DISTRIBUTION OF DRUGS

For Class- B.Pharmacy 6th Semester

Subject- BIOPHARMACEUTICS AND PHARMACOKINETICS (BP604T)

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DRUG DISTRIBUTION

Once a drug enter in 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.**

DEFINITION

Drug Distribution is defined as the Reversible transfer of drug between one compartment (blood) to another (extra vascular tissue)

Significance

Pharmacological action of drug depends upon its concentration at the site of action.

Thus distribution plays important role in-

- **Onset of Action**
- **Intensity of Action**
- **Duration of Action**

STEPS IN DRUG DISTRIBUTION

- **Permeation of Free Drug through capillary wall & entry in to ECF.**
- **Permeation of drugs from ECF to ICF through membrane of tissue cell.**

Rate Limiting Steps

- Rate of Perfusion to the ECF
- Membrane Permeability of the Drug

DISTRIBUTION PROCESS

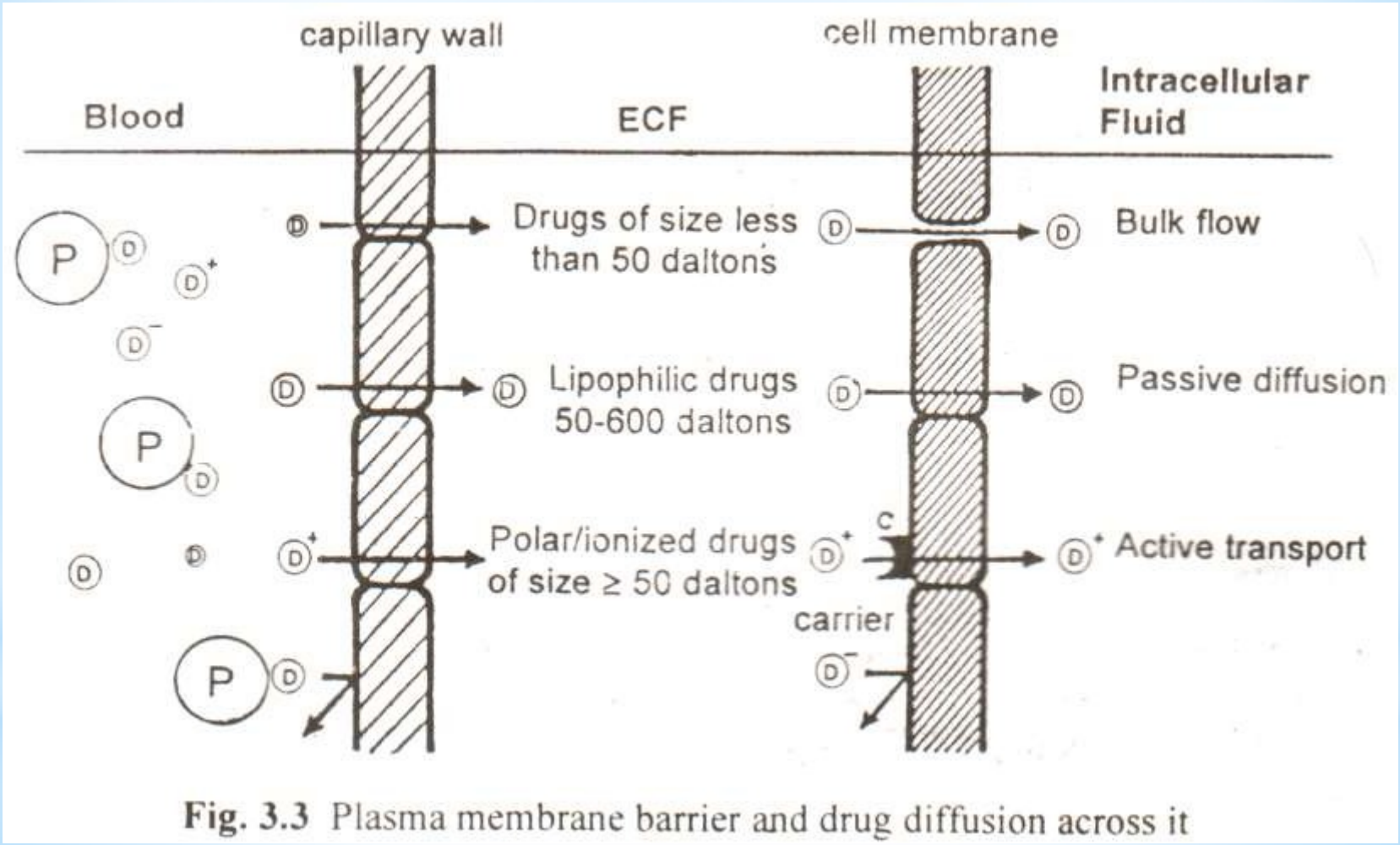
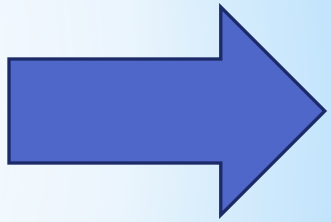


Fig. 3.3 Plasma membrane barrier and drug diffusion across it

*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 OF DRUG IS NOT UNIFORM THROUGHOUT THE BODY—WHY?

Because tissue receive the drug from plasma at different rates & different extents.

Organ perfused	Blood flow (mL/min)	Organ mass (kg)	Normalized blood flow (mL/min/kg)
Liver	1700	2.5	680
Kidney	1000	0.3	3333
CNS	800	1.3	615
Myocardium	250	0.3	833
Fat	250	10	25
Other (muscle...)	1400	55.6	25
total	5400	70	

FACTORS AFFECTING DISTRIBUTION OF DRUGS

1. **Tissue Permeability of Drugs**
   - **Physicochemical Properties of drug like Mol.size, pK_a, o/w Partition Coefficient**
   - **Physiological barriers to diffusion of drugs**

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

3. **Binding of drugs to tissue components.**
   - **binding of drug to blood components**
   - **binding of drug to extra cellular components**

4. **Miscellaneous**

TISSUE PERMEABILITY OF DRUGS

Physicochemical Properties of drug

- Molecular size,
- pKa
- o/w Partition Co Efficient.

Physiological barriers to Diffusion of Drugs

- Simple Capillary Endothelial Barrier
- Simple Cell Membrane Barrier
- Blood Brain Barrier
- Blood – CSF Barrier
- Blood Placental Barrier
- Blood Testis Barrier

1). TISSUE PERMEABILITY OF DRUG

a. physicochemical property:

I) Molecular Size;

Mol wt less then 500 to 600 Dalton easily pass capillary membrane to extra cellular fluid.

Penetration of drug from ECF to cells is function of Mol size, ionization constant & lipophilicity of drug

From extra cellular fluid to cross cell membrane through aqueous filled channels need particle size less then 50 Dalton (small) with hydrophilic property .

Large mol size restricted or require specialized transport system

1). TISSUE PERMEABILITY OF DRUG

a. Physicochemical Property

ii) Degree of Ionization (pKa)

♫The pH at which half of a drug is unionized is called pKa

A weak acid becomes unionized in a strong acidic environment.

A weak acid becomes ionized in a neutral or basic environment.

&

A weak base becomes unionized in a strong basic environment.

A weak base becomes ionized in a neutral or acidic environment.

BUT

The PH of Blood plasma, extra cellular fluid and CSF is 7.4(constant)

Except in acidosis and alkalosis

All the drugs ionize at plasma pH (i.e. Polar , Hydrophilic Drugs)

Can not penetrate the Lipoidal cell membrane

1). TISSUE PERMEABILITY OF DRUG

a. Physicochemical Property

iii) o/w permiability

- **Polar and hydrophilic drugs are less likely to cross the cell membrane**

Where,,,,,,,,

- **Nonpolar and hydrophobic drugs are more likely to cross the cell membrane**

EFFECTIVE $K_{O/W}$ = Fraction unionized at pH 7.4 x $K_{O/W}$ of unionized drug

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 ……..that can be calculated by above formula

- **Lipoidal drug penetrate the tissue rapidly. Among Drugs with same Ko/w but diff in ionization of blood pH.**

- **One which has less ionization show better distribution.**

  E.g. Phenobarbital > salicylic acid

  Both are having same Ko/w but phenobarbitol have more unionized at blood pH

- **highly specialized and less permeable to water soluble drugs.**

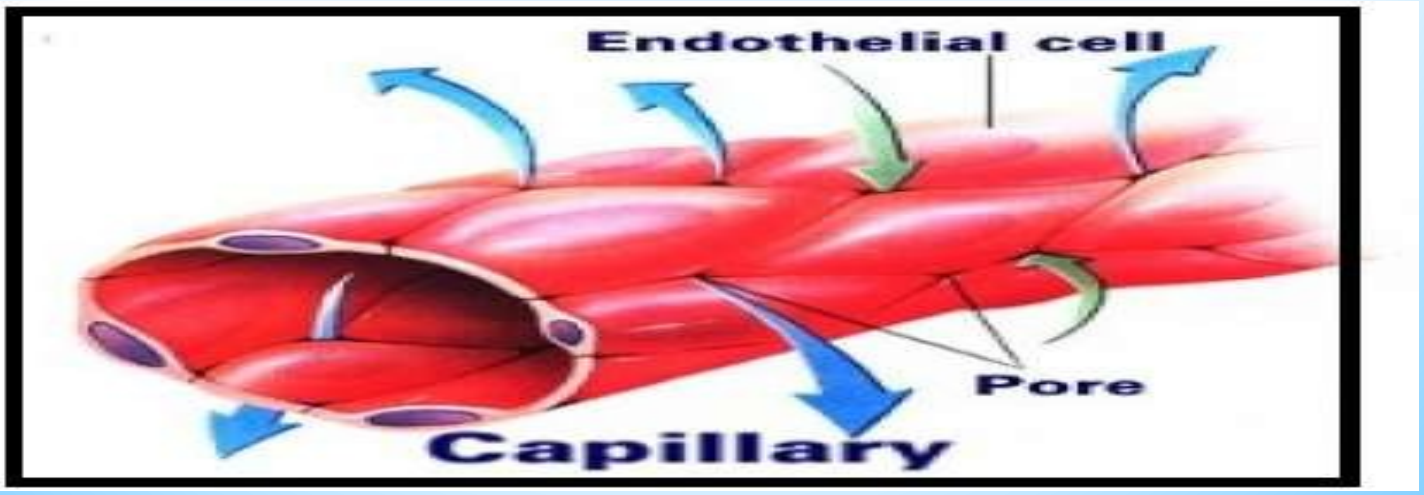
B. PHYSIOLOGICAL BARRIERS

1) The simple capillary endothelial barrier

Capillary supply the blood to the most inner tissue

All drugs ionized or unionized molecular size less than 600dalton diffuse through the capillary endothelium to interstitial fluid

Only drugs that bound to that blood components can't pass through this barrier Because of larger size of complex



B. PHYSIOLOGICAL BARRIERS

2. Simple cell membrane barrier

once the drug diffuse through capillary to extracellular fluid ,its further entry in to cells of most tissue is limited.

Simple cell Membrane is similar to the lipoidal barrier (absorption)

Non polar & hydrophillic drugs will passes through it (passively).

Lipophilic drugs with 50-600 dalton mol size &

Hydrophilic, Polar drugs with ‹50dalton will pass this membrane

B. PHYSIOLOGICAL BARRIERS

3) Blood brain barrier

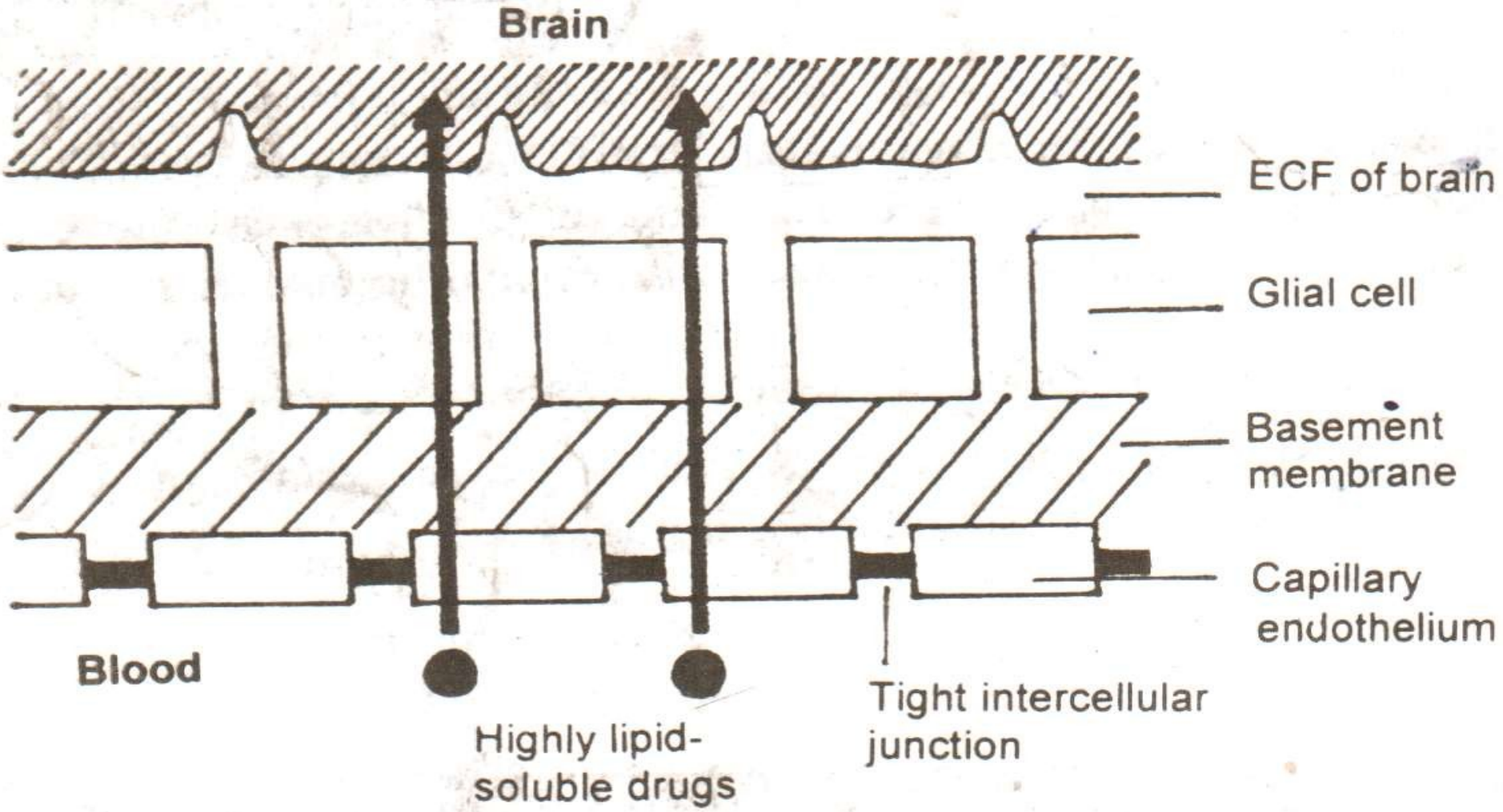


Fig. 3.4 Blood-brain barrier

B. PHYSIOLOGICAL BARRIERS

3) Blood brain barrier

Capillary in brain is highly specialized & much less permeable to water soluble drugs

ENDOTHELIAL CELLS ;- Tightly bonded with each other by intracellular junctions

ASTROCYTES :- present @ the base of endothelial tissue and act as supporting materials

& it Form Envelop around the capillary thus intercellular passage get blocked.

BBB is lipoidal barrier, thus drugs with high o/w partition coefficient diffuse passively others (moderately lipid soluble and partially ionised molecules passes slowly.

Polar natural substance (sugar & amino acid) transported to brain actively thus structurally similar drug can pass easily to BBB.

DIFFERENT APPROACHES TO CROSS BBB

A) **Permeation Enhancers** ;- **Dymethyl Sulfoxide**

B) **Pro- Drug Approach** ;- **Dopamine---- Levodopa**

(Parkinsonism)

and osmatic disruption of the BBB BY infusing

internal carotid artery with mannitol

C) **carrier system** ;- **Dihydropyridine (Lipid soluble) moiety redox system (highly lipophilic & cross the BBB)**

Complex formation (DRUG-DHP). After entering in brain DHP gets metabolize by (CNS) enzyme in brain and drug gets trapped in side the brain.

Polar pyridinium ion can not diffuse back out of the brain.

Ex. Steroidal drug

B. PHYSIOLOGICAL BARRIERS

4) Cerebral spinal fluid barrier ;-

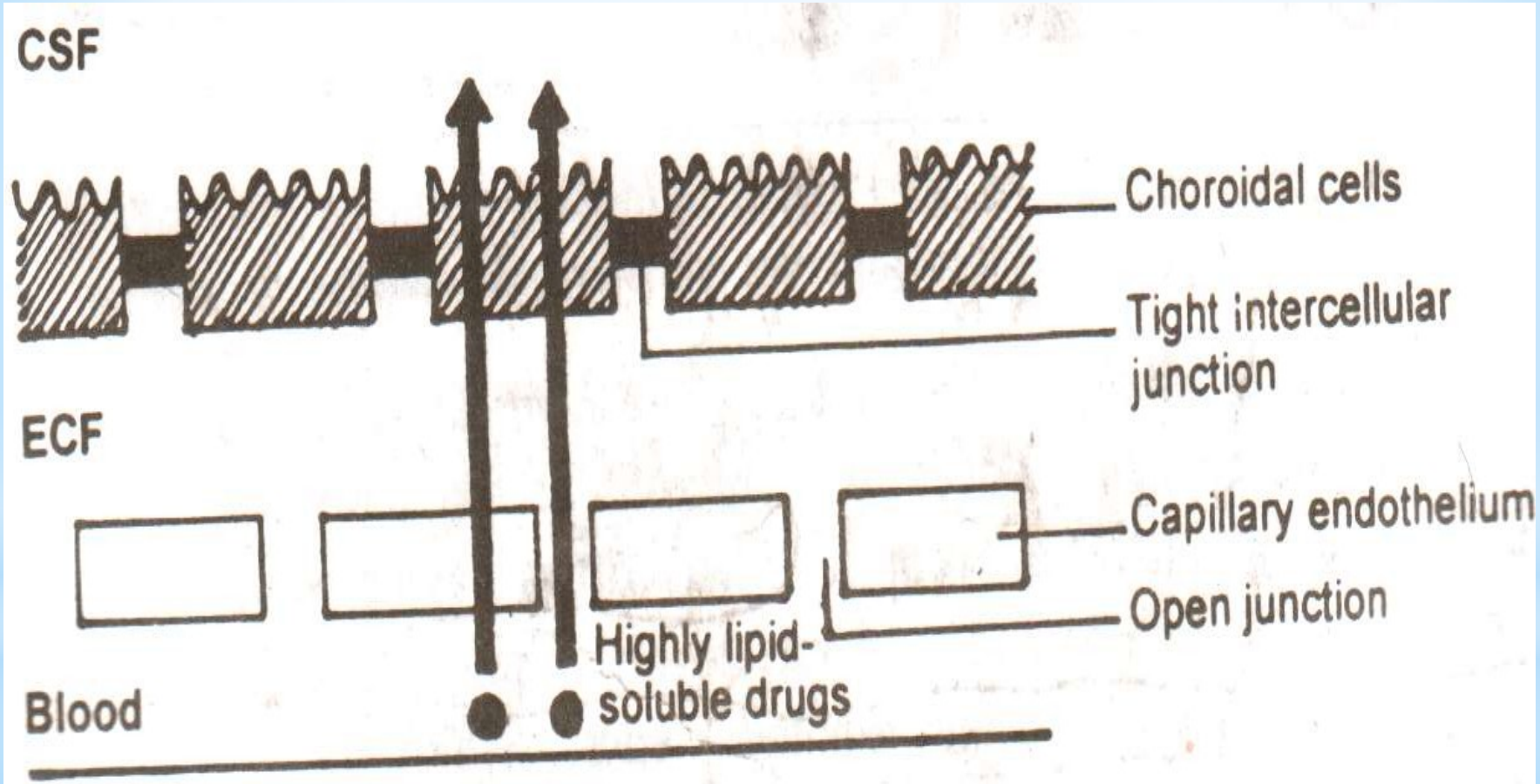


Fig. 3.5 The blood-CSF barrier

B. PHYSIOLOGICAL BARRIERS

4) Cerebral Spinal Fluid Barrier;-

Capillary endothelial cells:- have **open junction** or gaps so…. Drugs can **flow freely b/w capillary wall & choroidal cells.**

Choroids plexus;- major components of CSF barriers is choroidal cells which are joined with each other by **tight junctions forming the blood-CSF barrier** (similar permeability to BBB)

Highly lipid soluble drugs can easily cross the blood-CSF Barrier but moderatly soluble & ionize drugs permeate slowly.

Mechanism of drug transport is **similar to CNS &CSF**

but the Degree of uptake may vary significantly.

B. PHYSIOLOGICAL BARRIERS

5) Placenta barriers ;-

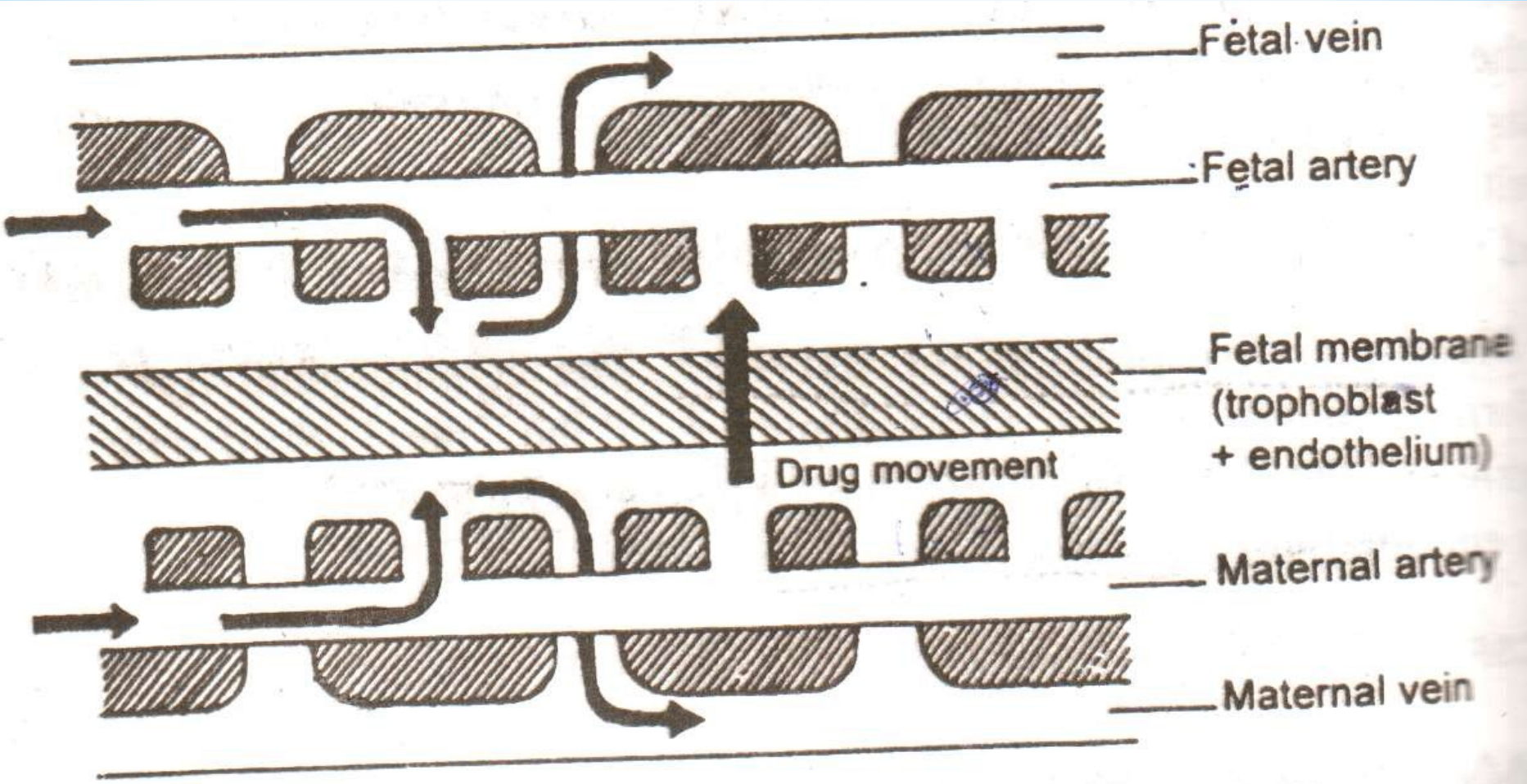


Fig. 3.6 Placental barrier and blood flow across it

B. PHYSIOLOGICAL BARRIERS

- **5) Placenta barriers ;-**
- **It's the barrier b/w Maternal & Fetal blood vessels**
- **Both are separated by fetal trofoblast basement membrane & endothelium .**
- **Thickness *25µ @ early pregnancy* later reduce up to *2µ* (even its effectiveness remain unchanged)**
- **Mol wt <1000 Dalton & moderate to high lipid solubility drugs like….. (Sulfonamides, Barbiturets, Steroids, Narcotic some Antibiotics) cross the barrier by Simple Diffusion rapidly**
- **Essential Nutrients for fetal growth transported by carrier-mediated processes.**
- **Immunoglobulines are transported by endocytosis.**
- **Drugs dangerous to fetus at Two stages**
- **Its advisable to avoid drugs during 1st trimester (fetal organ development) some drugs produce teratogenic effect ex. Phenytoin, methotrexate**
- **later stage pregnancy affect physiological functions like respiratory depression ex. morphine**
- **Better to restrict all drugs during pregnancy.**

B. PHYSIOLOGICAL BARRIERS

6) Blood - Testis Barrier :-

This barrier not located @ capillary endothelium level.

But at sertoli - sertoli cell junction.

It is the tight junction / barrier b/w neighboring sertoli cells that act as blood-testis barrier .

This barrier restrict the passage of drugs to spermatocytes & spermatids.

2). 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 (ml/min/ml)***

Perfusion rate - limited ***when……..***

1) *Drug is highly lipophilic*

2) *Membrane across which the drug is supposed to diffuse*

Above both the cases Greater the blood flow , Faster the distribution

Organ perfused	Blood flow (mL/min)	Organ mass (kg)	Normalized blood flow (mL/min/kg)
Liver	1700	2.5	680
Kidney	1000	0.3	3333
CNS	800	1.3	615
Myocardium	250	0.3	833
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Other (muscle...)	1400	55.6	25
total	5400	70	

- **Distribution is permeability rate - limited in following cases**
  - **When the drug is ionic/polar/water soluble**
  - **Where the highly selective physiology barrier restrict the diffusion of such drugs to the inside of cell.**

- **Distribution will be perfusion rate - limited**
  - **When the drug is highly lipohilic**
  - **When the membrane is highly permeable.**

It is defined as the volume of the blood that flows per unit time per unit volume of the tissue.

Unit: ml/min/ml

(Distribution Rate Constant) Kt = perfusion rate / $K_{t/b}$

Distribution half life = 0.693/Kt

=0.693$K_{t/b}$/perfusion rate

$K_{t/b}$ tissue/blood partition coefficient

Highly lipophilic drugs can cross most selective barrier like BBB, ex. thiopental,

Highly permeable capillary wall permits passage of almost all drugs (except those bound to plasma protein).

Highly perfused tissues Lungs, Kidneys, Liver, Heart, Brain are rapidly equlibriated with lipid soluble drugs

Drug is distributed in a particular tissue or organ depends upon the **size of tissue** (Volume) & **Tissue/blood** partition coefficient

Ex.Thiopental i.v (liphopillic drug) & high tissue/blood partition coefficient towards brain & adipose tissue

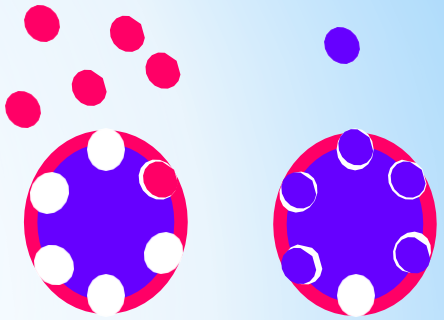
But brain is **highly perfused organ** so drug is distributed **fast** and shows **rapid onset of action than** poorly perfused adipose tissue.

3)Binding of drug to blood and other tissue components

- Binding of drugs to blood components
  - Blood cells
  - Plasma proteins
- Binding of drugs to extra vascular tissues

3).BINDING OF DRUG TO TISSUE COMPONENTS

a) Binding of drug to blood components;-



i) Plasma protein bindings

- Human serum albumin:-all types drug
- $\acute{\alpha}_{1}$- acid glycoprotein **:-basic drugs(impr)**
- Lipoproteins :-basic, lipophilic drugs(chlorpromazin)
- $\acute{\alpha}_{1}$-Globuline :-steroids like corticosterone ,vit-B12
- $\acute{\alpha}_{2}$-Globuline :-vit-A,D,E,K,cupric ions.
- Hemoglobin :-Phenytoin, phenothiazines.

ii) Blood cells bindings:-

RBC : 40% of blood comprise of blood cells

out of that 95% cells are RBC (RBC comprise of hemoglobin)

drugs like, phenytoin,phenobarbiton binds with Hb

,imipramine,chlorpromazine binds with RBC Cell wall

The major component of blood is RBC

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

- **Hemoglobin**
- **Carbonic Anhydrase**
- **Cell Membrane**

BINDING OF DRUGS TO PLASMA PROTEINS

- The binding of drug to plasma protein is reversible
  - The extent or order of binding of drugs to various plasma proteins is:

Albumin >α_1-Acid Glycoprotein> Lipoproteins > Globulins

Human Serum Albumin

- Most abundant plasma protein with large drug binding capacity
- Both endogenous compounds and drugs bind to HSA
- Four different sites on HSA:

  Site I: warfarin and azapropazone binding site

  Site II: diazepam binding site

  Site III: digitoxin binding site

  Site IV: tamxifen binding site

3).BINDING OF DRUG TO TISSUE COMPONENTS

B. Extra Vascular Tissue proteins

- **40% of total body weight comprise of vascular tissues**
- **Tissue-drug binding result in localization of drug at specific site in body and serve as reservoir**
- **As binding increases it also increase bio-logical half life.**
- **Irreversible binding leads to drug toxicity. (carbamazepin-autoinduction)**
- **liver>kidney>lungs>muscle>skin>eye>bone>Hair, nail**

4). Miscellaneous Factors

- **Age:**
  - a) Total body water
  - b) Fat content
  - c) Skeletal muscles
  - d) Organ composition
  - e) Plasma protein content
- **Pregnancy**
- **Obesity**
- **Diet**
- **Disease states**

4). MISCELLANEOUS FACTORS

a) AGE:-

Difference in distribution pattern is mainly due to

Total body water -(both ICF &ECF) greater in infants

Fat content - higher in infants & elderly

Skeletal muscle - lesser in infants & elderly

organ composition – BBBis poorly developed in infants & myelin content is low & cerebral blood flow is high, hence greater penetration of drug in brain

plasma protein content- low albumin in both infants & elderly

b) PREGNANCY:-

During Pregnancy, due to growth of UTERUS,PLECENTA,FETUS…

Increases the volume available for distribution drug.

fetus have separate compartment for drug distribution, plasma & ECF Volume also increase but albumin content is low.

C) OBECITY :-

In obese persons, high adipose (fatty acid) tissue so high distribution of lipophilic drugs

4). MISCELLANEOUS FACTORS

d) DIET:- A diet high in fats will increases free fatty acid levels in circulation thereby affecting binding of acidic drugs (NSAIDs to albumin)

e) DISEASE STATES:- mechanism involved in alteration of drug distribution in disease states.

i) Altered albumin & other drug-binding protein concentration.

ii) Alteration or reduced perfusion to organ or tissue

iii) Altered tissue pH.

iv) Alteration of permeability of physiological barrier (BBB)

EX- BBB(in meningitis & encephalities) BBBbecomes more permeable polar antibiotics ampicilin, penicilin G. &

patient affect CCF, Perfusion rate to entire body decreases it affect distribution.

f) DRUG INTERACTION:-Displacement interaction occurs when two drugs administered which having similar binding site affinity.

Ex.A.Warfarin (Displaced Drug)&B.Phenylbutabutazone (Displacer)HSA

Apparent Volume Of Distribution

The apparent volume of distribution is a proportionality constant relating the plasma concentration to the total amount of drug in the body.

$$X \alpha C$$

$$X = Vd.C$$

$$Vd = X/C$$

Apparent volume of distribution = amount of drug in the body/ plasma drug concentration

Apparent volume of distribution is dependent on concentration of drug in plasma.

Drugs with a large apparent volume are more concentrated in extra vascular tissues and less concentrated intravascular.

In certain pathological cases, the Vd for the drug may be altered if the distribution of the drug is changed.

Vd=X/C

$Vd=X_0/C_o$

=i.v. bolus dose/concentration of drug in plasma

for drugs given as i.v. bolus:

$$Vd_{(area)}=X0/K_E(AUC)$$

For drugs administered extravascularly:

$$Vd_{(area)} = FXo/K_E(AUC)$$