

Drug Biotransformation

Yacoub Irshaid MD, PhD, ABCP
Department of Pharmacology

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/or 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.
- **Phase I reactions** usually convert the drug to more polar metabolites by introducing (or unmasking) a functional group (- OH, - NH₂, - SH), which makes them more and can 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. These conjugation reactions are **phase II reactions**.

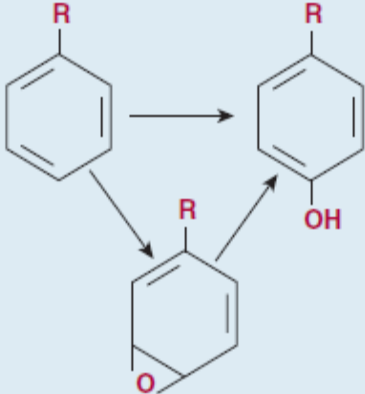
Phase I Biotransformation reactions

- 1. Oxidation mainly by the microsomal mixed function oxidase system or cytochromes P450 enzymes.**
- 2. Reduction reactions may be cytochrome P450 dependent systems or by dehydrogenases and other reductases.**
- 3. Hydrolysis of esters and amides by esterases and amidases, respectively.**

Phase I Biotransformation reactions

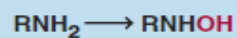
- **Cytochrome P450 enzymes are located in the endoplasmic reticulum.**
- **They can metabolize a wide range of structurally different and lipid soluble drugs.**

TABLE 4-1 Phase I reactions.

Reaction Class	Structural Change	Drug Substrates
Oxidations		
<i>Cytochrome P450-dependent oxidations:</i>		
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17 α -ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations	$\begin{array}{l} \text{RCH}_2\text{CH}_3 \longrightarrow \text{RCH}_2\text{CH}_2\text{OH} \\ \text{RCH}_2\text{CH}_3 \longrightarrow \text{RCH}(\text{OH})\text{CH}_3 \end{array}$	Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation	$\text{RCH}=\text{CHR} \longrightarrow \begin{array}{c} \text{H} \quad \text{O} \quad \text{H} \\ \diagdown \quad / \quad \diagdown \\ \text{R}-\text{C} \quad \text{C}-\text{R} \\ / \quad \backslash \quad / \end{array}$	Aldrin
Oxidative dealkylation		
N-Dealkylation	$\text{RNHCH}_3 \longrightarrow \text{RNH}_2 + \text{CH}_2\text{O}$	Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation	$\text{ROCH}_3 \longrightarrow \text{ROH} + \text{CH}_2\text{O}$	Codeine, <i>p</i> -nitroanisole
S-Dealkylation	$\text{RSCH}_3 \longrightarrow \text{RSH} + \text{CH}_2\text{O}$	6-Methylthiopurine, methitural

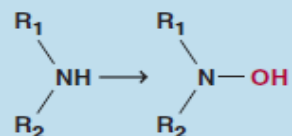
N-Oxidation

Primary amines



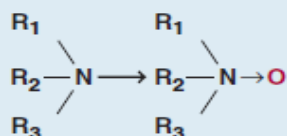
Aniline, chlorphentermine

Secondary amines



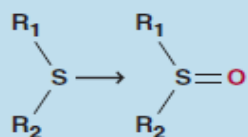
2-Acetylaminofluorene, acetaminophen

Tertiary amines



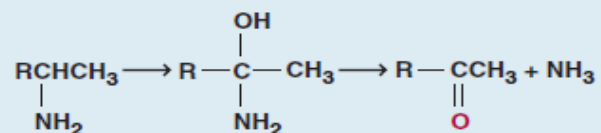
Nicotine, methaqualone

S-Oxidation



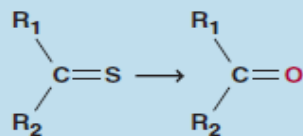
Thioridazine, cimetidine, chlorpromazine

Deamination

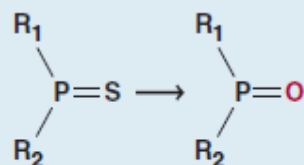


Amphetamine, diazepam

Desulfuration

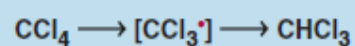


Thiopental



Parathion

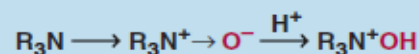
Dechlorination



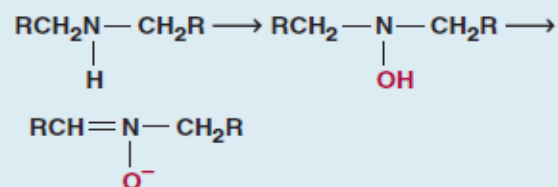
Carbon tetrachloride

Cytochrome P450-independent oxidations:

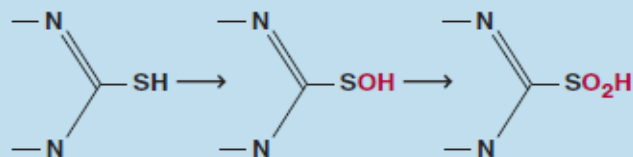
Flavin monooxygenase
(Ziegler's enzyme)



Chlorpromazine, amitriptyline,
benzphetamine

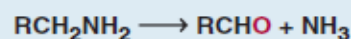


Desipramine, nortriptyline



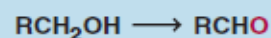
Methimazole, propylthiouracil

Amine oxidases



Phenylethylamine, epinephrine

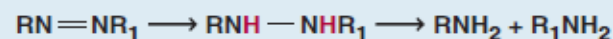
Dehydrogenations



Ethanol

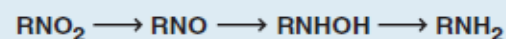
Reductions

Azo reductions



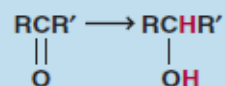
Prontosil, tartrazine

Nitro reductions



Nitrobenzene, chloramphenicol, clonazepam,
dantrolene

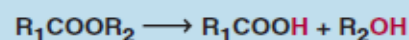
Carbonyl reductions



Metyrapone, methadone, naloxone

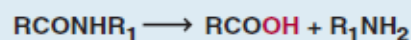
Hydrolyses

Esters



Procaine, succinylcholine, aspirin, clofibrate,
methylphenidate

Amides



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**.
- **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 ($R-Cl \rightarrow R-SG$).**
 - **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).**

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, <i>N</i> -hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	<i>N</i> -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, methyl dopa
Methylation	<i>S</i> -Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes) (cytosol)	Arene oxides, <i>cis</i> -disubstituted and monosubstituted oxiranes Alkene oxides, fatty acid epoxides	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide 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-hydroxyacetaminofluorine**
- 3. N-acetylation of isoniazid**
- 4. Sulfation leads to activation of the prodrug minoxidil.**
- 5. 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.**
- **An example is acetaminophen (paracetamol)-induced hepatotoxicity.**
- **It normally undergoes glucuronidation and sulfation, which make up 95% of the total excreted metabolites.**

Metabolism of Drugs to Toxic Product

- **A minor toxic metabolite (P450-dependent) may accumulate in case of paracetamol over dose.**
- **This metabolite can be eliminated normally by GSH conjugation pathway.**
- **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 overdose 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.**
- 2. Drugs:** barbiturates, phenytoin, carbamazepine, rifampin.
- 3. Cruciferous vegetables.**
- 4. St. John's wort.**

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. Macrolide antibiotics such as erythromycin, inactivate (CYP3A).
2. Suicide inhibitors (inactivators) include grapefruit furanocoumarins
3. Substrates compete with each other for the same active site of the enzyme.
4. Deficiency of cofactors impair drug metabolism.

Enzyme Inhibition

- 5. Inhibitors of nucleic acid and protein synthesis impair enzyme synthesis and, thus, drug metabolism.**
- 6. Malnutrition.**
- 7. Impairment of hepatic function.**

Enzyme Inhibition

- **Enzyme inhibition leads to accumulation of the drug in the body, thus increasing its adverse reactions and toxicity.**
- **In case of prodrugs, there will be failure of drug response.**
- **Both enzyme inhibition and induction are mechanisms of certain drug-drug interactions.**