

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 admin

(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.

Date

- 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 - Ethanol
chloral hydrate
chlorpromazine
sulphonamides
Barbiturates
Anesthetics
Analgesia
Steroids



readily pass through

- 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

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(vi) Blood-Testis barrier:

- Tightest blood-tissue barrier of mammalian body.

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

- Hydrophilic
↑ Mol. weight] → Do not cross the barrier.