Absorption

Drug Movement Across Membranes

- Drugs must cross cell membranes to be absorbed
- Cell membranes have hydrophilic heads and hydrophobic tails

Characteristics That Facilitate Movement

- pH
- Ionisation
- Surface area

LogP vs LogD

- LogP describes a drug's lipophilicity and predicts movement in cell membranes
- P = [compound] organic/ [compound] aqueous

- LogD also describes a drug's lipophilicity
- Aqueous phase is adjusted to a specific pH

Transporters Involved in Drug Disposition

- Peptides
- Amino acids
- Glucose
- Aqueous diffusion – simple diffusion, concentration gradient
- Lipid diffusion
- Intestinal epithelia
- Hepatocytes (liver)
- Kidney proximal tubules
- BBB

Plasma Protein Binding

- After absorption, some drugs are bound to proteins in the blood (plasma)
- Proteins involved in the binding of drugs include o Albumin
  - Alpha-1-acid glycoprotein o Some lipoproteins
- Only free drug can be distributed to tissues (drugs bound to protein cannot cross the cell membrane)

Blood Brain Barrier

- BBB
  - Endothelial cells of the capillaries o Basement membrane is continuous o Limited number of small, aqueous pores
- Basically a lipid barrier
- Lipid soluble drugs can dissolve in the membrane and enter the brain by passive diffusion
- Water soluble drugs cannot enter the brain
- BBB represents significant barrier to development of CNS drugs

First Pass Metabolism

- When a drug is swallowed it is absorbed from the stomach/ small intestine
- Enters portal circulation and carried via portal vein to liver
- Liver is the major organ for drug metabolism
- If a drug has a high first pass metabolism, a higher dose is required
- Avoiding first pass metabolism is considered a good thing
- Sublingual, rectal, transdermal, injections avoid first pass metabolism, such routes of administration are absorbed into the veins which drain into the heart without entering the portal system (liver)

Routes of Administration

Oral

- Convenient, relatively safe, no need for sterility
- Affected by o Gut content (fed vs fasted) o Gastrointestinal motility o Splanchnic blood flow o Particle size and formulation

Sublingual (under the tongue)

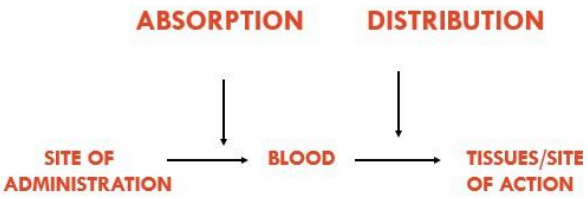
- Convenient, relatively safe, no need for sterility, avoids first pass metabolism and acid/enzymes in the stomach, tastes important

Eye Drops

- Must be sterile, localised treatment e.g. eye infection, glaucoma

Injection

- Must be sterile, avoids first pass metabolism, faster onset of action, difficult to administer, adverse reactions, can be subcutaneous, intramuscular, intravenous



<u>Distribution</u>

Drug Distribution

- For a drug to have any effect, it must be distributed to a site of action
- Most drugs are distributed via passive diffusion
- Lipophilic drugs can traverse membranes
- Hydrophilic drugs are trapped in the plasma
- Factors that affect drug distribution are o logP, between 0 and 5 is good o Molecular weight, less than 500 is good o Water solubility o Lipid solubility
    - Molecular size of water-soluble drugs o Whether the drug is carried by transporters o Protein binding o Blood flow to the tissue
    - Specialised barriers within the body e.g. BBB

Volume of Distribution (Vd)

- Body water is divided into 3 distinct groups o Plasma (3L) o Interstitial (9L) o Intracellular (28L)
- Lipophilic drugs can traverse membranes (Vd>3L)
- Hydrophilic drugs are trapped in the plasma (Vd=3L)

Tissue Affinity

- Some drugs accumulate in certain tissues or cell types for which they have affinity - Drugs with an affinity for plasma proteins remain in the blood longer
- Drugs with an affinity for melanin remain in pigmented tissues for longer etc.

Metabolism

Drug Metabolism

- Increases the water solubility of a drug facilitating elimination
- The liver is the main drug metabolising organ
- Occurs via faeces or urine
- While it facilitates elimination it may also increase toxicity or pharmacological effect
- Metabolism results in metabolites, they are less active and more water soluble (polar) than the parent compound

Phase I Metabolism Reactions

- Catabolic
- E.g., oxidation, reduction and hydrolysis

- Occurs mainly in the liver
- It is the chemical conversion of a chemical into something more water soluble (polar)
- Cytochrome P450 enzymes are the main enzymes involved in phase I reactions, CYP450
- Different CYPs metabolise different drugs
- Sometimes the drug is metabolised to be more toxic, sometimes to be more pharmacological - Some drugs are inactive until they have been metabolised
- E.g. codeine o Converted to morphine by CYP2D6
    - Genetic polymorphisms exist, some will have poor analgesic effect, others will have opioid effect
    - Dependent on race, genetics

Phase II Metabolism Reactions

- Anabolic/ conjugation
- Making the molecule bigger and more polar; more likely to be excreted
- Polar group is attached to the drug by a “handle”
- E.g., glucuronidation, sulphation, glutathione, acetylation
- Glucuronidation o Most common phase II o Catalysed by UGTs
- Glutathione o In the liver
    - Non-enzyme
    - For paracetamol metabolism, paracetamol overdose