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Drug Metabolism Part II

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10:00 AM

1. Define Phase II enzymes. What are the reactions catalyzed by these enzymes?
    a. Drug + Cofactor --> Conjugated Drug
        i. Glucurondiation: UDP-Glucuronosyl transferase
        ii. Glutathione conjugation: Glutathione S-transferase
        iii. Sulfation: Sulfotransferase
        iv. Acteylation: N-Acetyltransferase
        v. Methylation: no enzyme named
        vi. Other
2. What are the cofactors needed for these enzymes?
    a. UDP-Glucouronosyl transferase: UDPGA
    b. Glutathione conjugation: glutathione, Acetyl-CoA
    c. Sulfotransferase: 3-Phosphoadenosine-4-phosphosulfate (PAPS)
    d. Acetylation: Acetyl-CoA
    e. Methylation: SAM
    f. Other
3. Recognize functional groups on drugs that can be conjugated Phase II enzymes. Determine possible products.
    a. Glucuronidation
        i. R-OH + UDPGA --> Glucuronide-OR + UDP
        ii. R-COOH + UDPGA --> Glucuronide-OC(O)R + UDP
        iii. R-NH2 + UDPGA --> Glucuronide-NHR + UDP
        iv. R-SH + UDPGA --> Glucuronide-OR + UDP
        v. Mutations in enzyme cause Crigler-Najjar and Gilbert's b/c bilirubin can't be conjugated and excreted in urine
    b. Glutathione conjugation
        i. RX + HS-Glutathione --> R-S-Glutathione + HX
        ii. Gamma-Glutamyltranspeptidase: R-S-Glutathione --> R-S-Cysteine-Glycine + Glu
        iii. Aminopeptidase M: R-S-Cysteine-Glycine --> RS-Cysteine + Gly
        iv. N-Acetyltransferase: RS-Cysteine + Acetyl-CoA --> mercapturic acid
        v. Beta lyase: RS-Cysteine --> R-SH
        vi. Thermodynamically favored so can happen w/o first enzyme, just slower
        vii. Protective mechanism against epoxides
    c. Sulfation
        i. R-OH + PAPS --> R-O-SO3 + PAP
        ii. High affinity, low capacity
        iii. Can convert certain drugs to carcinogenics
    d. Acteylation
        i. Requires Acteyl-CoA
        ii. -NH2 --> NHCOCH3
    e. Methylation
        i. Common but minor, doesn't always make it more polar
        ii. Requires SAM
        iii. O-Methylation: -OH --> -OCH3
        iv. N-Methylation: -NHR --> -N(CH3)R
        v. S-Methylation: -SH --> -SCH3
    f. Other