DRUG DISTRIBUTION

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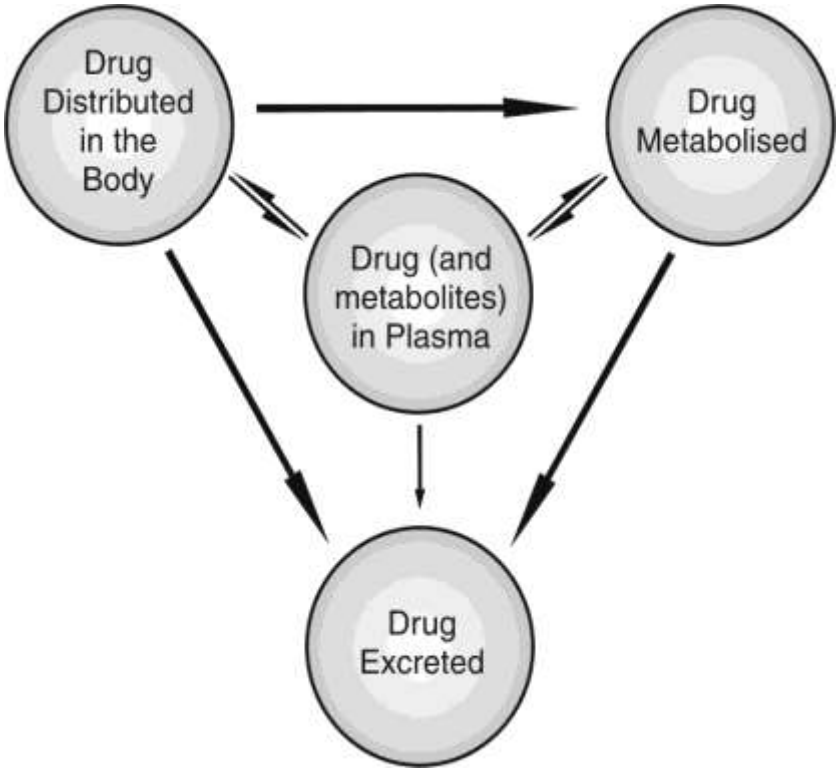
- After entry into the systemic circulation, either by intravascular injection or by absorption from any of the various extravascular sites, the drug is subjected to a number of processes called as disposition processes.

- **Disposition** *is defined as the processes that tend to lower the plasma concentration of drug.* The two major drug disposition processes are –

- **Distribution** *which involves reversible transfer of a drug between compartments.*

- **Elimination** *which causes irreversible loss of drug from the body.* Elimination is further divided into two processes –
  - **Biotransformation** (metabolism)
  - **Excretion.**

INTERRELATIONSHIP BETWEEN DIFFERENT PROCESSES OF DRUG DISPOSITION



- **Distribution** *is defined as the reversible transfer of a drug between one compartment and another.*

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

- Distribution is a passive process, for which, the driving force is concentration gradient between the blood and the extravascular tissues.

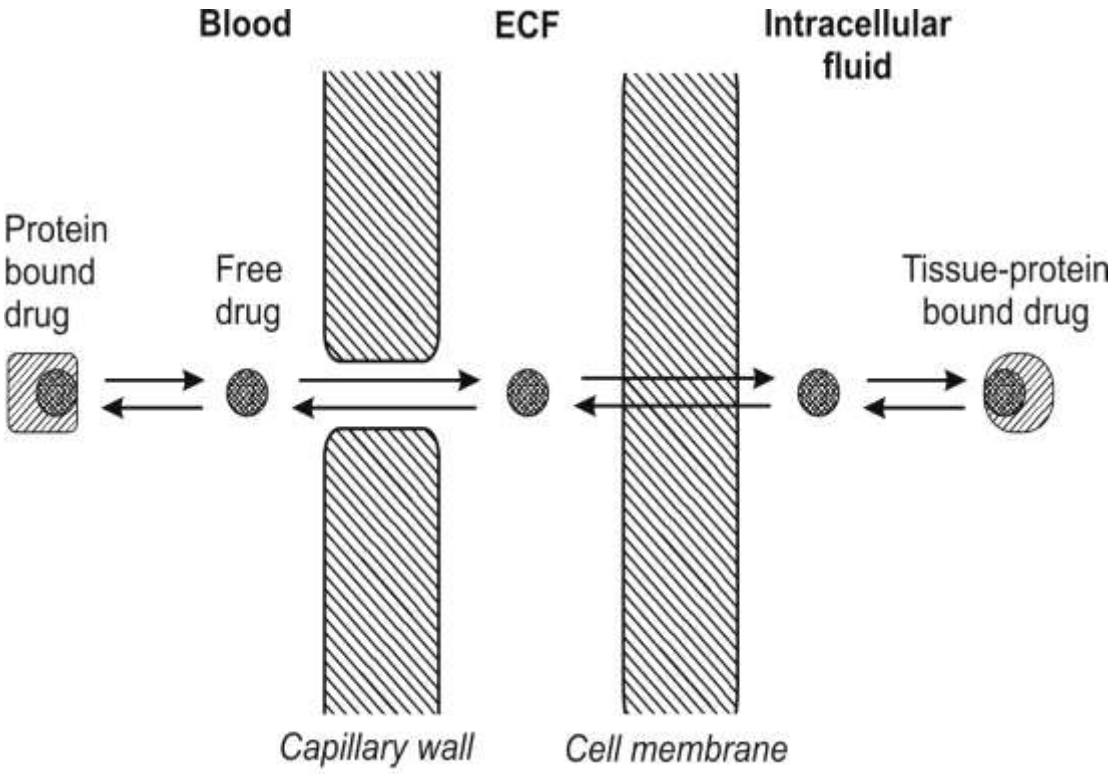
- The process occurs by diffusion of free drug only until equilibrium is achieved.

- 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 sometimes duration of drug action.

STEPS IN DRUG DISTRIBUTION

- Distribution of drug present in systemic circulation to extravascular tissues involves following steps
  - 1. **Permeation of free or unbound drug present in the blood through the capillary wall (occurs rapidly) and entry into the interstitial/extracellular fluid (ECF).**
  - **2. 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 –**
    - Rate of perfusion to the extra cellular tissue
    - Membrane permeability of the drug.

SCHEMATIC OF THE STEPS INVOLVED IN DRUG DISTRIBUTION



FACTORS AFFECTING DISTRIBUTION OF DRUGS

- 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.
- Differences in drug distribution arise due to various factors …..

1. Tissue permeability of the drug:

   ✓ Physicochemical properties of the drug like molecular size, pKa and 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 drugs to blood components

✓Binding of drugs to extravascular tissue proteins

4. Miscellaneous factors:

   ✓Age
   ✓Pregnancy
   ✓Obesity
   ✓Diet
   ✓Disease states
   ✓Drug interactions.

TISSUE PERMEABILITY OF DRUGS

- The two major rate-determining steps in the distribution of drugs are:
  - Rate of tissue permeation, and
  - Rate of blood perfusion.
- If the blood flow to the entire body tissues were rapid and uniform, differences in the degree of distribution between tissues will be indicative of differences in the tissue penetrability of the drug and the process will be *tissue permeation rate-limited*.
- Tissue permeability of a drug depends upon the physicochemical properties of the drug as well as the physiological barriers that restrict diffusion of drug into tissues.

PHYSICOCHEMICAL PROPERTIES OF THE DRUG

- Important physicochemical properties of drug that influence its distribution are

  - ❑Molecular size,
  - ❑Degree of ionisation,
  - ❑Partition coefficient and
  - ❑Stereochemical nature.

- Almost all drugs having molecular weight less than 500 to 600 Daltons easily cross the capillary membrane to diffuse into the extracellular interstitial fluids.

- Penetration of drugs from the extracellular fluid into the cells is a function of molecular size, ionisation constant and lipophilicity of the drug.

- Only small, water-soluble molecules and ions of size below 50 Daltons enter the cell through aqueous filled channels whereas those of larger size are restricted unless a specialized transport system exists for them.

- The degree of ionisation of a drug is an important determinant in its tissue penetrability.

- The pH of the blood and the extravascular fluid also play a role in the ionisation and diffusion of drugs into cells.

- A drug that remains unionised at these pH values can permeate the cells relatively more rapidly. Since the blood and the ECF pH normally remain constant at 7.4, they do not have much of an influence on drug diffusion unless altered in conditions such as systemic acidosis or alkalosis.

- Most drugs are either weak acids or weak bases and their degree of ionisation at plasma or ECF pH depends upon their pKa.

- 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.

- Only unionised drugs which are generally lipophilic, rapidly cross the cell membrane.

- Among the drugs that have same o/w partition coefficient but differ in the extent of ionisation at blood pH, the one that ionises to a lesser extent will have greater penetrability than that which ionises to a larger extent;
    - for example, pentobarbital and salicylic acid have almost the same K o/w but the former is more unionised at blood pH and therefore distributes rapidly.
- The influence of drug p Ka and K o/w on distribution is illustrated by the example that thiopental, a nonpolar, lipophilic drug, largely unionised at plasma pH, readily diffuses into the brain whereas penicillins which are polar, water-soluble and ionised at plasma pH do not cross the blood-brain barrier.
- The extent to which a drug exists in unionised form governs the distribution pattern

- Situations that result in alteration of blood pH affect such a pattern; for example, acidosis (metabolic or respiratory) results in decreased ionisation of acidic drugs and thus increased intracellular drug concentration and pharmacological action.

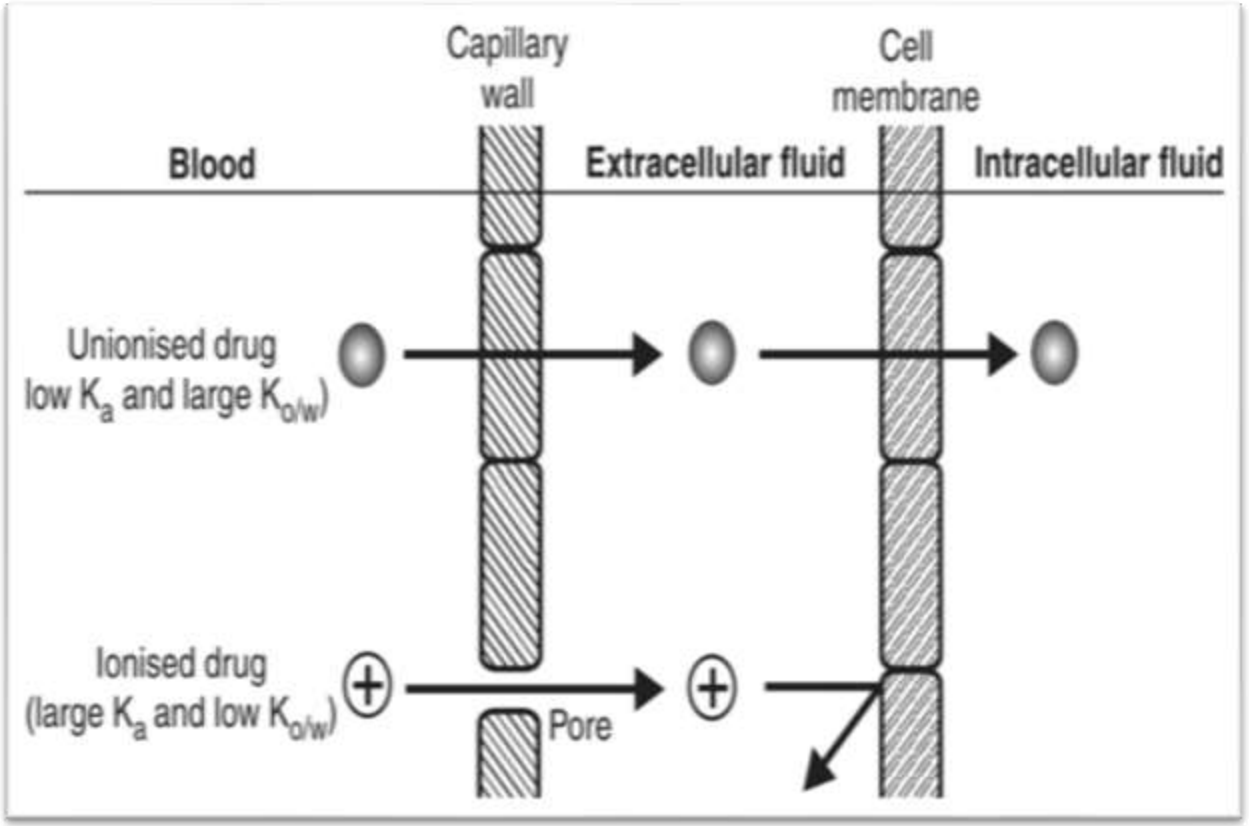
- Opposite is the influence of alkalosis. Sodium bicarbonate induced alkalosis is sometimes useful in the treatment of barbiturate (and other acidic drugs) poisoning to drive the drug out and prevent further entry into the CNS and promote their urinary excretion by favouring ionisation.

- Converse is true for basic drugs; acidosis favours extracellular whereas alkalosis, intracellular distribution.

- *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 Surface Area = (fraction Unionised at pH7.4) (K o/w of unionised drug)

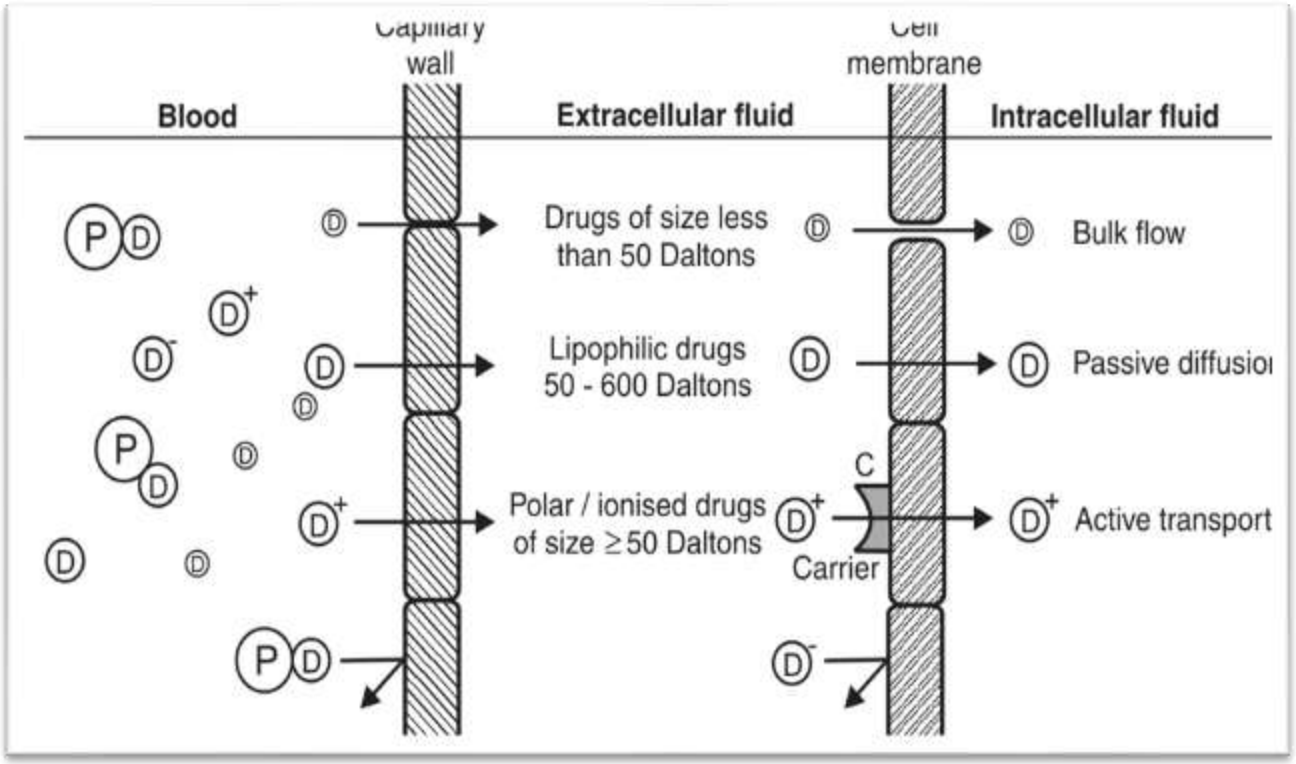
PERMEATION OF UNIONISED AND IONISED DRUGS ACROSS THE CAPILLARY AND THE CELL MEMBRANE



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.

PLASMA MEMBRANE BARRIER AND DRUG DIFFUSION ACROSS IT



- Important simple and specialized physiological barriers are:
  - Simple capillary endothelial barrier
  - Simple cell membrane barrier
  - Blood-brain barrier
  - Blood-CSF barrier
  - Blood- placental barrier
  - Blood-testis barrier.

THE SIMPLE CAPILLARY ENDOTHELIAL BARRIER

- The membrane of capillaries that supply blood to most tissues is, practically speaking, not a barrier to moieties which we call drugs.
- Thus, all drugs, ionised or unionised, with a molecular size less than 600 Daltons, diffuse through the capillary endothelium and into the interstitial fluid.
- Only drugs bound to the blood components are restricted because of the large molecular size of the complex.

THE SIMPLE CELL MEMBRANE BARRIER

- Once a drug diffuses from the capillary wall into the extracellular fluid, its further entry into cells of most tissues is limited by its permeability through the membrane that lines such cells.

- Simple cell membrane is similar to the lipoidal barrier in the GI absorption of drugs

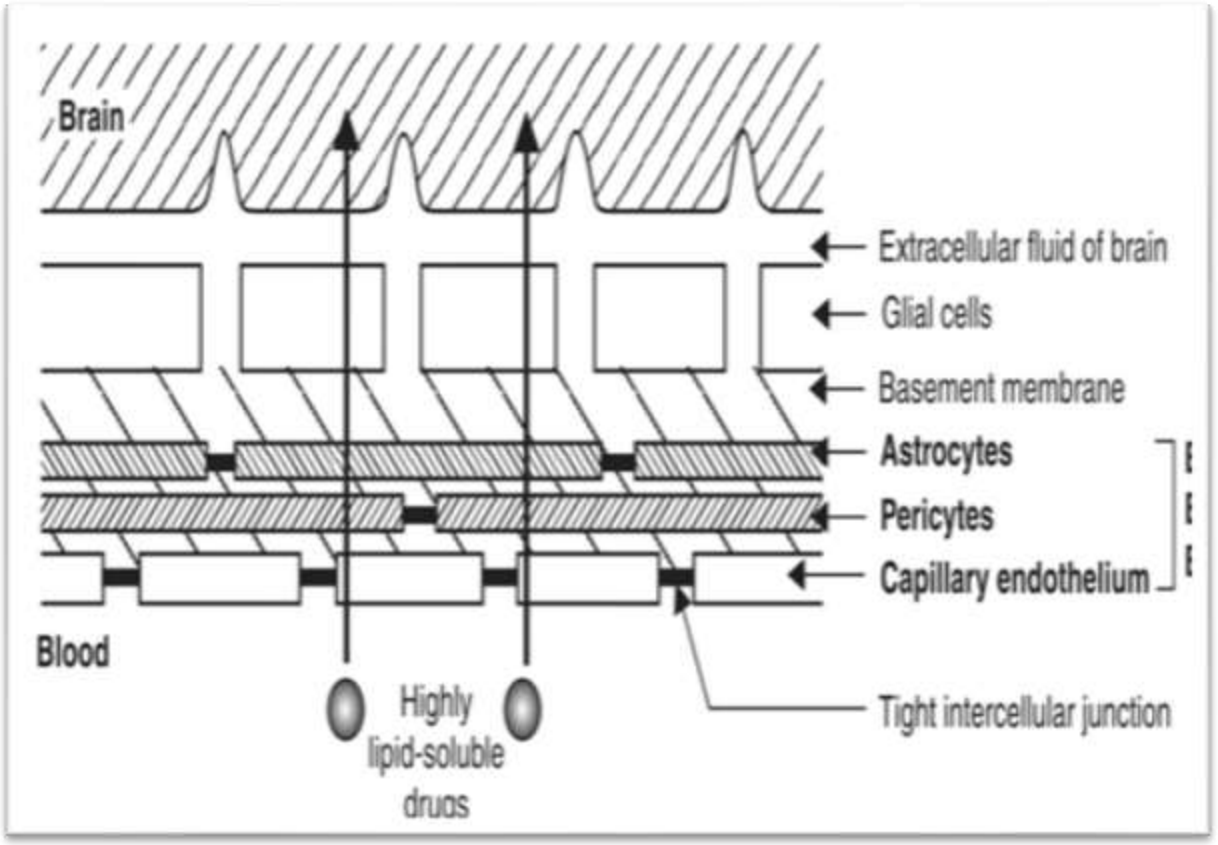
BLOOD-BRAIN BARRIER (BBB)

- Unlike the capillaries found in other parts of the body, the capillaries in the brain are highly specialized and much less permeable to water-soluble drugs.

- The brain capillaries consist of endothelial cells which are joined to one another by continuous tight intercellular junctions comprising what is called as the **blood-brain barrier** .

- The presence of special cells called as **Pericytes** and **Astrocytes**, which are the elements of the supporting tissue found at the base of endothelial membrane, form a solid envelope around the brain capillaries.

BLOOD-BRAIN BARRIER



- As a result, the intercellular (paracellular) passage is blocked and for a drug to gain access from the capillary circulation into the brain, it has to pass through the cells (transcellular) rather than between them.

- There are specific sites in the brain where the BBB does not exist, namely, the trigger area and the median hypothalamic eminence.

- Drugs administered intranasally may diffuse directly into the CNS because of the continuity between submucosal areas of the nose and the subarachnoid space of the olfactory lobe.

- There is also virtual absence of pinocytosis in brain.

- A solute may thus gain access to brain via only one of two pathways:
    - Passive diffusion through the lipoidal barrier – which is restricted to small molecules (with a molecular weight less than a threshold of approximately 700 Daltons) having high o/w partition coefficient.
    - Active transport of essential nutrients such as sugars and amino acids. Thus, structurally similar foreign molecules can also penetrate the BBB by the same mechanism.

- The effective partition coefficient of thiopental, a highly lipid soluble drug is 50 times that of pentobarbital and crosses the BBB much more rapidly.
- Most antibiotics such as penicillin which are polar, water-soluble and ionised at plasma pH, do not cross the BBB under normal circumstances.

- The selective permeability of lipid soluble moieties through the BBB makes appropriate choice of a drug to treat CNS disorders an essential part of therapy;

  for example, Parkinsonism, a disease characterized by depletion of dopamine in the brain, cannot be treated by administration of dopamine as it does not cross the BBB. Hence, levodopa, which can penetrate the CNS where it is metabolised to dopamine, is used in its treatment.

- Targeting of polar drugs to brain in certain conditions such as tumour had always been a problem.

- Three different approaches have been utilized successfully to promote crossing the BBB by drugs:

  - Use of permeation enhancers such as dimethyl sulphoxide (DMSO).
  - Osmotic disruption of the BBB by infusing internal carotid artery with mannitol.
  - Use of *dihydropyridine redox system* as drug carriers to the brain.

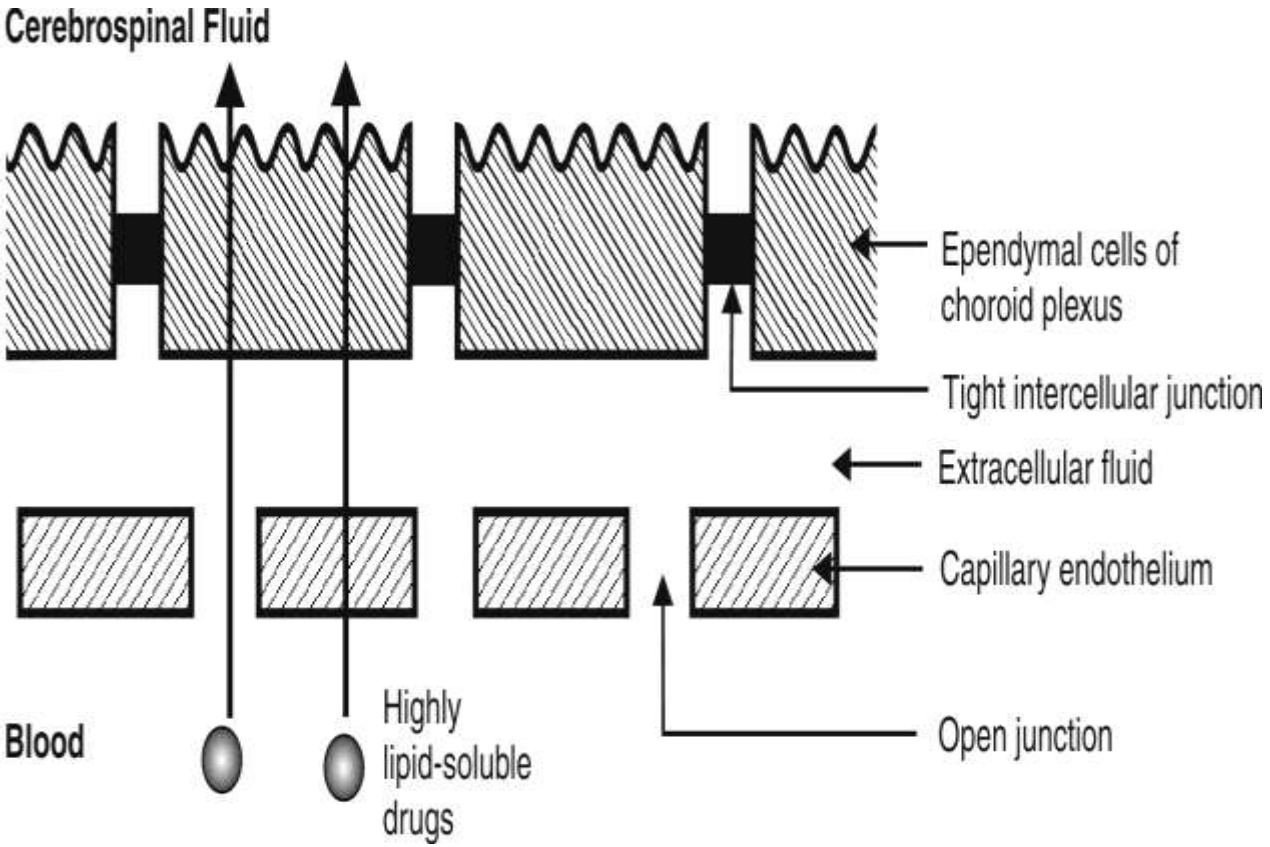
BLOOD-CEREBROSPINAL FLUID BARRIER

- The cerebrospinal fluid (CSF) is formed mainly by the choroid plexus of the lateral, third and fourth ventricles and is similar in composition to the ECF of brain.

- The capillary endothelium that lines the choroid plexus have open junctions or gaps and drugs can flow freely into the extracellular space between the capillary wall and the choroidal cells.

- However, the choroidal cells are joined to each other by tight junctions forming the blood-CSF barrier which has permeability characteristics similar to that of the BBB

BLOOD-CSF BARRIER



- As in the case of BBB, only highly lipid soluble drugs can cross the blood-CSF barrier with relative ease whereas moderately lipid soluble and partially ionised drugs permeate slowly.

- A drug that enters the CSF slowly cannot achieve a high concentration as the bulk flow of CSF continuously removes the drug. For any given drug, its concentration in the brain will always be higher than in the CSF.

- Although the mechanisms for diffusion of drugs into the CNS and CSF are similar, the degree of uptake may vary significantly. In some cases, CSF drug concentration may be higher than its cerebral concentration.

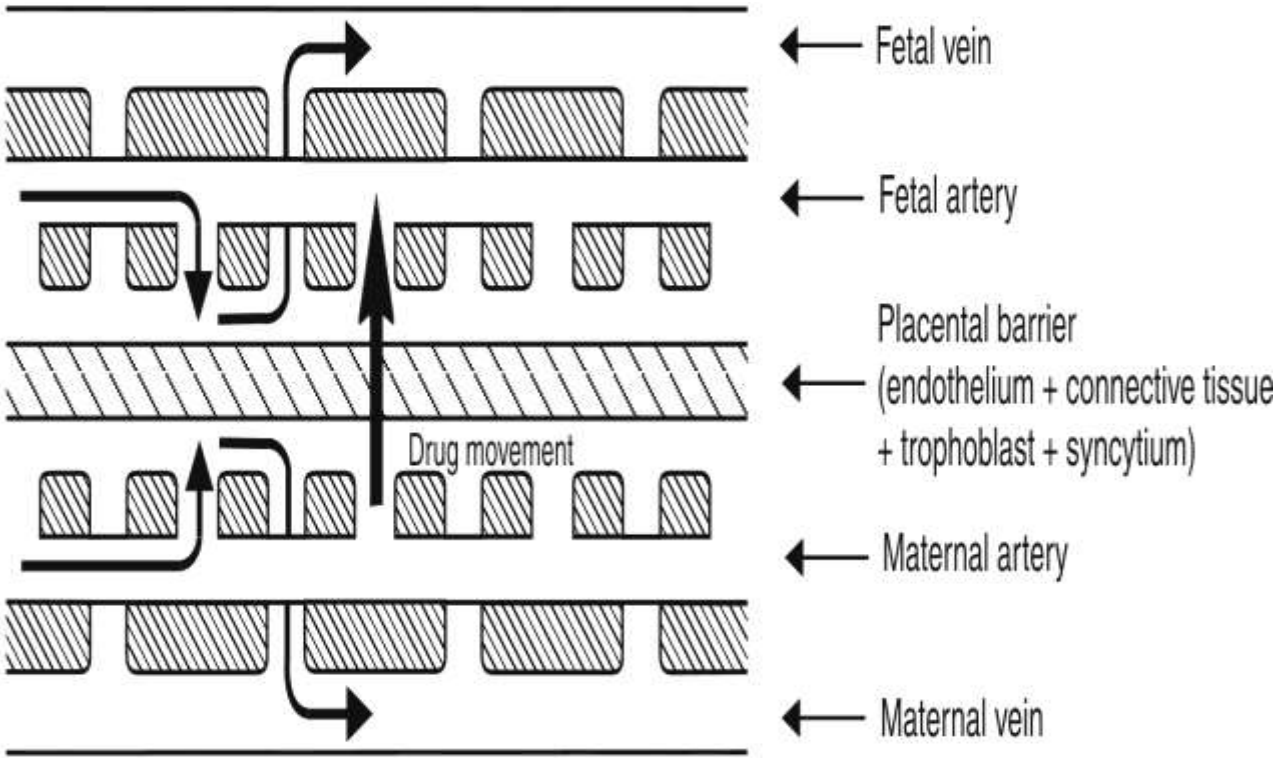
BLOOD-PLACENTAL BARRIER

- The maternal and the foetal blood vessels are separated by a number of tissue layers made of foetal trophoblast basement membrane and the endothelium which together constitute the placental barrier.

- The human placental barrier has a mean thickness of 25 microns in early pregnancy that reduces to 2 microns at full term which however does not reduce its effectiveness.

- Many drugs having molecular weight less than 1000 Daltons and moderate to high lipid solubility e.g. ethanol, sulphonamides, barbiturates, gaseous anaesthetics, steroids, narcotic analgesics, anticonvulsants and some antibiotics, cross the barrier by simple diffusion quite rapidly, which shows that the placental barrier is not as effective a barrier as BBB.

PLACENTAL BARRIER AND BLOOD FLOW ACROSS IT



- Nutrients essential for the foetal growth are transported by carrier-mediated processes. Immunoglobulins are transported by endocytosis.

- An agent that causes toxic effects on foetus is called as teratogen.

- Teratogenecity is defined as foetal abnormalities caused by administration of drugs during pregnancy.

BLOOD-TESTIS BARRIER

- This barrier is located not at the capillary endothelium level but at sertoli-sertoli cell junction.

- It is the tight junctions between the neighbouring sertoli cells that act as the blood-testis barrier. This barrier restricts the passage of drugs to spermatocytes and spermatids.

MISCELLANEOUS FACTORS AFFECTING DRUG DISTRIBUTION

AGE

Differences in distribution pattern of a drug in different age groups are mainly due to differences in—

- *Total body water* (both intracellular and extracellular) — is much greater in infants
- *Fat content* — is also higher in infants and elderly
- *Skeletal muscles* — are lesser in infants and in elderly
- *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
- *Plasma protein content* — low albumin content in both infants and in elderly

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.

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.