⇩ binding – diazepam

  - propanolol

  ⇧ binding - warferin

  Acidic drug like – sod. Salicilate , sod . Benzoate , sulfonamide displace bilirubin from its albumin binding site result in neonate it cross to BBB and precipitate toxicity (kernicterus)

Patient related factor

Age

- Neonate – albumin content is low in new born as result in increase conc. of unbound drug that primarily bind to albumin eg. Phenytoin , diazepam
- **Elderly -**albumin content is lowerd result in increase conc. of unbound drug that primarily bind to albumin

➢ In old age AAG level is increase thus decrease conc. of free drug that bind to AAG

Disease state

Disease	Influence on plasma protein	Influence on protein drug binding
Renal failure (uremia)	⇩ albumin content	Decrease binding of acidic drug , neutral or basic drug are unaffected
Hepatic failure	⇩ albumin synthesis	Decrease binding of acidic drug ,binding of basic drug is normal or reduced depending on AAG level.
Inflammatory state (trauma , burn, infection)	⇧ AAG levels	Increase binding of basic drug , neutral and acidic drug unaffected

Significant of protein binding of drug

- **Absorption –**the binding of absorbed drug to plasma proteins decrease free drug conc. And disturb equilibrium . Thus sink condition and conc. Gradient are established which now act as the driving force for further absorption
- **Systemic solubility of drug** water insoluble drugs , neutral endogenous macromolecules , like heparin , steroids , and oil soluble vitamin are circulated and distributed to tissue by binding especially to lipoprotein act as a barrier for such drug hydrophobic compound .
- **Distribution -T**he plasma protein-drug binding thus favors uniform distribution of drug throughout the body by its buffer function . A protein bound drug in particular does not cross the BBB, placental barrier and the glomerulus

Tissue binding, apperent volume of distribution and drug storage

- ✓ A drug that bind to blood component remains confined to blood have small volume of distribution.
- ✓ Drug that show extra-vascular tissue binding have large volume of distribution .
- ❑ the relationship b/w tissue drug binding and apparent volume of distribution-

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}} = \frac{X}{C}$$

the amount of drug in the body $X = V_d \cdot C$

SIMILAR , amount of drug in plasma = Vp . S

Amount of drug in extravascular tissue = Vt .Ct

- The total amount of drug in the body

$V_d \cdot C = Vp.C + Vt.\ Ct$

where , Vp is volume of plasma

Vt is volume of extravascular tissue

Ct is tissue drug concentration

$Vd = Vp + Vt\ Ct/C$ …….(1)

Dividing both side by C in above equation

The fraction of unbound drug in plasma (fu)

$$fu = \frac{\text{conc. of unbound drug in plasma}}{\text{total plasma drug concentration}} = \frac{Cu}{C}$$

The fraction unbound drug in tissue (fut)

$$fut = \frac{Cut}{Ct}$$

Assuming that equilibrium unbound or free drug conc. In plasma and tissue is equal

$$\frac{C_t}{C} = \frac{fu}{fut}$$

mean Cu = Cut then ,

$$Vd = Vp + \frac{Vt \cdot fu}{fut}$$

substituting the above value in equa. 1

It is clear that greater the unbound or free concentration of drug in plasma larger its Vd

Displacement interaction and toxicity

	Drug A	Drug B
% DRUG BEFORE DISPLACEMENT		
BOUND	99	90
FREE	1	10
% DRUG AFTER DISPLACEMENT		
BOUND	98	89
FREE	2	11
% INCREASE IN FREE DRUG CONCENTRATION	100	10

Eg; kernicterus – DI of bilirubin by NSAID'S drugs

Displacement of digoxine by qunidine

Displacement of warferin by phenylbutazone

Interaction is significant if drug bind more than 95%

Kinetics of protein drug binding

- The kinetics of reversible drug–protein binding for a protein with one simple binding site can be described by the *law of mass action*, as follows:

$$\text{Protein} + \text{drug} \Leftrightarrow \text{drug-protein-complex}$$

or

$$[P] + [D] \Leftrightarrow [PD] \qquad \text{.....1}$$

The law of mass action, an association constant, K_a, can be expressed as the ratio of the molar concentration of the products and the molar concentration of the reactants. This equation assumes only one-binding site per protein molecule

$$K_a = \frac{[PD]}{[P][D]} \qquad \text{.....2}$$

Experimentally, both the free drug [D] and the protein-bound drug [PD], as well as the total protein concentration [P] + [PD], may be determined. To study the binding behavior of drugs, a determinable ratio (r)is defined, as follows

$$r = \frac{\text{moles of drug bound}}{\text{total moles of protein}}$$

moles of drug bound is [*PD*] and the total moles of protein is [*P*] + [*PD*], this equation becomes

$$r = \frac{[PD]}{[PD] + [P]} \qquad \text{.....3}$$

Substituting the value of PD from equa. 2

$$r = \frac{K_a[P][D]}{K_a[P][D] + [P]}$$

$$r = \frac{K_a[D]}{1 + K_a[D]} \qquad \text{.....4}$$

This equation describes the simplest situation, in which 1 mole of drug binds to 1 mole of protein in a 1:1 complex. This case assumes only one independent binding site for each molecule of drug. If there are *n* identical independent binding sites per protein molecule, then the following is used:

$$r = \frac{nK_a[D]}{1 + K_a[D]} \qquad \text{.....5}$$

- In terms of K_d, which is $1/K_a$, Equation 6 reduces to

$$r = \frac{n[D]}{K_d + [D]} \quad \text{.....6}$$

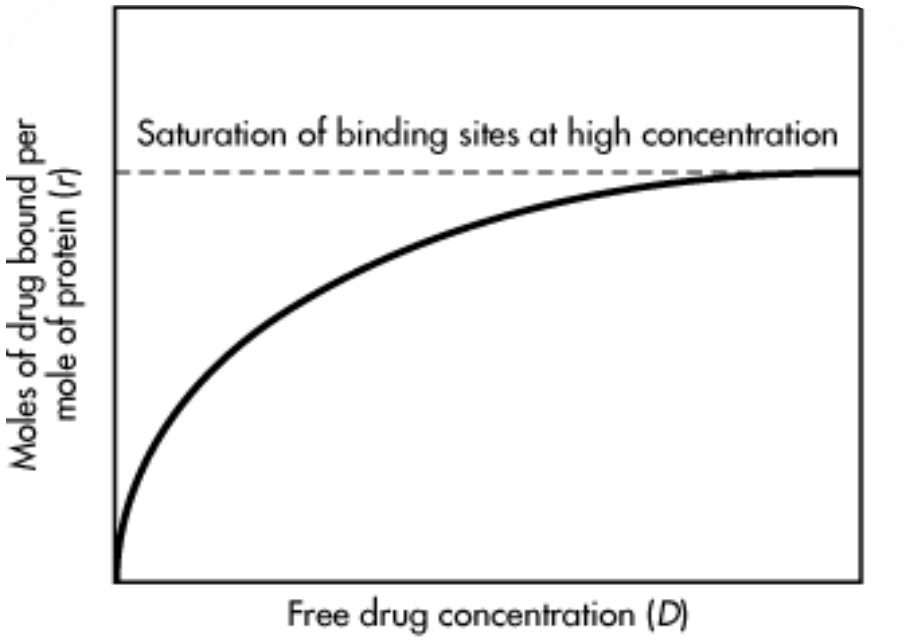
- Protein molecules are quite large compared to drug molecules and may contain more than one type of binding site for the drug. If there is more than one type of binding site and the drug binds independently on each binding site with its own association constant, then Equation 6 expands to

$$r = \frac{n_1 K_1[P]}{1 + K_1[D]} + \frac{n_2 K_2[P]}{1 + K_2[D]} + \cdots \quad \text{.....7}$$

The values for the association constants and the number of binding sites are obtained by various graphic methods.

1. Direct plot

It is made by plotting r vresus (D)



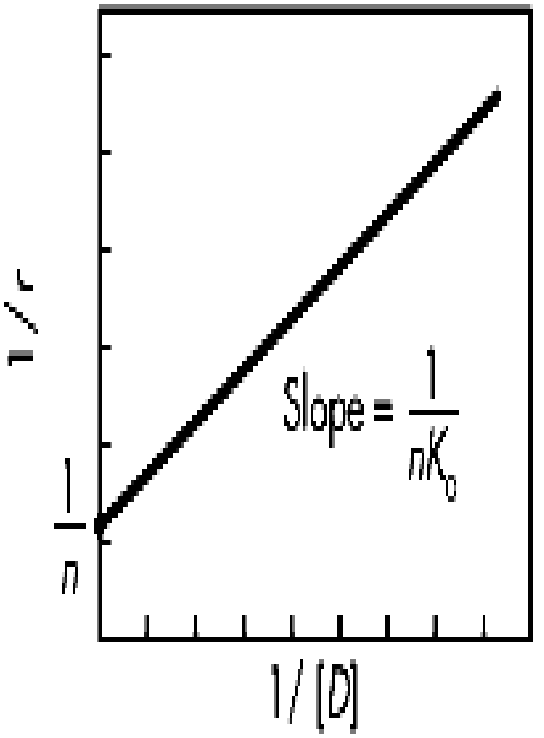
2. Double reciprocal plot

The reciprocal of Equation 6 gives the following equation

$$\frac{1}{r} = \frac{1 + K_a[D]}{nK_a[D]}$$

$$\frac{1}{r} = \frac{1}{nK_a[D]} + \frac{1}{n}$$

- A graph of 1/*r* versus 1/[*D*] is called a *double reciprocal plot*. The *y* intercept is 1/*n* and the slope is 1/*nKa* . From this graph , the number of binding sites may be determined from the *y* intercept, and the association constant may be determined from the slope, if the value for *n* is known.



3. Scatchardplot

is a rearrangement of Equation 6 The Scatchard plot spreads the data to give a better line for the estimation of the binding constants and binding sites. From Equation 6 , we obtain

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