

**DISTRIBUTION:**

The process of reversible movement of a drug to and from the blood and various tissues of the body is called as distribution.

◦ Factors affecting drug distribution:

- (1) Lipid solubility
- (2) Ionization of drug at physiologic pH (pKa value of the drug).
- (3) Extent of plasma and tissue protein binding.
- (4) Influence of diseases.
- (5) Perfusion rate
- (6) Presence of various barriers
- (7) Other factors (Age, diet, obesity)

◦ Physiological barriers:

There are certain barriers that are present in the body which act as permeability membrane for the distribution of drugs.

Only selective substances can pass through these membranes.

- (i) simple capillary endothelial barrier
- (ii) simple cell membrane barrier
- (iii) Blood brain barrier.
- (iv) Blood - CSF barrier.
- (v) Blood - Placental barrier
- (vi) Blood - Testes barrier.

(i) simple capillary endothelial barrier:

- Capillaries are microscopic vessels that supply blood to the innermost tissues.
- It has simple endothelium arranged as the basement membrane.
- The drugs (ionized & unionized) with molecular size of less than 600 dalton can diffuse through it.
- The molecules bound to the plasma cannot diffuse because of larger molecular size.

(ii) simple cell membrane barrier:

- It acts as a barrier for certain molecules and ions.
  - Occurs after the drug crosses the capillary wall into ECF.
  - Only non-polar substances which are lipid soluble can cross the cell membrane.
- But water-soluble substances can't pass through it.

(iii) Blood-Brain Barrier:

- Brain capillaries consist of endothelial cells which are joint together by continuous tight intracellular junctions called as Blood-Brain Barrier.
- BBB is highly regulated interface that separate peripheral circulation

from CNS.

- Astrocyte cells are the projections that provide support to the BBB.
- Molecules cross the BBB by paracellular or transcellular pathways.
- In paracellular pathway, Ions and some utilize concentration gradient to pass through the BBB.
- In transcellular pathway, different mechanisms like passive diffusion, receptor-mediated transport and transcytosis is involved.
- Factors like mol. weight, charge, lipid solubility, surface activity affect the BBB crossing.

• Lipid soluble  
 Mol. wt 400-600 Da  
 Highly ionized

} → Crosses BBB.

- To overcome the difficulty in CNS penetration, various drug delivery systems are adopted:
  - (1) Use of lipophilic analogues.
  - (2) Use of permeation enhancer like dimethyl sulphoxide.

- (3) Use of carrier mediated pathway
- (4) Use of IV or IA route of adm<sup>n</sup>

(IV) Blood - CSF barrier.

- A fluid-brain barrier that separates blood from CSF and CSF from brain tissues.
- CSF is a colorless liquid which contains glucose.
- Forms in choroid plexus of lateral ventricle made up of capillaries covered by ependymal cells.
- More permeable than BBB (through pinocytosis or active transport.)
- There is a valve/flap present which prevent the back flow of CSF. This valve opens when the hydrostatic pressure in subarachnoid space is greater than venous sinuses.

• Non-ionized  
 ↑ o/w partition co. eff

} → Easily pass the CSF barrier.

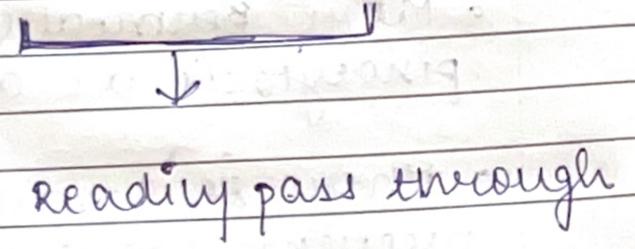
(V) Blood - Placenta barrier:

- Placenta is an organ that connects the foetus with uterus of the mother.

• Essential nutrients,  $O_2$ ,  $CO_2$  can pass through it.

• It serves as a barrier to prevent the infectious and toxic agents from reaching the uterus.

- Lipid soluble compounds - Ethanol, chloral hydrate, chlorpromazine, sulphonamides, Barbiturates, Antihistatics, Analgesia, steroids



• Quaternary  $NH_3^+$  muscle relaxants ] → do not cross the barrier.

• RBCs, WBCs, Platelets ] → do not cross the barrier

• Immunoglobulin's IgG alone crosses the barrier

Anti-Pn

(vi) Blood-Testis barrier:

• Tightest blood-tissue barrier of mammalian body.

• Prevents immune response of the body to the sperm cell.

• Hydrophilic ] → do not cross the barrier.  
↑ Mol. weight ]