School of medical and Allied Sciences

Course Code : BP604T Course Name: BIOPHARMACEUTICS AND PHARMACOKINETICS

TOPIC: ABSORPTION AND DISTRIBUTION

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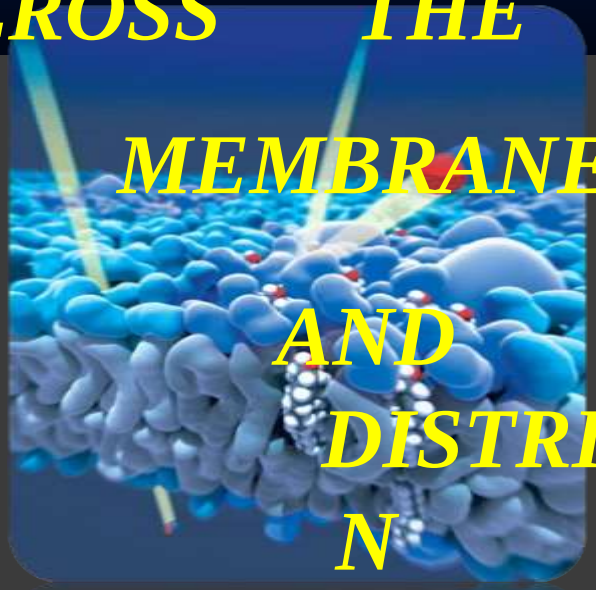
PASSAGE OF DRUG MOLECULES ACROSS THE CELL MEMBRANE AND DISTRIBUTION



INTRODUCTION

- The movement or translocation of drug from one side of biological barrier to other is called Biotransport and the mechanism underlying the transfer of drug across biological barriers are called the Transport mechanism.

The major transport mechanism are :

1.Passive Diffusion 2.Carrier Mediated transport

A. Facilitated Diffusion

B. Active Transport 3.Pinocytosis or Phagocytosis 4.Filtration

1. PASSIVE DIFFUSION

•Passive diffusion is the process by which the drug molecules pass through a biological barrier from a phase of higher concentration to the phase of lower concentration without requiring any expenditure of energy.

•Nonionised drugs can diffuse passively across the biological barrier at a rate proportional to their lipid : water partition coefficient.

•For a weak electrolytes Diffusion depends upon the degree of ionisation of the drug, the PH of the surrounding environment and the lipid :water partition coefficient

- Many drugs are acidic or basic compounds, which are ionized to a certain degree in aqueous medium. Their degree of ionization depends on their dissociation constant (pKa) and the pH of the environment and extension of ionisation.
- Henderson-Hasselbach equation:

For Acidic drug:

$$pKa = pH + \log \frac{\text{Conc. Of nonionised Acid}}{\text{Conc.Of ionised Acid}}$$

For Basic drug:

$$pKa = pH + \log \frac{\text{Conc. Of ionised base}}{\text{Coc. Of non ionised base}}$$

Carrier-mediated transport

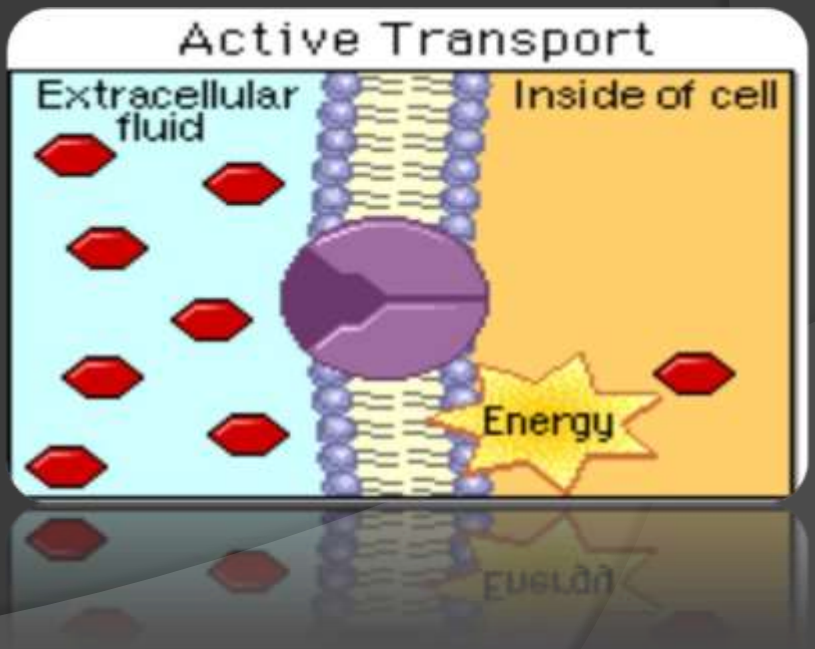
- Polar compounds like sugar and amino acids and certain drugs of therapeutic interest cannot penetrate through membrane by passive diffusion but are moved by a carrier system present on the membrane surface
- Carrier molecules are usually proteins which combine with a drug substrate and form a complex
- After the complex crosses the membrane ; carrier dissociates from the drug and carrier returns to the original side of membrane for reuse.

Facilitated diffusion :

- Carrier-mediated transport from higher to lower concentration without needing energy and translocates the substrate in the direction of electrochemical gradient.
- e.g. GLUT 4 enhances the permeation of glucose across a muscle cell membrane

Active transport

- Transport of drug is energy dependent
- Carrier mediated transport against a concentration gradient
- From lower to higher concentration



Absorption

Absorption is movement of a drug from site of administration to the central compartment and the extent to which this occurs.

- Only lipid soluble drugs can cross the biological Membranes
- Lipid soluble drugs is unionised ,ionised form is water soluble

Absorption via GI tract

Mouth :

Saliva pH is slightly acidic.

lipid soluble or non ionised basic drugs can be absorbed from this site.

After sublingual absorption directly reaches systemic circulation bypassing first –pass metabolism.

Eg :Isosorbide dinitrate

Stomach : pH is Acidic

lipid soluble unionised acidic drug can be absorbed

Absorption pass through hepatic portal system –First pass metabolism

Intestine :

pH Alkaline

drug have to go hepatic portal before reaching systemic circulation

Colon :

pH is alkaline

From external haemorrhoidal vein major amount of drug enter directly to systemic circulation

Parentral route :

Drug injected I V completely and rapidly distributed

Reaches blood stream directly without crossing any membrane

Lungs :

Vapourised form and spray of suspended microfined particles are absorbed by simple diffussion from pulmunary epithelium and mucous membrane of trachea and lungs

Eg : Salbutamol , General anaesthetics

Factors that Affect the rate and Extent of Drug Absorption

1. Dosage form / Drug formulation
2. Physicochemical Properties of the Drug
    - molecular weight
    - pH
    - lipophilic vs hydrophilic
        * Partition coefficient

Eg - Phenylbutazone, Salicylates & Sulfonamides displaces Tolbutamide → hypoglycemia

- Salicylates,Indomethacin,Phenytoin & Tolbutamide displaces Warfarin → haemorrhage.

- Sulfonamides & vitamin K displace endogenous ligands like bilirubin→ kernicterus in neonates.

- Drug extensively protien binding has smaller apparent volume of distribution.

- warfarin- 99% bound, Tolbutamide- 98% bound,
- Phenytoin- 90% bound causes toxicity after getting displaced from plasma protein binding sites.

Compartments of drug distribution:

Cellular reservoir :

- A drug may have a great affinity for plasma proteins, yet be primarily distributed in tissues, This situation would occur if the tissue have higher affinity for drug.
- Eg: - Digoxin and Emetin in skeletal muscles, heart, liver and kidney

  Iodine in thyroid

Fat Reservoir:

- Highly lipid- soluble drugs like thiopentone selectively accumulated in fat and adipose tissue.

Transcellular Reservoir :

- Aqueous humour – eg Chloramphenicol and Prednisolone
- CSF – Eg: Aminosugars and Sucrose
- Endolymph, joint fluids – Eg: Ampicillin

Bones and Connective Tissue Reservoirs :

- Many drugs like Tetracycline ,Lead, Arsenic and Fluoride , form a complex with bone salt and get deposited in nails, bones and in teeth.

Plasma Protein Binding Drug Reservoir:

- Drugs bind to plasma and cellular proteins in a reversible manner and in dynamic equilibrium.
- Free drug + Protein <=>Drug-Protein complex

Redistribution-

- Termination of drug effect, after the withdrawal of drug, because of its redistribution in to vicera, muscle mass, lean tissue and fat
- when highly lipid soluble drugs given by I.V enters the brain rapidly .

  Eg : Thiopentone

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