UNIT I

MECHANISMS

OF

DRUG PERMEATION / TRANSPORT

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Mechanisms of drug permeation

Permeation: is the movement of drug molecules into & within the biological environment. It involves several processes of drug transport across the cell membranes.
• Generally the drugs are administered away from their site of action.
• To reach their site of action they are permeate from one compartment to another by crossing the different barriers.
• So the drugs have to cross the cell membranes.
• Examples:
Figure 1-1. The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action. Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.
Cell membrane:

- Fluid bi-layer of phospholipids.
  - Scattered membrane protein molecules embedded in bi-layer serve as
    - Receptors --- selective targets for drug action
    - Ion channels
    - Transporters
  - Lipid molecules are capable of lateral movement.
- It is flexible
- Has high electrical resistance
- Relatively impermeable to highly polar molecules
- Highly permeable to lipid soluble drug molecules
Fig. 2.2: Illustration of the organisation of biological membrane
Main Mechanisms Of Drug Permeation / Transport

1. Passive diffusion
   - Lipid diffusion
   - Aqueous diffusion

2. Carrier mediated transport
   - Active transport
   - Facilitated diffusion

3. Pinocytosis
   - Endocytosis
   - Exocytosis
Fig. 7.1 Routes by which solutes can traverse cell membranes. (Molecules can also cross cellular barriers by pinocytosis.)
Passive Diffusion

Drugs cross the cell membranes along the concentration and electrical gradient without expenditure of energy according to Fick’s Law.

**Fick’s Law:**

\[
\text{Flux (molecules per unit time)} = (C_1 - C_2) \times \text{Area} \times \text{Permeability Coefficient} \times \text{Thickness}
\]

**Permeability Co-efficient:**

It is a measure of the mobility of the drug molecules in the medium of diffusion path.
Lipid diffusion

The most important mechanism for transport of majority of drugs in the body. It is the passive movement of lipid soluble molecules through membranes or other lipid structures.
Characteristics of Lipid Diffusion:

- Passive process, governed by Fick’s Law.
- Along a concentration gradient.
- Only lipid soluble drug molecules can cross.
- It occurs through the cells, by dissolving in the lipid matrix of the membrane.
- Energy not required.
- Not saturable or capacity limited
- Not inhibitable by other substances.

**Example:** Most of the drugs
Factors Affecting the Lipid Diffusion

1. **Concentration gradient** From higher $\rightarrow$ lower
2. **Surface Area** Larger the SA $\rightarrow$ greater the diffusion
3. **Lipid solubility** The most important factor. It is dependent upon:-
   a) Lipid aqueous partition coefficient.
   b) Degree of ionization. It depends on
      - pKa of drug (Ionization constant)
      - pH of the medium.
Lipid aqueous partition co-efficient

It determines how readily the drug molecules can move between aqueous & lipid media.

Greater the co-efficient – Faster the diffusion

Degree of Ionization: It depends on

• **pKa of a drug:** When pH is same as pKa, 50% drug is ionized and 50% is unionized.
  
  Aspirin 3.5, Morphine 7.9

• **pH of the medium:** Ionization of weak electrolytes is pH dependent.
Ionization of weak electrolyte drugs (weak acidic or weak basic) is pH dependent, they lose/gain protons as follows:

**Weak acidic drug:**

Neutral aspirin $\leftrightarrow$ Aspirin anion + Proton

$HA \leftrightarrow A^- + H^+$

**weak basic drug:**

Pyrimethamine cation $\leftrightarrow$ Neutral Pyrimethamine + Proton

$BH^+ \leftrightarrow B + H^+$

At low pH

Reaction moves towards left

At high pH

Reaction moves towards right

So Weak Acidic drugs are mostly non-ionized at low pH & weak basic drugs are non-ionized at high pH or vice versa.
<table>
<thead>
<tr>
<th>Non-ionized drug:</th>
<th>Ionized drug:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncharged, Non polar</td>
<td>Charged, Polar</td>
</tr>
<tr>
<td>Lipid soluble</td>
<td>Lipid insoluble, Water soluble</td>
</tr>
<tr>
<td>Permeates membrane rapidly by lipid diffusion.</td>
<td>Does not permeates rapidly by lipid diffusion.</td>
</tr>
</tbody>
</table>

**Ionization ↓ lipid solubility so** Permeable form of a drug is determined by relative concentration of its Ionized & Non-ionized forms.
• This relationship is given by **HENDERSON-HASSELBALCH EQUATION** as

\[
\log \left( \frac{[\text{Protonated}]}{[\text{Unprotonated}]} \right) = pK_a - pH
\]

For acids: \( pK_a = pH + \log \left( \frac{[HA]}{[A^-]} \right) \) Or \( \text{Molecular Conc. Of Non-Ionized acid} \)
\( \text{Molecular Conc. Of Ionized acid} \)

For bases: \( pK_a = pH + \log \left( \frac{[BH^+]}{[B]} \right) \) Or \( \text{Molecular Conc. Of Ionized base} \)
\( \text{Molecular Conc. Of Non-Ionized base} \)

If \([A^-] = [HA]\) then \([HA] = 1\)

\([A^-]\)

Since \( \log 1 = 0 \), under this condition \( pK_a = pH \)
So when \( pKa = p\text{H} \), 50% drug is ionized & 50% is Non-ionized --- ratio is \( 1/1 \)

one degree change in pH alters unionized : ionized , 10 folds.

<table>
<thead>
<tr>
<th>pH</th>
<th>Weak acidic drugs Un-ionized : ionized</th>
<th>Weak basic drugs Un-ionized : ionized</th>
</tr>
</thead>
<tbody>
<tr>
<td>( =pK_a -3 \text{ units} )</td>
<td>1:0.0001</td>
<td>1:1000</td>
</tr>
<tr>
<td>( =pK_a -2 \text{ units} )</td>
<td>1:0.001</td>
<td>1:100</td>
</tr>
<tr>
<td>( =pK_a -1 \text{ unit} )</td>
<td>1:0.01</td>
<td>1:10</td>
</tr>
<tr>
<td>( =pK_a )</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>( =pK_a + 1 \text{ unit} )</td>
<td>1:10</td>
<td>1:0.01</td>
</tr>
<tr>
<td>( =pK_a + 2 \text{ units} )</td>
<td>1:100</td>
<td>1:0.001</td>
</tr>
<tr>
<td>( =pK_a + 3 \text{ units} )</td>
<td>1:1000</td>
<td>1:0.0001</td>
</tr>
</tbody>
</table>
Figure 1–2. Influence of pH on the distribution of a weak acid between plasma and gastric juice separated by a lipid barrier.
Q: Aspirin is a weak organic acid with a pKₐ of 3.5. What percentage of a given dose will be in the lipid-soluble form in the duodenum at a pH of 4.5?

a) About 1%
b) About 10%
c) About 50%
d) About 90%
e) About 99%
• **Important implications of HHE relationship are:**

  1. Enhancing the urinary excretion of weak electrolytes.
  2. Ion trapping / pH partition.

  1. Manipulation of pH of urine can help in enhancing urinary excretion of drugs in case of over dosage.

**Weak acids are excreted faster in alkaline urine**

**Weak bases are excreted faster in acidic urine.**

Alkalization of urine with Sodium bicarbonate can promote excretion of weak acidic drugs i.e **Aspirin** in over dosage.

Acidification with Ammonium chloride can promote excretion of weak basic drugs i.e phenobarbitone in over dosage.
2. **Ion Trapping (pH partition):** It means that weak acids tend to accumulate in the compartments of relatively high pH whereas weak basis do the reverse.

- So drugs can be trapped due to pH difference in:
  - Stomach, intestinal contents
  - Breast milk, prostatic/vaginal secretions.
- Increasing plasma pH causes weakly acidic drugs to be extracted from the C.N.S into plasma.
Table 1–3. Body fluids with potential for drug “trapping” through the pH-partitioning phenomenon.

<table>
<thead>
<tr>
<th>Body Fluid</th>
<th>Range of pH</th>
<th>Total Fluid: Blood Concentration Ratios for Sulfadiazine (acid, pKₐ 6.5)¹</th>
<th>Total Fluid: Blood Concentration Ratios for Pyrimethamine (base, pKₐ 7.0)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>5.0–8.0</td>
<td>0.12–4.65</td>
<td>72.24–0.79</td>
</tr>
<tr>
<td>Breast milk</td>
<td>6.4–7.6²</td>
<td>0.2–1.77</td>
<td>3.56–0.89</td>
</tr>
<tr>
<td>Jejunum, ileum contents</td>
<td>7.5–8.0³</td>
<td>1.23–3.54</td>
<td>0.94–0.79</td>
</tr>
<tr>
<td>Stomach contents</td>
<td>1.92–2.59²</td>
<td>0.11⁴</td>
<td>85,993–18,386</td>
</tr>
<tr>
<td>Prostatic secretions</td>
<td>6.45–7.4²</td>
<td>0.21</td>
<td>3.25–1.0</td>
</tr>
<tr>
<td>Vaginal secretions</td>
<td>3.4–4.2³</td>
<td>0.11⁴</td>
<td>2848–452</td>
</tr>
</tbody>
</table>

¹) Receptors largely determine the quantitative relations between dose or concentration of drug and pharmacologic effect. The results are derived from published data.
Aqueous Diffusion
(Intracellular/ Paracellular diffusion/ filtration)

• Passive diffusion
• Through the aqueous pores
• Along a concentration gradient
• Small water soluble drug molecules in solution form (M.W up to 20,000 – 30,000)
• If the drug is charged, its flux is also influenced by electrical fields (e.g. the membrane potential, transtubular potential)
Importance

• The most important mechanism by which drugs pass through capillary endothelium membrane.
• Important in glomerular filtration.
• Protein bound drug molecules can not pass.
• Brain and testes are protected from many circulating drugs.
**Carrier Mediated Transport**

- Important for drug molecules too large or too insoluble in lipid to diffuse passively through membranes.
- Carriers are trans-membrane proteins. The drug molecules chemically related to naturally occurring peptides, amino-acids, or sugars can use these carriers.
- Carrier binds one or more molecules or ions, changes conformation & releases them on the other site of membrane.
Main sites:

• Renal tubule.
• Biliary tract.
• Blood brain barrier. (BBB)
• Gastrointestinal tract. (GIT)

Types:

• Active Transport
• Facilitated Diffusion:
Active transport: The characteristics are:

1. Against the concentration gradient
2. Energy dependent, obtained from hydrolysis of ATP
3. Carrier is required
4. Selective
5. Saturable
6. Competitive inhibition by another drug binding to same carrier.
Examples:
1. Transport of LEVODOPA into the brain.
2. Active absorption of 5FLUOROURACIL through the Gut wall.
3. Active proximal renal tubular secretion of PENICILLIN & PROBENECID.
   So excretion of PENICILLIN can be inhibited by PROBENECID.
4. Some drugs can block natural carriers i.e. COCAINE can block catecholamine uptake at adrenergic nerve endings.
**Reverse transporters:** Carriers specialized in expelling foreign molecules as the enter the cells.

One large family is ABC (ATP binding cassette) family & includes.

1. P-glycoprotein or multidrug resistance type 1 (MDR1) transporter, found in the brain, testes & other tissues and in some drug resistant neoplastic cells

   It can be inhibited by grape fruit juice & certain drugs i.e VERAPAMIL.

2. Multidrug resistance –associated protein (MRP) transporters play important role in excretion of drug or its metabolites into urine or bile.
Facilitated Diffusion: A mechanism to enhance diffusion of drugs with low lipid solubility.

- Along a concentration gradient
- Carrier mediated:
  - Carrier increases lipid solubility of drug $\rightarrow \uparrow$ rate of diffusion
- Not energy dependent
- Saturable
- Competitive inhibition

E.g. Glucose entry into the cell by Glucose transporters-GLUT1-GLUT5
**Pinocytosis (Endocytosis & Exocytosis)**

Specific receptors for transport proteins must be present for this process to work.

**Endocytosis:** Drugs which have very large molecules (macromolecules) can be engulfed by the cell membrane in a vesicle & carried into the cell & released within the cell by pinching off the vesicle & breakdown of its membrane.

**Examples:**
- Transport of vitamin $\text{B}_{12}$ with a binding protein (intrinsic factor) across gut wall.
- Iron is transported into hemoglobin synthesizing RBCs precursors with transferrin.
Exocytosis:

**Exocytosis is the** reverse of endocytosis. It is responsible for secretion of many substances from cells.

E.g. **Expulsion of neurotransmitters into the synaptic cleft.**

The neurotransmitter substances are stored in membrane bound vesicles in nerve endings to protect them from metabolic destruction.

Appropriate activation of nerve ending causes expulsion of its contents into the synaptic cleft.