open.michigan

Author(s): Aken Desai, Michael Mathis, 2008

Drug Metabolism Part I

Tuesday, January 22, 2008
10:00 AM

1. Define Phase I metabolism.
    a. Oxidation reduction reactions of lipophilic xenobiotics
    b. Increases water solubility and promotes excretion
    c. Introduces/exposes a functional group (-OH, -NH2, -SH, -COOH)
2. What are the Phase I enzymes and what are the reactions they catalyze?
    a. Hydrolysis: esterases, peptidases, hydrolases
    b. Reduction: reductases
    c. Oxidation: dehydrogenases, oxidases, synthases and Cytochrome P450
3. Why do we need to metabolize drugs?
    a. To excrete them
    b. Evolutionarily, we adapted these mechanisms in response to a diet that contained many poisons and the metabolism of those substances was crucial to our survival
4. Is metabolism always beneficial?
    a. No can actually metabolize to a more harmful substance
5. What are cytochrome P450 enzymes?
    a. A group of closely related enzymes that are very active in drug metabolism
    b. Contain heme group and can oxidize or reduce
        i. Oxidation when oxygen present
        ii. Reduction when not enough oxygen
        iii. Requires NADPH
    c. Activated by O2 via three reactions
        i. NADPH donates 2e- to flavoprotein to reduce it (Cyt P450 reductase)
        ii. Cyt P450 is reduced from Fe3+ --> Fe2+
        iii. Oxygen binds and additional reduction results in activated oxygen
        iv. Drug is oxidized and Cyt P450 is returned to resting state
        v. Carbon monoxide binds to Fe2+ P450 to inactivate it
    d. Multiple isoforms w/ overlapping substrate specificity
        i. CYP1,2,3
        ii. CYP2 family has 40% sequence identity, CYP2E subfamily is 70% identical, CYP2E1 is specific enzyme
        iii. CYP3A, 2E1, 1A2, 2D6 are a large portion of the enzymes responsible for liver metabolism
    e. Regulation - all sorts of regulation
        i. Transcriptional
        ii. mRNA degradation
        iii. Translational regulation
        iv. Inactivation
        v. Inhibition
        vi. Activation
        vii. Reductase
    f. Dietary effects
        i. Charcoal broiled beef/tobacco smoke induce CYP1A2 --> increase P450 levels
        ii. This means certain drugs have lowered effects due to diet
    g. Many drugs are influenced by P450
        i. Case: Heart transplant pt. given immunosupressives. 3 wks prior to admission pt given St. John's Wort for depression and anxiety. Cyclosporin levels drop below therapeutic range and biopsy shows transplant rejection. Stop St. John's Wort and cyclosporin returns to normal. No further rejection.
        ii. Reasoning: St. John's Wort induces CYP3A4 which metabolizes cyclosporin and decreased

plasma levels.

iii. Grapefruitjuice and CYP3A
    1) Grapefruit juice (skin) blocks CYP3A and P-glycoprotein
    2) Therefore drug not metabolized and not excreted
    3) Effective overdose
iv. Genetic lack of CYP2D6 (o-dealkylation) leads to Codeine not getting metabolized to morphine and therefore not being efficacious

6. Be able to recognize functional groups on drugs and determine possible Phase I metabolites. What enzymes catalyze these reactions?
    a. Reactions carried out by P450
        i. Aromatic hydroxylation: places an -OH on aromatic ring
        ii. Aliphatic hydroxylation: places an -OH on a carbon chain
        iii. O-dealkylation: -OR --> -OH
        iv. N-dealkylation: -NHR --> NH2
        v. N-oxidation: -NH2 --> -NHOH
        vi. S-oxidation: -SR2 --> -SR2=O
        vii. Deamination: -NH2 --> =O
        viii. Reduction
            1) Azo-reduction: R1-N=N-R2 --> R1-NH2 + H2N-R2
            2) Nitro-reduction: R-NO2 -->R-NO --> R-NOH --> R-NH2
            3) Reductive dehalogenation: CCl4 --> CCl3. --> CHCl3
    b. Flaving Monoxygenase
        i. FMO-FADHOOH(NADP+) + X --> XO
            1) FMO-FADHOH(NADP+) --> NADP+ + H2O + FMO-FAD
            2) FMO-FAD + NADPH + H+ --> FMO-FADH2 (NADP+)
            3) FMO-FADH2(NADP+) + O2 --> FMO-FADHOOH(NADP+)
        ii. Oxidation: R-N --> R-N-O
            1) Trimethylamine smells bad
            2) FMO oxidizes to Trimethylamine-N-Oxide
            3) Genetic mutation in FMO results in fish odor
    c. Alcohol Dehydrogenase
        i. EtOH + NAD+ --> Acetaldehyde + NADH
        ii. Lacking in 85% of Japanese
        iii. Aldehyde DH: Acetaldehyde + NAD+ --> Acetic Acid + NADH
            1) Lacking in 50% of Japanese
            2) Acetaldehyde makes face get blood red
            3) Antabuse blocks it (adjuvant to alcoholism treatment)
        iv. Methanol, ethylene glycol metabolites are toxic
            1) Can give ethanol to treat ingestion of these substances b/c it competes for dehydrogenases
            2) 100 mg/dL (.10 BAC)
            3) 4 methyl pyrazole blocks alcohol dehydrogenase but orphan drug
        v. Esterases
            1) RCOOR' --> RCOH + R'OH
            2) RCONR' --> RCOH + RNH (slower --> more systemic effects)
        vi. Epoxide hydrolases
            1) Epoxides created by P450
            2) Hyrdolases take C1-O-C2-C1 --> HOC1-C2OH
7. What are the cofactors needed for metabolism?