Drug Metabolism Part II

Wednesday, January 23, 2008
10:00 AM

1. Define Phase II enzymes. What are the reactions catalyzed by these enzymes?
   a. Drug + Cofactor → Conjugated Drug
      i. Glucuronidation: UDP-Glucuronosyl transferase
      ii. Glutathione conjugation: Glutathione S-transferase
      iii. Sulfation: Sulfotransferase
      iv. Acetylation: N-Acetyltransferase
      v. Methylation: no enzyme named
      vi. Other

2. What are the cofactors needed for these enzymes?
   a. UDP-Glucuronosyl 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. Acetylation
      i. Requires Acetyl-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