Pharmacology

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Pharmacokinetics

- It is what the body does to the drug including absorption, distribution, biotransformation and excretion
  - *Absorption:* Is the movement of drug molecules from the site of administration *into the circulation*
  - *Distribution:* Is the movement of drug molecules from the circulation *to tissues* and between different parts of the body
  - *Biotransformation*: Is conversion of the drug from one chemical structure into another by the action of metabolic enzymes (*metabolism*)
  - *Excretion:* Is the movement of drug molecules *out of the body* through urine and/or bile

- The goal of therapeutics is to achieve a ***desired beneficial effect*** with the ***minimal adverse effects*** possible, by a well-determined dose
  - The **concentration** of the drug in the site of action is related to it beneficial and toxic effects

Drug permeation

- Movement of the drug between compartments and passage through membranes
- It is important in drug absorption, distribution and elimination
- It includes:

1. *Passive diffusion*

- The most important mechanism
- Diffusion ***through lipid*** **down the concentration** gradient
- **Lipid soluble** determine the rate of diffusion through the membrane, but they should be sufficiently water soluble to reach the membrane
- Fick's Law if diffusion: Flux = (C1-C2) * Area * Permeability / Thickness

- The **ionization state** of the drug affects its solubility
  - Ionized drugs = *Polar* = Water Soluble
  - Unionized drugs = *Non-polar* = Lipid soluble

- Ionization state is determined by environmental pH and drug pKa
- Henderson-Hasselbalch Equation:
  Log (protonated/unprotonated) = pKa – pH

- *Example 1:* Pyrimethamine as a weak base drug with a pKa of 7.0
  What is the proportion of ionized and unionized drug in blood (pH = 7.4) and urine (pH = 6)?

- *Example 2:* Phenobarbital is a weak acid with a pKa of 7.4
  What is the proportion of ionized and unionized drug in blood (pH = 7.4) and urine (pH = 6)?

Weak Acid: Dissociate into an anion and proton reversibly
- Protonated = Unionized
- Deprotonated = Ionized

Weak Base: Accept (combine with) proton reversibly
- Protonated = Ionized
- Deprotonated = Unionized

- *Acid* drugs in an *acid* environment are *unionized* (non-polar), and ionized in alkaline environment
- *Bases* in an *alkaline* environment are *unionized* (non-polar), and ionized in acidic environment
  - The lower the pH relative to the pKa, the greater the fraction of the drug in the protonated form

- Drug must be ***ionized*** in the urine to ***prevent its reabsorption*** by kidney tubules and ***accelerate excretion***
  - ***Weak bases*** can be excreted rapidly in ***acidic urine***
    - ✓ Urine can be ***acidified*** by *ascorbic acid (vitamin C)* or *ammonium chloride (NH_4Cl)*
  - ***Weak acids*** can be excreted rapidly in ***alkaline urine***
    - ✓ Urine can be ***alkalinized*** by *sodium bicarbonate ($NaHCO_3$)* given orally or intravenously

2. *Aqueous diffusion*

- Diffusion through aqueous ***pores*** in membranes
- Also driven by the concentration gradient (**down the gradient**)
- If the drug is ***charged***, its flux is influenced by ***electrical fields*** (membrane potentials)

Drugs bound to plasma proteins do not permeate aqueous pores

3. *Carrier-Mediated transport*

- For molecules that are too ***large*** or too ***lipid-insoluble*** (peptides, amino acids, glucose)
- It involves *facilitated diffusion* (passive) and *active transport*

- They are highly ***selective***, ***saturable*** and ***inhibitable***
  - Many cells contain less selective membrane carriers that are specialized in expelling foreign

- Examples:
  - *ATP-binding cassette (ABC) family*, which include:
    - ✓ *P-glycoprotein* or the *multidrug-resistance type 1 (MDR1)* transporter which is found in the brain, intestine, testes, neoplastic cells, and other tissues
    - ✓ *Multidrug-resistance associated protein (MRP)* transporters
      - They mediate the ***resistance*** of some tumors to ***chemotherapeutic agents***
  - *Solute carrier families (SLC)*
    - ✓ They ***do not bind ATP*** but use *ion gradients* for transport energy
    - ✓ They are important in the transport or the *uptake of neurotransmitters* across nerve ending membranes

4. *Endocytosis and exocytosis*

- Endocytosis is responsible for transport of:
  - *Vitamin B12* complexed with the *intrinsic factor* across the wall of the *gut* into the blood
  - *Iron* associated with *transferrin* into *RBCs*

- Exocytosis is responsible for secretion of many substances from cells such as:
  - Neurotransmitters
  - Hormones

- Permeation processes determine how rapidly and for how long the drug will appear in the target organ, the site of action, and organs of elimination

- Barriers against drug permeation and transport:
  - *Tight junctions* between endothelial cells and absence of pores.
  - The presence of *thick basement membrane* at which endothelial cells lie.
  - The presence of *connective tissue* cells around endothelial cells
    - ✓ such as *astrocytes* in the Brain forming the blood brain barrier
  - The presence of *drug export pumps*.
  - The presence of intracellular and extracellular *enzymes that metabolize* drugs

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