There is no god but Allah

Physiological barriers to transport of drugs.

Physiological barriers

After entering the blood circulation ,the drugs are distributed within the blood & out side of the blood to various tissues.

The drugs have to cross various barriers in the body to reach the sites of their action.

This process is accomplished by diffusion, & infiltration mechanism.

- Blood brain barrier
- Tissue binding
- Plasma protein binding
- Breast milk (mammary barrier)
- Body fat reservoir
- Blood testicular barrier
- Placenta barrier

Drugs with high molecular weight like heparin

Strongly bound with plasma protein like warfarin

Drugs are largely restricted to the vascular compartment

Because they cannot cross the capillary membrane.

Drugs that can cross the capillary membrane but cannot cross the cell membrane like mannitol

Drugs that can easily cross both the capillary membrane & the cell membrane.

These are equally distributed within the body fluid like alcohol, salicylates.

Drugs having special affinity for certain tissues .

e.g. iodine having special affinity for thyroid & digoxin for the hear tissue.

Blood Brain Barrier (penetration into brain & CSF)

The capillary endothelial cells in brain have tight junctions lack large intercellular pores.

Further , an investment of neural tissue covers the capillaries.

Blood CSF barrier is located in the choroid plexus ,capillaries are lined by choroidal epithelium

Only lipid soluble and unionsed drugs can pass through it.

There is also an enzymatic blood barrier such as monoamine oxidase, cholinesterase etc are present in capillary wall or cells lining them.

Inflammation of meninges or brain ↑s permeability of barrier.

The BBB is deficient at CTZ in the medulla oblongata & at certain periventricular sites.

Efflux transporters like P-gp & anion transporters present in brain and choroid vessels to extrude many drugs that enter brain by other processes

Tissue binding

Certain drugs get specially bound to certain tissues e.g

Thiopentone sodium to fatty tissue

Chloroquine to eye

Tetracycline to bone

Digitalis to the heart

Plasma protein binding

A number of drugs bind to the plasma protein.

Some drugs are highly bound with plasma protein, for example, **Tolbutamide Diazepam, Warfarin Phenytoin**

Some drugs are only slightly bound to plasma proteins, Such as **Streptomycin Amoxycillin Morphine**

Some drugs are not bound to plasma protein such as **Gabapentin**

Plasma binding proteins are**Albumin, β-globulin ,Lipoproteins α_1 acid glycoprotein**

Plasma protein binding

The drug after absorption in blood are found in two forms

Free fraction of drug

Protein bound fraction

Free fraction of drug

This part moves freely in the blood

It is pharmacologically active.

This fraction is metabolised and excreted from the body.

Plasma protein binding

Protein bound fraction

This fraction is confined to plasma.

This part pharmacologically inactive.

It cannot leave the vascular space and is no metabolised or eliminated

Protein binding is reversible.

Plasma protein bound and free form of the drug in blood are always in equilibrum.

Binding of drugs with plasma protein is nonspecific ,therefore, when the two drugs bind at the same site on plasma protein one drug may displace the other from its binding site,

Clinical significance plasma protein binding

1.Highly plasma protein bound drugs are confined to vascular compartment b/c they cannot cross the membrane, so they have smaller volume of distribution .

2.High degree of protein binding make the drug long acting b/c it is not available for metabolism and excretion.

3.In case of poisoning ,highly plasma protein bound drugs are difficult to removed by haemodialysis.

Clinical significance plasma protein binding

4.In disease states such as anaemia, renal failure and chronic liver diseases etc plasma albumin level are low , so there will be an ↑ in the free form of the drug ,which can lead to drug toxicity

5.Plasma protein binding can cause displacement interaction, the drug with higher affinity will displace the one having lower binding affinity.

Salicylates displace sulfonylureas & methotrexate

Indomethacin , phenytoin displace Warfarin .

Sulphonamides & vit K displace Bilirubin.

Breast milk (mammary barrier)

Non ionized drugs cross the mammary barrier.

Normal pH of in mammary gland is slightly acidic.

When basic drugs pass through mammary gland they are ionized in Acidic pH & get trapped.

These drugs cannot diffuse back into blood & are secreted in the milk.

Breast milk (mammary barrier)

In inflammatory conditions e.g. mastitis, the pH is ↑ed .

Which keep the basic drugs in unionized form & ↑s their diffusion back into blood.

Placenta barrier

The placental barrier consists of the trophoblastic epithelium, covering the villi, the chorionic connective tissue & the fetal capillary endothelium.

Lipid soluble and unionised drugs can cross the placenta by simple diffusion these are morphine anaesthetics, Corticosteroids.

Quaternary ammonium compounds & substances with high molecular weight can not cross the placental barrier such as, d-tubocurarine, insulin.

Blood Testicular barrier

In each seminiferous tubule, the cells of sertoli & spermatogonia are tightly attached to the basement membrane & to each other.

These tight junctions prevent the accidental entry of sperm fragments into blood & development of anti sperm antibodies

These junctions also prevent maternal infectious agents or toxins from entering the seminiferous tubules.

This barrier is disrupted by any injury or vasectomy which can cause infertility.

Body fat reservoir

Some lipid soluble drugs are stored in fatty tissues..

Drugs like barbiturate & phenoxybenzamine are rapidly removed from blood store in the body fat & skeletal muscles, thus decreasing their duration of action.

Important physiological barriers

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