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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 \rightarrow 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-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. $R-OH + UDPGA \rightarrow Glucuronide-OR + UDP$
 - ii. $R-COOH + UDPGA \rightarrow Glucuronide-OC(O)R + UDP$
 - iii. $R-NH_2 + UDPGA \rightarrow Glucuronide-NHR + UDP$
 - iv. $R-SH + UDPGA \rightarrow Glucuronide-OR + UDP$
 - 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. $RX + HS-Glutathione \rightarrow R-S-Glutathione + HX$
 - ii. Gamma-Glutamyltranspeptidase: $R-S-Glutathione \rightarrow R-S-Cysteine-Glycine + Glu$
 - iii. Aminopeptidase M: $R-S-Cysteine-Glycine \rightarrow RS-Cysteine + Gly$
 - iv. N-Acetyltransferase: $RS-Cysteine + Acetyl-CoA \rightarrow mercapturic\ acid$
 - v. Beta lyase: $RS-Cysteine \rightarrow R-SH$
 - vi. Thermodynamically favored so can happen w/o first enzyme, just slower
 - vii. Protective mechanism against epoxides
 - c. Sulfation
 - i. $R-OH + PAPS \rightarrow R-O-SO_3 + PAP$
 - ii. High affinity, low capacity
 - iii. Can convert certain drugs to carcinogenics
 - d. Acetylation
 - i. Requires Acetyl-CoA
 - ii. $-NH_2 \rightarrow NHCOCH_3$
 - e. Methylation
 - i. Common but minor, doesn't always make it more polar
 - ii. Requires SAM
 - iii. O-Methylation: $-OH \rightarrow -OCH_3$
 - iv. N-Methylation: $-NHR \rightarrow -N(CH_3)R$
 - v. S-Methylation: $-SH \rightarrow -SCH_3$
 - f. Other