Drug Metabolism

Cytochromes

- Heme containg proteins
  - Heme is made of a porphyrin ring containing an atom of iron
    - Prohyrin a group of heterocyclic macrocycle organic compounds, composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges (=CH−)
      "[illegible]
      Never mind my friend"
- In the electron transport chain
  - They are involved as carriers of electrons
- The major respiratory cytochromes are classified as a, b, or c, depending on the wavelengths of the spectral absorption peaks
- Cytochromes are also found in the endoplasmic reticulum eg P450, b5
- Cytochrome P450
  - Is found inthe smooth endoplasmic reticulum particularly in the liver
    - Got its name because when reduced and complexed with carbon monoxide it exhibited a spectral absorbance maximum at 450 nm
  - It uses iron to oxidise molecules to makes them water-soluble and thus easy to dispose out of body
  - The iron acts as an electron carrier by
    - Oxidation of Ferrous Fe+2 to Ferric Fe+3
    - Reduction of Ferric F3+3 to Ferrous Fe+2

Oxidation means the addition of oxygen to a molecule or the removal of hydrogen from a molecule

Drug metabosim reactions

- Phase I
  - Involves
    - Oxidation
      - Involves the addition of oxygen or removal of hydrogen by mixed function oxidases in the liver
      - Most common
    - Reduction
    - Hydroxylation
    - Hydrolysis
    - Cyclization
    - Decyclization
- Phase II
  - Metabolites that are not sufficiently polar may undergo phase II metabolism
  - Involves
    - Sulfation (SO4 -2)
    - Methylation
      - Example methylation process helps convert the amino acid (homocysteine) into a amino acid (methionine)
    - Glucuronidation
      - D-Glucuronic Acid is a sugar acid formed by the oxidation of the C-6 carbon of glucose
    - Connjugation
      - Conjugation of the metabolite or drug with large molecular groups that further reduced the biological activity of the metabolite
        - And increase its solubility even further
      - Conjugation occurs with
        - Glucuronic acid
        - Sulfonates
        - Glutathione
        - Amino acid
      - Functional groups that are often attached to these large molecules include
        - Carboxyl
        - Hydroxyl
        - Amino
        - Sulhydryl

Xenobiotic is the chemical substances that are foreign to animal life

P450 Mechanism of Oxidation!

Refer to slide 7

- Steps
  - 1. Converting Fe+3 to Fe+2, Why? Because in the 2nd step we need to Oxidize the Iron heme and Fe+3 cann't be oxidized
    - How do we convert Fe+3 to Fe+2? By adding (1 electron)
      - How do we get this electron? By NADPH
        - Surprise! NADPH donates 2e not 1, and we only need 1e, So? NADPH donates the 2e to FADH2
          - Then FADH2 donates 1e to Fe+3, resulting in Fe+2, Hallelujah! Now you are ready for oxidation
  - 2. Adding the O2 to Fe+2
  - 3. Making the Oxygen atom Superoxide (O2-), but how?
    - Remeber the 2nd e we neglected before? It's the time to use it, by adding the 2nd e to O2, you will have a superoxide (O2-)
      - Superoxide is way too active
  - 4. Adding 2H+
    - This helps getting rid of one Oxygen atom as a form of H2O
  - 5. Donating the 2nd Oxygen atom to the substrate which originally have a Hydrogen atom
    - O + H = Alochol, congrats your substrate is polar now, and it can be excreted with water

Nomenclature of Cytochrome P450

- CYP 3A4
  - Cytochrome P450
    - Is abbreviated to CYP
  - The "3"
    - Means it's from the 3 family
  - The "A"
    - Means it's from the A subfamily
  - The "4"
    - Means it's the "4" isoform

1st No. for family
Letter for subfamily
2nd No. for specific isoform

Role of cytochromes P- 450 in the metabolism of Steroid hormones

- Cholesterol is the precursor of all steroid hormones
- Steroid hormones contain 21 or fewer carbon atoms
  - Whereas cholesterol contains 27
- The first stage in the synthesis of steroid hormones
  - Is the removal of a six-carbon unit from the side chain of cholesterol to form pregnenolone
    - The removal is accomplished by Cytochrome P450SCC (desmolase) that cleaves the bond
      - P450SCC is Cholesterol Side-Chain Cleavage Enzyme
      - Desmolase that include P450SCC is found in the mitochondria of tissues that synthesize steroids
        - Mainly the adrenal glands and gonads
- Other steroid hormones are produced from progesterone by reactions that involve members of the P450 family

Few points on CYP & Drugs

- Different people have different activity of CYP due to genetic variation (polymorphism) that result
  - This can lead to differences in drug metabolism
    - Poor metabolizer
    - Normal metabolizer
    - High metabolizer
- Some of drugs intermediates are toxic specially if accumulated at high concentrations
  - So if a patient is a high drug metabolizer this may lead to patient toxicity
- Some drugs are given for special purposes that inhibit P450 enzymes
  - To prolong the activity of some other drugs
- Some drugs that have a narrow range of effective dose before they become toxic might be overdosed in a poor metabolizer
- Poorer P450 substrates drugs would last longer in the body before elimination, which is desirable for some drugs
- CYP may lead to making some drugs ineffective while activating others

Bile

Characterstics

- Is an important product released by the hepatocytes
- It promotes the digestion of fats from food by emulsifying them in the small intestine
- The emulsifying components of bile mainly consist of bile acids and bile salts plus free cholesterol
- Forms
  - Bile Acide
    - Primary
    - Secondary
  - Bile salts

All made of Cholestrol, but cholestrol has 27 C atoms, and Bile has 24 C atoms, so we need a Vhestrol modificatrion — Cytochrome P450 in the sER is involved in many of the steps

Formation of Primary Bile Acid (PBA)

- Two types of PBA are
  - Cholic Acid
  - Chenodeoxycholic Acid
  - They are activated with coenzyme A
- Steps
  - 1. The side chain is shortened by three C atoms converting it from 27 C atoms to 24 — And the terminal C atom is oxidized to a carboxylate group
  - 2. Cholesterol double bond is removed
  - 3. Monooxygenases then introduce one or two additional OH groups into steroid ring
    - To atoms 7, 12 in Cholic acid
    - Atom 7 to chenodeoxycholic acid
  - 4. Altering A and B rings from trans to cis — So the hydrophilic groups in the bile acids lie on one side of the molecule

Conversion of PBA into bile salts

- After activating of PBA via coenzyme A — PBA gets conjugated with Glycine or Taurine (an end-product of cysteine metabolism) — Resulting in bile salts — So bile salts are conjugated PBA
- Bile salts include glycocholic and glycochenodeoxycholic acids, and taurocholic and taurochenodeoxycholic acids
- Bile salts are more amphipathic than the primary products
- Bile salts are more effective detergents than bile acids because of their enhanced amphipathic nature — Therefore, only bile salt are found in the bile
- Mechanism of action of bile salts
  - Triglycerides are not soluble in water they aggregate into large droplet in the small intestine lumen
  - Bile salt adsorb on the surface of fat droplet — That is the lipid soluble part of the bile salt dissolves in the fat droplet — Leaving the charged water soluble part projecting from the surface of the droplet
  - Intestinal mixing movement break up large fat droplet into smaller ones — These small droplets would quickly come together were it not for the bile salt adsorbing on their surface — Creating a shell of water-soluble negatively charged groups on the surface of each little droplet
  - Because like charges repel these negatively charged groups on the droplet surface — Cause the fat droplet to repel each other and prevent their come together in to large droplet — Thus produces emulsion that increases the surface area available for lipase action

Formation of Secondary Bile Acid (SBA)

- Intestinal bacteria deconjugate and dehydroxylate the bile salts — By removing the
  - Glycine and taurine residues
  - The hydroxyl group at position 7

  And thus regenerating bile acid
- The bile acids that lack a hydroxyl group at position 7 are called secondary bile acid
- The deconjugated and dehydroxylated bile acids are less soluble and — therefore, less readily absorbed from the intestinal lumen than the bile acids that have not been subjected to bacterial action
- Lithocholic acid
  - A secondary bile acid that has a hydroxyl group only at position 3
  - Is the least soluble bile acid
  - Its major fate is excretion