Drug permeation: how they get into the cells

There are several ways to gain entry into the cell, if your receptor happens to be intracellular.

CARRIERS:

- Grab the drug from the extracellular fluid and actively transport the drug into the cell.

ENDOCYTOSIS:

- for some huge drugs like the Vit.B12-intrinsic factor complex, or the equally enormous iron-transferrin complex, the cells need to vacuolate and endocytose ("pinocytose") the drugs

AQUEOUS DIFFUSION:

- Passing through tight junctions, or large aqueous compartments (i.e. from one end of the blood stream to the other)
- Occurs along a concentration gradient
- Protein-bound drugs have trouble getting though the aqueous pores of the capillaries

How fast a molecule gets from A to B by aqueous diffusion is governed by Fick's Law.

FICK'S LAW OF DIFFUSION

$$\text{(high concentration minus low concentration)} \times \frac{\text{Area} \times \text{Permability coefficient}}{\text{Thickness}}$$

LIPID DIFFUSION:

- Most important, as the barriers between compartments are mainly lipid.
- Obviously if you're a charged molecule you will have more trouble getting through the nonpolar barrier of lipid membranes. Nonpolar molecules can just waltz into a cell.

- Whether you are polar or nonpolar in a solution depends on the acidity of the solution.
- This ratio of polar to non-polar is described by the Henderson-Hasselbalch equation

HENDERSON HASSELBALCH EQUATION

$$\text{Log} \frac{\text{[Concentration of the ionized form of the substance]}}{\text{[Concentration of the non-ionised form of the substance]}} = pK_a - pH$$

pK_a: the Acid Dissociation Constant;

- the larger the value, the stronger the acid;
- i.e. the more of the acid molecules have donated their protons.
- The pKa is the pH at which concentration of ionized and non-ionised forms is equal.

The bottom line: Weak acids are more lipid-soluble in acidic solutions
Weak bases are more lipid-soluble in alkaline solution
Conversely, Weak acids are more WATER-soluble in alkaline urine
Weak bases are more WATER-soluble in acidic urine

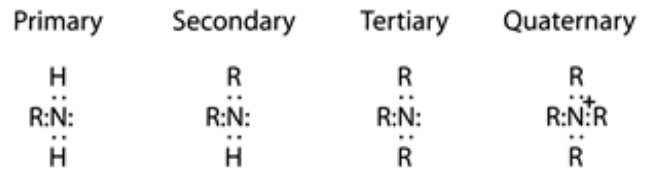
From "Goodman & Gilman's The Pharmacological Basis of Therapeutics" 11th ed by Brunton et al,and "Basic & Clinical Pharmacology" 11th ed. By Katzung et al

Seeing as many drugs are either weak acids or weak bases, they will either be charged or uncharged in solutions with different pH.

- a weak acid will be neural until it dissociates into a negatively charged ion (anion) and a proton.
  - While it hangs onto its proton, its still neutral and thus lipid-soluble.
  - In an alkaline environment, there are few protons, and the acid will tend to donate them.
  - THUS: IN AN ALKALINE ENVIRONMENT, WEAK ACIDS ARE NON-LIPID-SOLUBLE
- A weak bas will become positively charged (cation) if it ever accepts a proton
  - While its still proton-free, the weak base will also be neutral and lipid-soluble.
  - In an acidic environment, there a tons of free protons and the base will tend to grab them
  - THUS: IN ACIDIC ENVIRONMENTS, WEAK BASES ARE NON-LIPID-SOLUBLE

The AMINES

Weak bases; many drugs fall into this category



- the "R" is the carbon atom

primary, secondary and tertiary amines can bind a free proton because they have a couple of unshared electrons.

Quarternary amines have no unshared electrons and are therefore permanently charged; they don't have a "neutral" lipid-soluble form and remain poorly lipid-soluble regardless of the pH

LIPID DIFFUSION:

- Most important, as the barriers between compartments are mainly lipid.
- Liquid:aqueous partition coefficient comes into play here
- Obviously if you're a charged molecule you will have more trouble getting through lipid membranes
- Ration of lipid-soluble to water:soluble is the Henderson-Hasselbalch equation

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THE HENDERSON- HASSELBALCH EQUATION:

$$\log \frac{(\text{Protonated})}{(\text{Unprotonated})} = pK_a - pH$$

pKa: the Acid Dissociation Constant; the larger the value, the stronger the acid i.e. the more of the acid molecules have donated their protons.
The pKa is the pH at which concentration of ionized and non-ionised forms is equal.

The bottom line:Weak acids are more lipid-soluble in acidic solutions
Weak bases are more lipid-soluble in alkaline solution
Conversely, Weak acids are more WATER-soluble in alkaline urine
Weak bases are more WATER-soluble in acidic urine

The higher the pKa, the more this is affected. A base with high pKa will clear faster into acidic urine than a base with low pKa

Why is this important?

- The VAST majority of drugs are filtered out by the glomerulus
- If the drug is in a neutral lipid-soluble form, like a weak acid in acidic urine, it will be REABSORBED
- If the drug is in a polar form, like a weak acid in alkaline urine, it will be water-soluble; and water-soluble drugs will BE TRAPPED IN THE URINE.
- If you are trying to prevent reabsorption, MAKE THE URINE pH OPPOSITE to the drugs acidity

Its not just urine. Native body fluid pH of vaginal/prostatic secretions, stomach juice and breast milk can all cause a trapping effect, concentrating drug molecules. Also, acidic environments of abscesses can interfere with polarity of local anaesthetics, making them less lipid soluble and thus less effective.

- to achieve selective binding to a drug target, a drug needs to be large enough
- a good size is a molecular weight of about 100.
- Drugs range from MW 7 (lithium) to MW 59,050(alteplase)
- Larger than MW1000, and you don't diffuse readily between tissue compartments

COVALENT BONDING:
- irreversible
- eg. aspirin and platelets, or DNA and alkylating chemotherapy agents

ELECTROSTATIC BONDING:
- reversible and weak
- this is the may most drugs bind their targets

HYDROPHOBIC BONDING:
- very feeble
- usually more related to highly lipophilic drugs and cell membranes

YOU DON'T NEED TO BOND AT ALL. Xenon exerts an anaesthetic effect, and its totally inert.