Drug Biotransformation

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Drug Biotransformation

- **Humans are exposed always to foreign compounds called xenobiotics, through the GIT, skin, lung, etc.**
- **Xenobiotics include drugs, environmental toxins and industrial toxins.**
- **Xenobiotics excreted by the kidney are usually small polar molecules, or ionized at physiologic pH.**

Drug Biotransformation

- Many drugs are lipophilic at physiologic pH, and are readily reabsorbed from the glomerular filtrate in the nephron.
- Lipophilic drugs bound to plasma proteins are not readily filtered at the glomerulus.
- Such drugs are metabolized in the liver to more polar molecules that can be excreted in urine and bile.

Drug Biotransformation

- **Metabolic products are often less active than the parent drug and may be even inactive.**

Exception:

1. **Some drug metabolites have enhanced activity or even toxicity.**
2. **Some drugs are inactive and need activation by metabolism (prodrugs) like levodopa, codeine.**
3. **Some drugs are metabolized into toxins.**

Drug Biotransformation

Examples:

a) Paracetamol may be converted to the hepatotoxin N-acetyl-p-benzoquinone imine.

b) Halothane is metabolized to free radicals that are hepatotoxic.

Drug Biotransformation

- **Biotransformation reactions can be classified as phase I or phase II reactions.**

1. **Phase I reactions usually convert the drug to more polar metabolites by introducing (or unmasking) a functional group (- OH, - NH_2, - SH), which makes them more polar to be excreted by the kidney.**

- **These metabolites can be inactive, less active or more active than the parent compound.**

Drug Biotransformation

- **Many phase I products may need a subsequent reaction to become polar enough to be readily excreted.**
- **The subsequent reactions are conjugation reactions with an endogenous substrate such as glucuronic acid, sulfuric acid, acetyl-CoA and glutathione.**
- **Conjugation is a phase II reactions.**

Phase I Biotransformation reactions

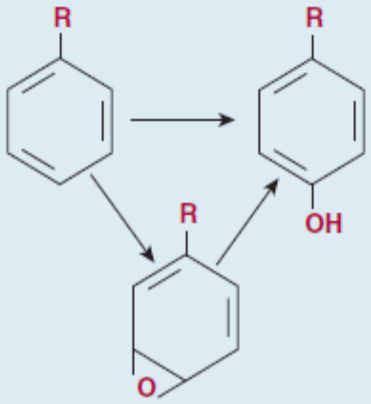
1. Oxidations
2. Reductions
3. Hydrolysis

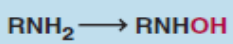
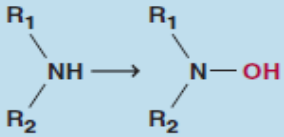
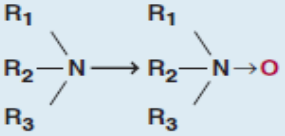
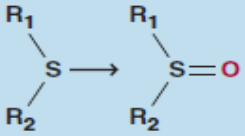
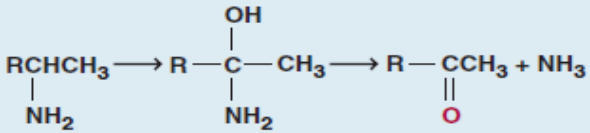
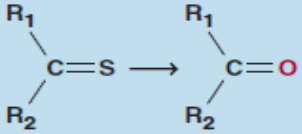
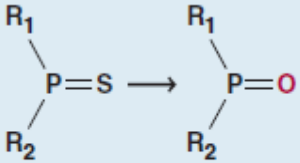
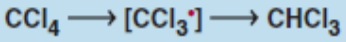
- Most oxidation-reduction reactions in drug metabolism are carried out by the microsomal mixed function oxidase system or cytochromes P450 enzymes.

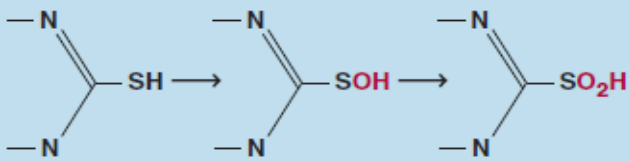
Phase I Biotransformation reactions

- Cytochrome P450 enzymes are located in the endoplasmic reticulum.
- They have very low substrate specificity, and slow reaction rates.
- High lipid solubility is common to the wide variety of structurally unrelated drugs metabolized by this system.

TABLE 4–1 Phase I reactions.

Reaction Class	Structural Change	Drug Substrates
Oxidations		
Cytochrome P450-dependent oxidations:		
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17α-ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations	$RCH_2CH_3 \longrightarrow RCH_2CH_2OH$ $RCH_2CH_3 \longrightarrow RCHCH_3$ (OH)	Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation	$RCH{=}CHR \longrightarrow R{-}C(H)(O){-}C(H){-}R$	Aldrin
Oxidative dealkylation		
N-Dealkylation	$RNHCH_3 \longrightarrow RNH_2 + CH_2O$	Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation	$ROCH_3 \longrightarrow ROH + CH_2O$	Codeine, *p*-nitroanisole
S-Dealkylation	$RSCH_3 \longrightarrow RSH + CH_2O$	6-Methylthiopurine, methitural

***N*-Oxidation**		
Primary amines		Aniline, chlorphentermine
Secondary amines		2-Acetylaminofluorene, acetaminophen
Tertiary amines		Nicotine, methaqualone
***S*-Oxidation**		Thioridazine, cimetidine, chlorpromazine
Deamination		Amphetamine, diazepam
Desulfuration		Thiopental
		Parathion
Dechlorination		Carbon tetrachloride

Cytochrome P450-independent oxidations:		
Flavin monooxygenase (Ziegler's enzyme)	$R_3N \longrightarrow R_3N^+ \rightarrow O^- \xrightarrow{H^+} R_3N^+OH$	Chlorpromazine, amitriptyline, benzphetamine
	$RCH_2N(H)-CH_2R \longrightarrow RCH_2-N(OH)-CH_2R \longrightarrow RCH=N(O^-)-CH_2R$	Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases	$RCH_2NH_2 \longrightarrow RCHO + NH_3$	Phenylethylamine, epinephrine
Dehydrogenations	$RCH_2OH \longrightarrow RCHO$	Ethanol
Reductions		
Azo reductions	$RN=NR_1 \longrightarrow RNH-NHR_1 \longrightarrow RNH_2 + R_1NH_2$	Prontosil, tartrazine
Nitro reductions	$RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2$	Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions	$RCR'(=O) \longrightarrow RCHR'(OH)$	Metyrapone, methadone, naloxone
Hydrolyses		
Esters	$R_1COOR_2 \longrightarrow R_1COOH + R_2OH$	Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides	$RCONHR_1 \longrightarrow RCOOH + R_1NH_2$	Procainamide, lidocaine, indomethacin

Human Liver Cytochrome P450 Enzymes

- There are numerous P450 isoenzymes.
- The most important are CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.
- CYP1A2, CYP2C9, and CYP3A4 acount for 15%, 20%, and 30% of the total human liver P450 content, respectively.
- CYP3A4 alone is responsible for the metabolism of > 50% of prescription drugs metabolized in the liver.

Phase II Biotransformation reactions

- **The drug is conjugated with endogenous substrates to yield drug conjugates.**
- **In general, conjugates are polar molecules readily excreted and inactive.**
- **Conjugations are synthetic reactions, involve high-energy intermediates and specific transfer enzymes called transferases.**

Phase II Biotransformation reactions

1. **Uridine 5'-diphosphate [UDP]-glucuronosyl transferases (UGTs) are the most dominant conjugating enzymes. Groups glucuronidated are –OH, -NH, -SH, -COOH, -NHOH.**
2. **Sulfotransferases (SULTs) use 3'-phosphoadenosine 5'-phosphosulfate (PAPS). Inorganic sulfate is a limiting factor for sulfation. Its sources are food and sulfur-containing amino acids.**

Phase II Biotransformation reactions

- Almost all chemical groups that are glucuronidated are also sulfated.
- Infants are more capable of sulfation than glucuronidation, but in adults glucuronidation predominates.

3. N-acetyltransferases (NATs) utilize acetyl CoA as the endogenous cofactor for conjugation.

Phase II Biotransformation reactions

4. **Glutathione (GSH) transferases (GSTs).**

- **The donor is glutathione (GSH), which is Glu-Cys-Gly.**
- **GSH is a nucleophile that reacts with and detoxifies electrophiles.**
- **Cause halogen replacement (R-Cl → R-SG).**
- **Conjugates epoxides.**

Phase II Biotransformation reactions

- **Glutathione conjugates do not appear in urine, but may appear in bile.**
- **They are metabolized further to cysteine conjugates and then to mercaptouric acid conjugates (N-acetylated cysteine conjugates), that appear in urine by an active transport process.**

Phase II Biotransformation reactions

5. **S-Adenosyl-L-methionine (SAM) mediate O-, N- and S-methylation of drugs and xenobiotics by methyltransferases (MTs).**

- **Phase II reactions are relatively faster than Phase I reactions.**

TABLE 4–3 Phase II reactions.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*–Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxycoumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, *cis*-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

Phase II Biotransformation reactions

- **Certain conjugation reactions may lead to formation of reactive species and drug toxicities.**

Examples:

1. **Acyl glucuronidation of nonsteroidal antiinflammatory drugs**
2. **O-sulfation of N-hydroxyacetylaminofluorine**
3. **N-acetylation of isoniazid**
4. **Sulfation leads to activation of the prodrug minoxidil.**
1. **Morphine-6-glucuronide is more potent than morphine.**

Metabolism of Drugs to Toxic Product

- **Several drugs may be metabolically transformed to reactive intermediates that are toxic to various organs.**
- **Such toxic reactions may become apparent at high drug doses, especially when alternative detoxification mechanisms are overwhelmed or endogenous detoxifying cosubstrates (GSH, glucuronic acid, sulfate) are depleted.**

Metabolism of Drugs to Toxic Product

- **An example is acetaminophen (paracetamol)-induced hepatotoxicity.**
- **It normally undergoes glucuronidation and sulfation, which make up 95% of the total excreted metabolites.**
- **The alternative P450-dependent GSH conjugation pathway accounts for the remaining 5%.**

Metabolism of Drugs to Toxic Product

- **No hepatotoxicity results as long as hepatic GSH is available for conjugation.**
- **At high paracetamol dose and when GSH is depleted, the toxic metabolite accumulates resulting in hepatotoxicity.**

Metabolism of Drugs to Toxic Product

- **Administration of N -acetylcysteine (antidote) within 8–16 hours after acetaminophen overdosage protects victims from fulminant hepatotoxicity and death.**
- **Administration of GSH is not effective because it does not cross cell membranes readily.**

Enzyme Induction

- It means enhanced rate of enzyme synthesis, or reduced rate of degradation.
- Results in accelerated drug metabolism, and usually in a decrease in the pharmacological action of the drug.
- Toxicity may increase if the drug is metabolized to reactive metabolites.
- Induction mostly starts at the gene level.

Enzyme Induction

Inducers include (but are not limited to):

1. **Environmental chemicals and pollutants such as polycyclic aromatic hydrocarbons present in tobacco smoke and charcoal-broiled meat, and other pyrolysis products (induce CYP1A).**
2. **Drugs: barbiturates, phenytoin, rifampin ritonavir, dexamethasone, clofibrate, oral contraceptives, spironolactone…**

Enzyme Induction

3. **Environmental chemicals known to induce specific P450s include the polychlorinated biphenyls (PCBs), and 2,3,7,8-tetrachlorodibenzo-*p*-*dioxin (dioxin, TCDD), a trace byproduct of* the chemical synthesis of the defoliant 2,4,5-T.**
4. **Cruciferous vegetables.**
5. **St. John's wort.**
6. **Ethanol (CYP2E1).**

Enzyme Induction

- **Autoinduction refers to a drug that induces its own metabolism, like carbamazepine.**
- **Autoinduction may lead to tolerance to drug action.**

Enzyme Inhibition

1. **Imidazole-containing drugs such as cimetidine and ketoconazole bind tightly to the P450 heme iron and effectively reduce the metabolism of drugs through competitive inhibition.**
2. **Macrolide antibiotics such as erythromycin, complex the cytochrome P450 heme iron and inactive it (CYP3A).**

Enzyme Inhibition

3. **Suicide inhibitors (inactivators) include certain steroids (ethinyl estradiol, norethindrone, and spironolactone); grapefruit furanocoumarins; selegiline; phencyclidine; ticlopidine and clopidogrel; ritonavir; and propylthiouracil…**

Enzyme Inhibition

4. Substrates compete with each other for the same active site of the enzyme.
5. Deficiency of cofactors impair drug metabolism.
6. Inhibitors of nucleic acid and protein synthesis impair enzyme synthesis and, thus, drug metabolism.
7. Malnutrition.
8. Impairment of hepatic function.