Absorption

Broad Concepts of Drug Absorption:

1. Drugs outside the cell are usually required to enter the cell to reach the site of action
2. Usually delivered to the tissue in blood
3. Must cross biological membranes to enter cell and interact with target receptors or enzymes

Mechanisms by Which Drugs Cross Cell Membranes	
Passive Diffusion ▪ Drugs must be sufficiently hydrophobic to penetrate membranes ▪ Must then pass through to the aqueous intracellular environment to reach drug target ▪ Mustn't be trapped by membranes	**Transporter-assisted Uptake** ▪ Specialised uptake transports for physiologically important organic anions and cations ▪ Can also accommodate many anionic and cationic drugs ▪ Assist these drugs to enter cells and reach cell targets

Ficks's Law: The Law of Passive Diffusion

Simple diffusion is governed by the permeability of the membrane and the concentration gradient. When the thickness of the barrier is small and/or the permeability, surface area of the starting concentration is high relatively to the receiving compartment, then flux across membranes is favoured.

Flux (across membrane) = PA ($C_1 - C_2$)

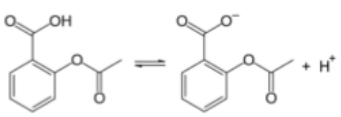
C_1 = concentration in original compartment
C_2 = concentration in receiving compartment
A = area across which diffusion path
P = permeability coefficient, which measures mobility of xenobiotic in medium of diffusion path

The Effect of Drug Ionization on Passive Diffusion

- Ionization influences the extend of drug movement between aqueous and lipid environments
- Strong acids/bases are ionized at any pH (very few drugs are strong acids or bases!)
- Weak acids/bases – the extent of ionization depends on the pH of the aqueous environment
- Mostly drugs are relatively neutral – the best kind for crossing membranes!

Ionization of an Acidic Drug

- Many drugs are weak acids or bases, and only partially dissociated in water
- The extent of dissociation is governed by the pKa:



definition: $K_a = \frac{[A^-][H^+]}{[HA]}$

Where [HA] is the acid and $[A^-]$ is its conjugate base

Henderson Hasselbalch Equation:

Describes the ratio between concentrations of an acid or base and its conjugate for in relation to the pH of the medium. Gives relative concentrations of acid and base based on pK of the acid and pH of the medium. Remember that $pK_a = -\log_{10} K_a$

$$HA + H_2O \leftrightarrow A^- + H_3O^+$$

$$K_a = \frac{[A^-][H^+]}{[HA]}$$

Take $-\log_{10}$ of both sides and rearrange to get:

$$pH = pK_a + log\frac{[A^-]}{[HA]}$$

The Effect of Tissue pH on Drug Disposition

- pH varies in different biological fluids, and it affects how much a weak acidic or basic drug is absorbed because only the unionized form can cross membranes.
- pH also affects drug excretion because membranes also have to be crossed.

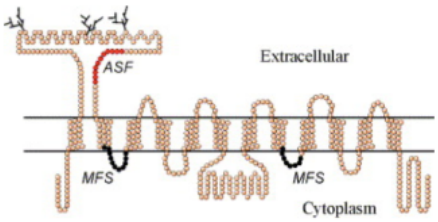
Example: Aspirin

- Stomach pH is 2.5 (one log unit below pKa)
- Thus, 10x higher concentration of acid form than conjugate base (less ionization)
- At pH 7.5 in intestine – 4 log units about pKa
- Aspirin absorption can occur in stomach as well as intestine

Influx Transporters:

- Solute Carrier Transporters (SLC): physiological role in anion and cation transport across membrane
- Also mediate uptake of numerous drugs
- Major classes for organic anions (OATs and OATPs) and cations (OCTs and OCTNs)
- Located on plasma membrane of cells in intestine, liver,
- kidney, brain and others
- Do not require energy – work by facilitated diffusion

OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OCTN	Organic cation transporter, novel



The Structure of SLC Influx Transporters

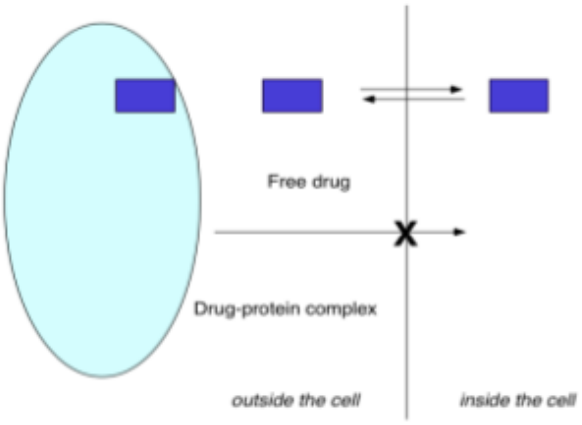
- Consists of 12 trans-membrane domains
- Several intracellular and extracellular loops orient the transport in the membrane

Plasma Protein Binding and the Free Fraction of Drug

- Plasma proteins limit the free drug concentration – only unbound drug in plasma can enter the cell, i.e. total drug in serum may not be available
- Serum albumin binds many acidic drugs
- α_1-acidglycoprotein (AAG) binds many basic drugs. Inflammatory conditions can increase AAG and alter free fraction of a drug.

Protein Binding Equilibrium:

- Only $[Drug]_f$ can cross membranes and is pharmacologically active
- $[Drug]_b$ cannot cross membranes due to its size and is unavailable to act
- $[Drug]_f$ is metabolized and eliminated
- Competition can displace one drug from protein binding sites



Protein and Tissue Binding:

- Total blood volume is 5-6 litres in a 70kg human
- Total body water is about 32-40 litres
- A pharmacokinetic parameter volume of distribution provides some information of protein and tissue binding.
    - Values for Vd close to blood volume reflect high degree of protein binding
    - Values near 30 litres reflect distribution in total body water
    - Values greater than 40 litres reflect binding in tissues (usually hydrophobic or basic chemicals)

<u>First Pass Metabolism of Drugs:</u>

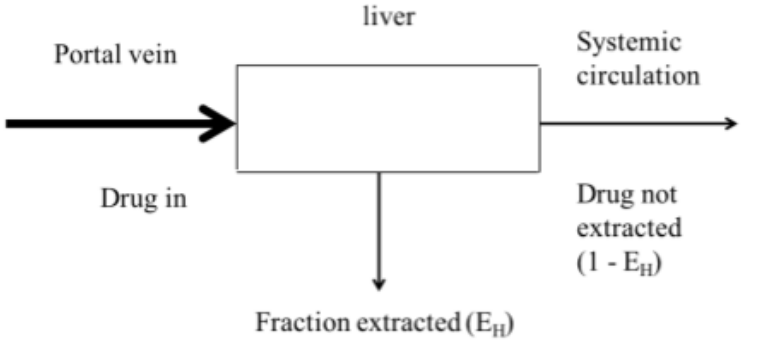
1. Oral Drug in Stomach
2. Absorption from Intestine

When a drug is administered orally…

- Drug released in the intestine is absorbed into the portal circulation
- Portal blood is then delivered to the liver
- The liver it he major organ of biotransformation
- Biotransformation soon after absorption means that the entire dose of a drug may not be available to act in the body

Presystemic Drug Metabolism in Gut: for some drugs, presystemic metabolism may also occur in intestinal enterocytes

Routes of Administration	
More Common:	**Less Common**
▪ Oral (tablets, capsules, suspensions) ▪ Injections (intravenous, intramuscular, intrathecal) ▪ Intracoular and intranasal ▪ Dermal application	▪ Rectal ▪ Sublingual ▪ Injections (subcutaneous, intraperitoneal)



Bioavailability

By definition, the bioavailability of an intravenous dose is taken as 1. That is, the entire dose is systemically available.

Relative Bioavailability: of an oral dose form is the traction that reaches the systemic circulation intact. Usually <1, can be quite low but mainly a problem when it is variable between doses or individuals.

Sites of Oral Absorption:

- Small intestine: major site of absorption, large surface area.
- Large intestine: some molecules preferentially absorbed in large intestine. Important for some delayed release dose forms
- Stomach: small surface area. Some drugs are unionized at stomach pH (i.e. acidic drugs with low pK values)

Influences of Relative Bioavailability:

- The amount of drug that is released from the oral dose form
- The amount of drug that is absorbed
- How much is taken out by Presystemic metabolism

Influences of Oral Absorption:

- **Gastric Emptying Time:** can be the rate limiting step. Food slows gastric emptying and decreases absorption further down intestine. Influenced by type of meal (solid/liquid). Blood flow in the gut alters emptying rate.
- **Formulation:** coatings can be used to prolong or delay absorption. This enables high doses to be administered safely or protects labile drugs from degradation while they are in the stomach.

Common Routes of Injection:

- **Intravenous:** drug immediately available in the body, therefore not reversible. Also some risk of infection or embolism.
- **Intramuscular:** oily infection, slow release effect sustained over weeks/months. Also for low compliant patients
- **Intrathecal:** drug directly into cerebrospinal fluid (e.g. spinal anaesthesia)

Injections avoid first-pass effect!

Intraocular and Intranasal Delivery: intended to act locally. This generally minimizes systemic effects, however, can be disproportionately high plasma concentration of drugs because some drugs can enter the systemic circulation. Also avoids first-pass effect (along with other topical drugs).

Sublingual of Buccal Delivery: small surface area for absorption but effective for lipophilic agents. Rapid absorption, avoids first pass effect. E.g. buprenorphine for pain.

Key Concepts

1. Most drugs absorbed by passive diffusion and transporter-assisted influx
2. Acid/base properties of drug control ionization and extend of absorption
3. Only the free fraction of drug crosses cell membranes, is metabolized and eliminated
4. Formulation strategies modify drug availability
5. Route of administration can influence amount of drug available in body (systemic availability)