DRUG DISTRIBUTION BARRIERS AND PLASMA PROTIEN BINDING

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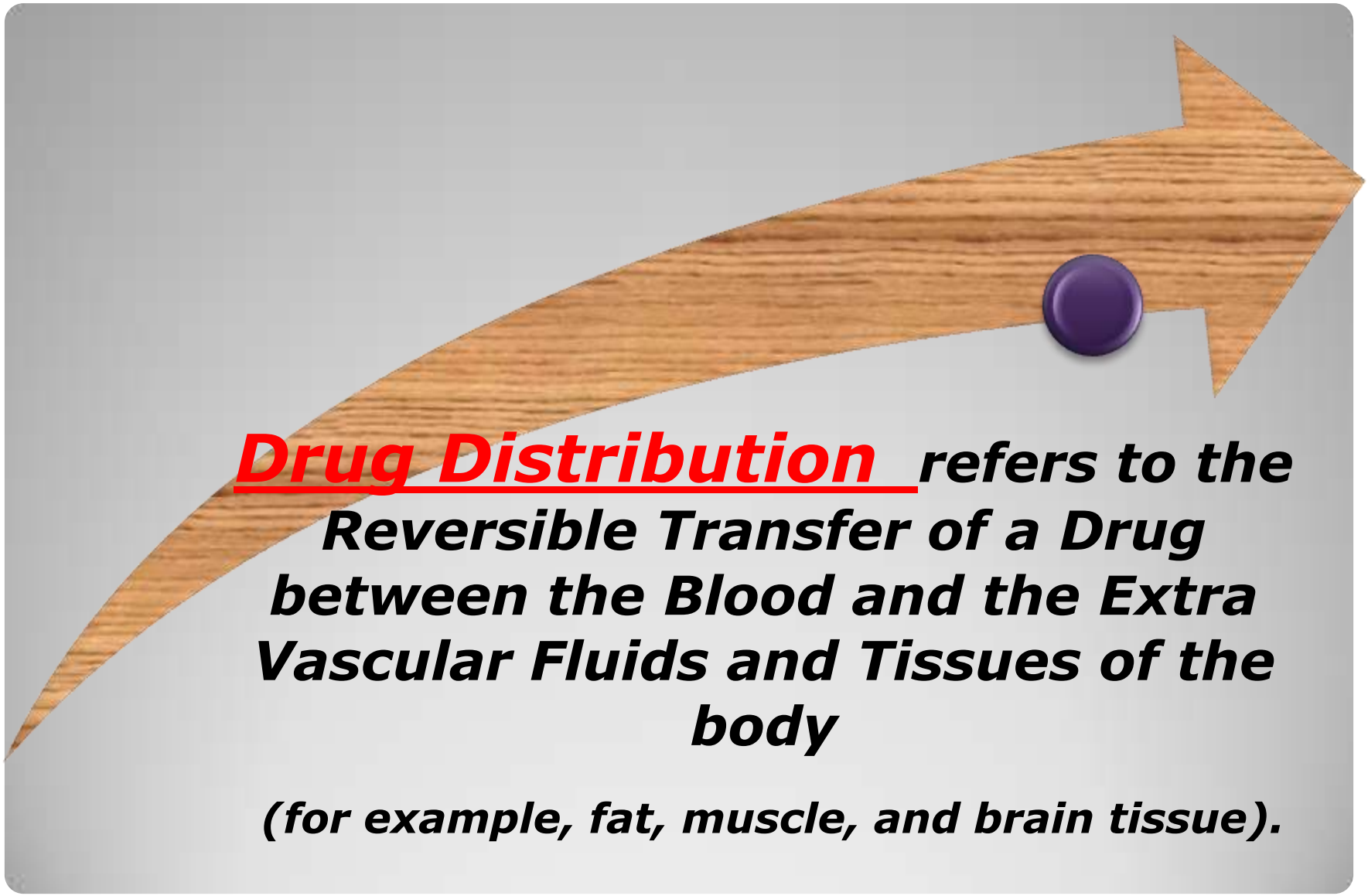
Introduction

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

DISTRIBUTION BARRIERS

THE SIMPLE CAPILLARY ENDOTHELIAL BARRIER

- All the drug ,ionized or unionized, with a molecular size less than 600 daltons,it will diffuse through the capillary endothelium and into the interstitial fluid.
- Only drugs bond to the blood components are restricted because of the large molecular size of complex.

SIMPLE CELL MEMBRANE BARRIER

- Once a drug diffuses from the capillary wall into the extracellular fluid, it's further entry into cells of most tissues is limited by it's permeability through the membrane that lines such cells.
- It is similar to the lipoidal barrier.

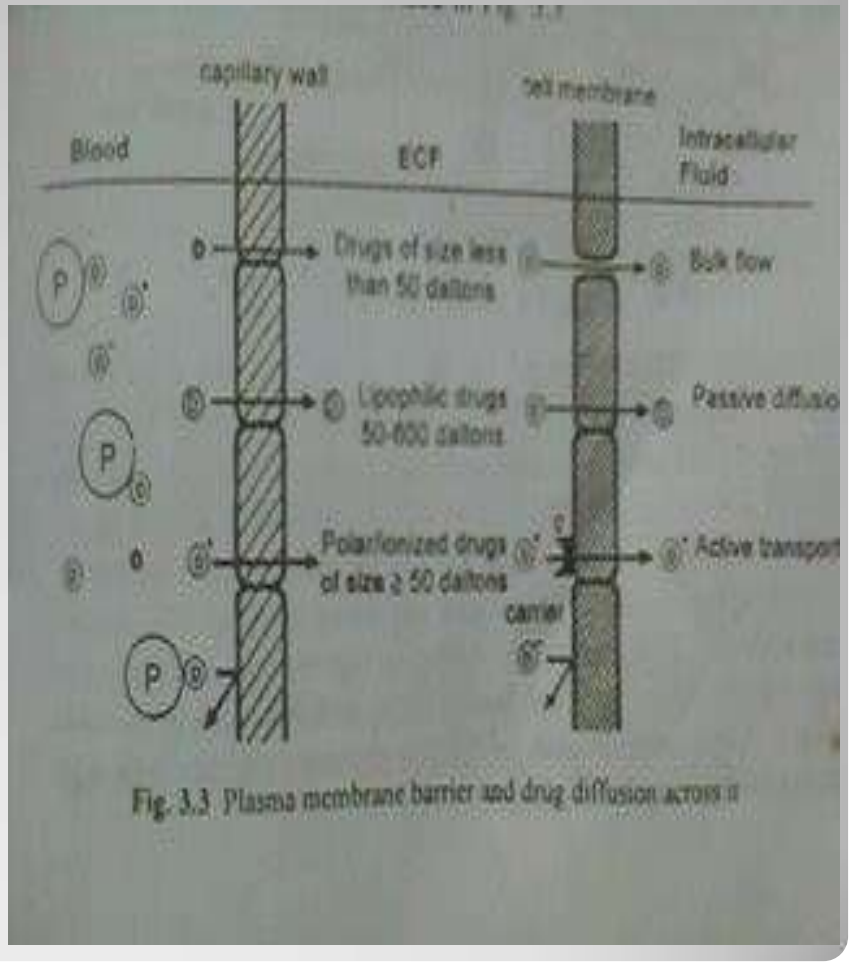


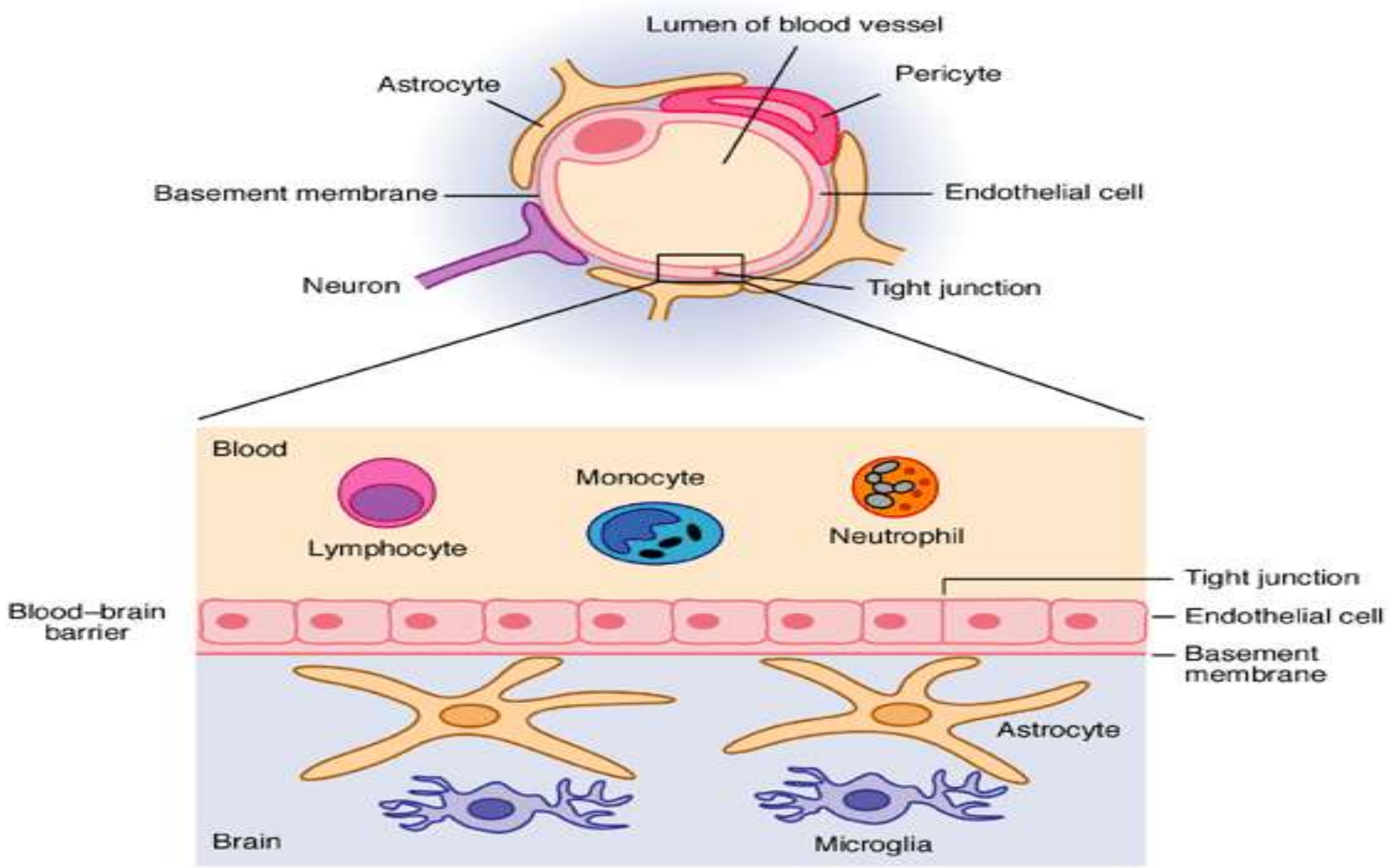
Fig. 3.3 Plasma membrane barrier and drug diffusion across it

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 hydrophilic 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.

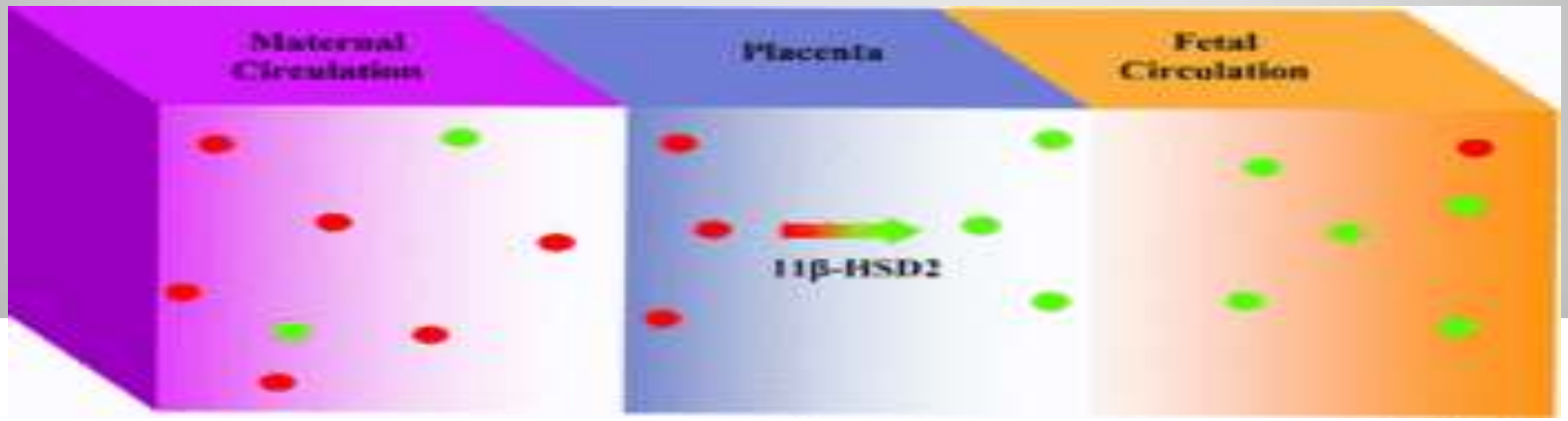
Various approaches to promote crossing BBB:

- 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.

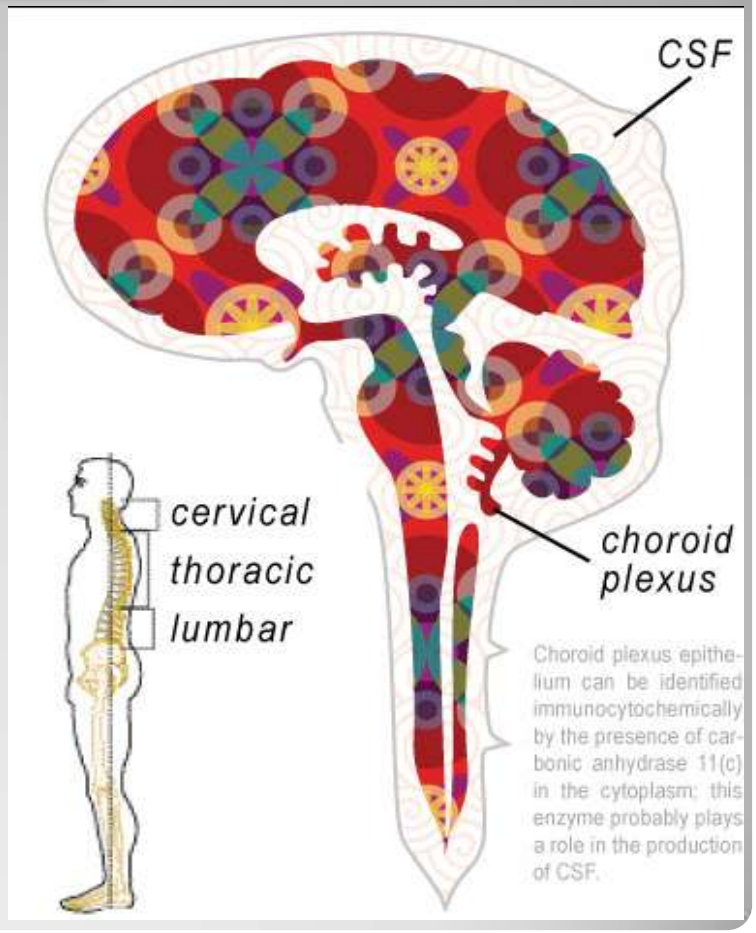


- Many drugs having mol. wt. < 1000 Daltons and moderate to high lipid solubility e.g. ethanol, sulfonamides, barbiturates, steroids, anticonvulsants and some antibiotics cross the barrier by simple diffusion quite rapidly .

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

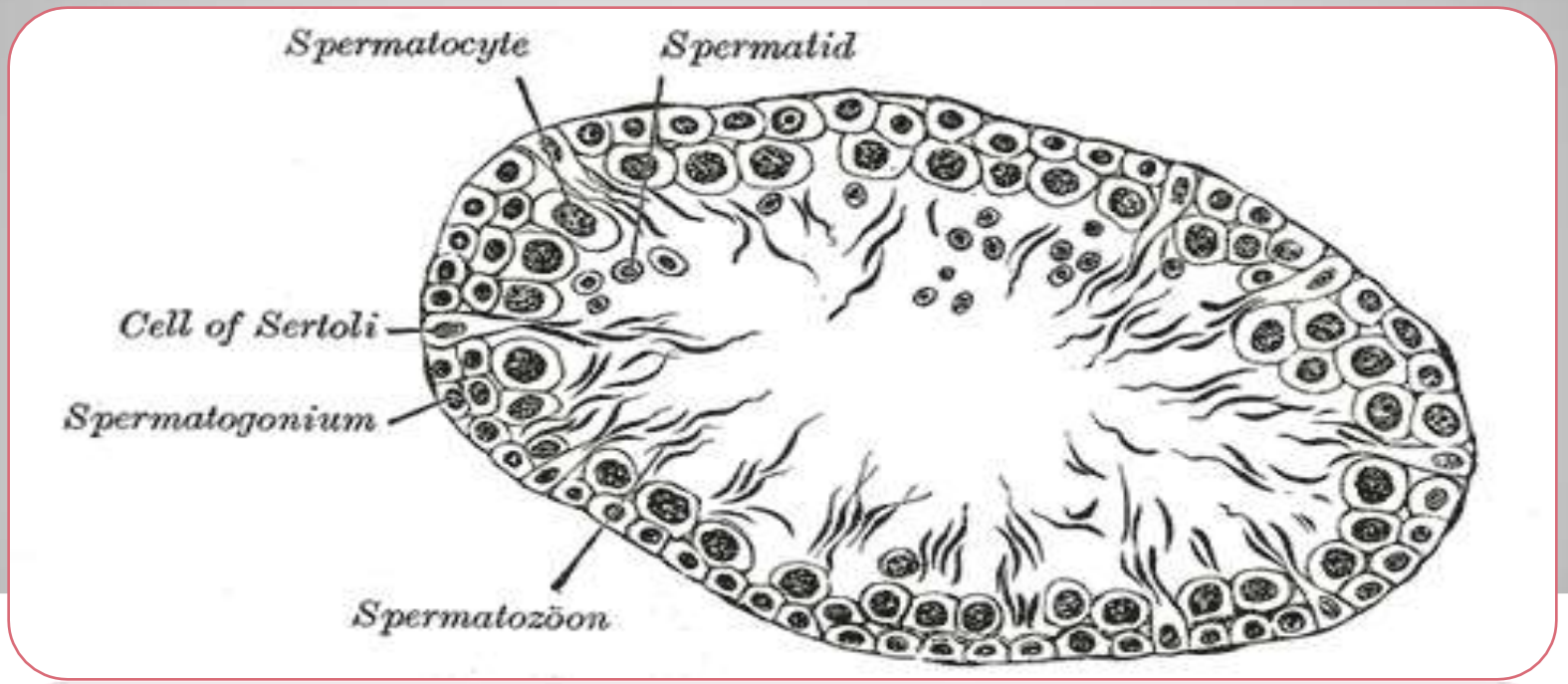
Blood – Cerebrospinal Fluid Barrier:

- 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.



PLASMA PROTEIN BINDING

PLASMA PROTIEN BINDING

- Following entry of drug in to systemic circulation , the first thing with it can interact are blood components like plasma protein blood cells and hemoglobin .

BINDING OF DRUGS TO HUMAN SERUM ALBUMIN

- The human serum albumin having a molecular weight of 65000 , is the most abundant plasma protein with a large drug binding capacity
- Four different sites on HSA have been identified for drug binding :
    1. Site 1 : warfarin and azapropazone binding site.
    2. Site 2 : diazepam binding site.
    3. Site 3 : digitoxin binding site.
    4. Site 4 : tamoxifen binding site.

SITE 1 : WARFARIN AND AZAPROPAZONE BINDING SITE

- It represents the region to which large number of drugs are bound ,
  - Example :
    - NSAIDs (phenyl butazone , indomethacin)
    - Sulphonamides
    - Phenytoin
    - Sodium valproate

SITE 2 : DIAZEPAM BINDING SITE.

- Drug which bind to this region include :
  - ✓Benzodiazepines
  - ✓Medium chain fatty acids
  - ✓Ibuprofen
  - ✓Ketoprofen
  - ✓Tryptophan
  - ✓Cloxacilin , etc…..

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	59000	.015-.06	Steroid , thyroxine Cynocobalamine
α2 globulin	13400		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

Factors Affecting Protein binding:

A)Drug Related:

1.Physicochemical Characteristics:

- Lipophilicity α binding.
- Anionic/Acidic binds : HAS
- Cationic/Basic binds : AAG

2. Concentration of Drug:

3.Drug protein/tissue affinity: Digoxine Affinity to cardiac muscle.

B)Protein/Tissue Related:

1.Physicochemical Characteristics :

Lipophilicity α binding.

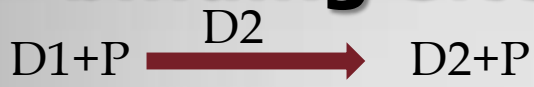
2. Concentration

3. Number of Binding Sites

- Alb. Has more.
- Tamoxifen & Dicumarol binds to 1^0 & 2^0 sites of alb.
- Indomethacine binds to 3 site.

C) Drug Interaction:

1.Competition between Drugs for binding site.



D1: Displaced Drug. D2: Displacer Drug.

E.g. Adm. Of Phenylbutazone to Warfarine therapy patient, result in Hemorrhagic reaction.

2. Competition Between Drug & Normal Constituents:

- FFA competes with HAS.
- Free FFA level increased during conditions :
  - Physiological C. (Fasting)
  - Pathological C. (Diabetes, M.I)
  - Pharmacological (Heparin & Caffeine adm.).
- Acidic Drug displaces : Bilurubine from Alb. & results in Kernictarus.

3.Allosteric Changes In Protein Molecule:

- By drug or its Metabolite.
- Allosteric Modulators: are agents responsible.
- E.g. Aspirins acetylating of Lysine of Alb. So modifying capacity of NSAIDS binding.

D) Patient Related:

1.Age:

Neonates: Low Alb. content: more free drug.

Young Infants: High dose of Digoxine due to large renal clearance.

Elderly: Low Alb. : so more free drug.

2.Intersubject Variability: Due to Genetic & Environmental Factors.

3. Disease State:

Disease	*Influence On Plasma Proteins*	*Binding to*		
		Acidic	*Basic*	*Neutral*
1.Renal failure	Alb. contents	No Effect		No Effect
2.Hepatic failure	Alb. Synthesis	Normal or No Effect		
3.Inflammatory states	AAG level	No Effect No Effect		

Volume Of Distribution

- At distribution Equilibrium : Conc. of drug in body is determined By: Vol. of Tissue in which drug is present.
- Different tissue have diff. conc. So Vd cannot have a true physiologic meaning.
- (Amount of drug in body) α (Conc. Of drug in plasma)

$$X \quad \alpha \quad C$$

$$X = Vd. \; C$$

Def: Hypothetical Vol. of body fluid into which drug is dissolved or distributed.

It is Apparent Vd : Because : All parts of body equilibrated with drug do not have equal conc.

- Real Vd : has direct physiological meaning,

Is related to body water.

Body fluid	Volume (lit.)	% of Body wt.	% of TWB
1.Vascular fluid (plasma)	6 (3)	9 (4.5)	15 (7.5)
2.Extracellular fluid (excl plasma)	12	14	28
3.Intracellular fluid (excl blood cells)	24	34	57
Total Body	42	60	100

Markers used to measure Real Vd

Physiological fluid compartment	Markers used	Approximate vol.
1.Plasma	Evans Blue, Indocyanine Green, I-131 alb.	3
2.Erythrocytes	Cr-51	2
3.Extracellular fluids	Non metabolizable saccharides like Raffinose, Inuline, Mannitol, & Radio isotopes of selected ions: Na^{+}, Cl^{-}, Br^{-}, So_4^{2-}.	15
Total body water	**D_2O, HTO, Antipyrine**	**42**

Clinically significant of plasma protein biding

- Highly plasma protein bound drugs are largely restricted to the vascular compartment because protein bound drug does not cross membranes .they tend to have smaller volumes of distribution.
- The bound fraction is not available for action. It is equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to the elimination.thus,it is called as the storage of the drug.

….continued

- High degree of protein binding generally makes the drug long acting, because bound fraction is not available for the metabolism or excretion, unless it is actively extracted by liver or kidney tubules.
- We can increase the half life of the drug with using the plasma protein binding.
- Generally expressed plasma concentrations of the drug refer to bound as well as free drug.

Thank you