Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 4- Drug Biotransformation

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Drug Biotransformation

Or

Drug Metabolism

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.**
- **Exposure may be accidental or intentional.**

Drug Biotransformation

- **Renal excretion plays an important role in removing xenobiotics from the body, and thus, terminating their biologic activity.**
- **Xenobiotics undergoing renal excretion are usually small molecules, that possess polar characteristics, or that are ionized at physiologic pH.**

Drug Biotransformation

- **Many drugs are not polar and tend to be lipophilic at physiologic pH, and are readily reabsorbed from the glomerular filtrate in the nephron.**
- **Some lipophilic drugs are bound to plasma proteins, and are not readily filtered at the glomerulus.**
- **An alternative process for elimination of such drugs is metabolism.**

Drug Biotransformation

- **In general, lipophilic drugs are transformed to more polar and hence more readily excreted products.**

1. **Metabolic products are often less active than the parent drug and may be even inactive.**
2. **Some biotransformation products have enhanced activity or even toxicity.**

Drug Biotransformation

3. Some drugs are inactive and need activation in the body by metabolism (Prodrugs). Levodopa, codeine.
4. Some drugs are metabolized into toxins. Paracetamol may be converted to the hepatotoxin N-acetyl-p-benzoquinone imine. 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, -NH_2, -SH).**

Drug Biotransformation

- **The increase in polarity may facilitate renal excretion.**
- **Many phase I products are not eliminated rapidly and may need a subsequent reaction to become polar enough to be readily excreted.**

Drug Biotransformation

- **Such subsequent reactions involve conjugation with an endogenous substrate such as glucuronic acid, sulfuric acid, …, which are called phase II reactions.**

Phase I Biotransformation reactions

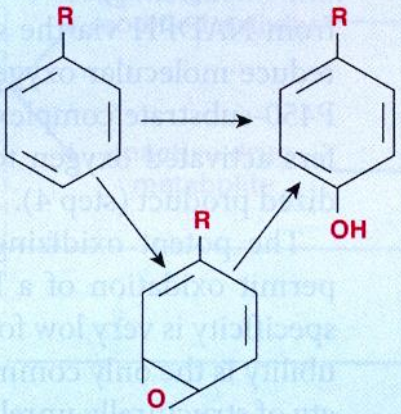
1. Oxidations
2. Reductions
3. Hydrolysis

- 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 membranes of the liver and other tissues.**
- **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	$RCH_2CH_3 \rightarrow RCH_2CH_2OH$ $RCH_2CH_3 \rightarrow RCHCH_3$ (OH)	Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation	$RCH{=}CHR \rightarrow R{-}\overset{H}{C}{-}\overset{O}{C}{-}\overset{H}{R}$	Aldrin
Oxidative dealkylation		
N-Dealkylation	$RNHCH_3 \rightarrow RNH_2 + CH_2O$	Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation	$ROCH_3 \rightarrow ROH + CH_2O$	Codeine, *p*-nitroanisole
S-Dealkylation	$RSCH_3 \rightarrow RSH + CH_2O$	6-Methylthiopurine, methitural

N-Oxidation

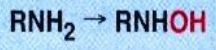
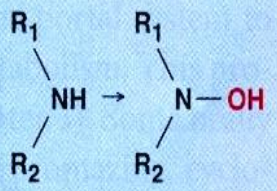
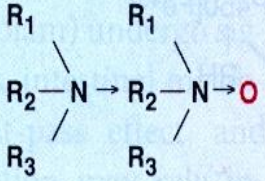
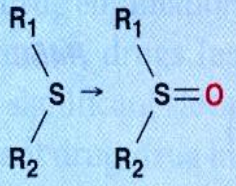
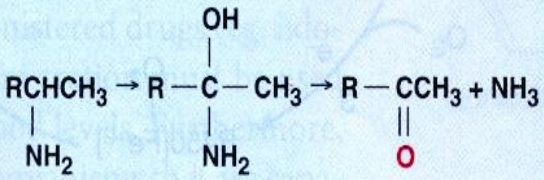
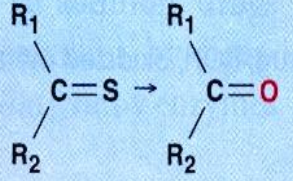
Primary amines		Aniline, chlorphentermine
Secondary amines		2-Acetylaminofluorene, acetaminophen
Tertiary amines		Nicotine, methaqualone
S-Oxidation		Thioridazine, cimetidine, chlorpromazine
Deamination		Amphetamine, diazepam
Desulfuration		Thiopental

TABLE 4–1 Phase I reactions. (Continued)

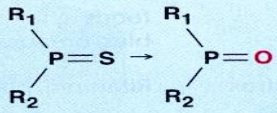
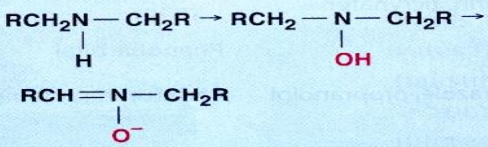
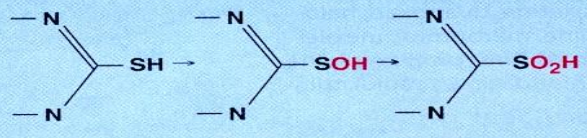
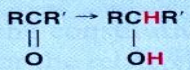
Reaction Class	Structural Change	Drug Substrates
Cytochrome P450- dependent oxidations: (continued)		
		Parathion
Dechlorination	$CCl_4 \rightarrow [CCl_3^{\cdot}] \rightarrow CHCl_3$	Carbon tetrachloride
Cytochrome P450-independent oxidations:		
Flavin monooxygenase (Ziegler's enzyme)	$R_3N \longrightarrow R_3N^+ \rightarrow O^- \xrightarrow{H^+} R_3N^+OH$	Chlorpromazine, amitriptyline, benzphetamine
		Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases	$RCH_2NH_2 \rightarrow RCHO + NH_3$	Phenylethylamine, epinephrine
Dehydrogenations	$RCH_2OH \rightarrow RCHO$	Ethanol
Reductions		
Azo reductions	$RN{=}NR_1 \rightarrow RNH{-}NHR_1 \rightarrow RNH_2 + R_1NH_2$	Prontosil, tartrazine
Nitro reductions	$RNO_2 \rightarrow RNO \rightarrow RNHOH \rightarrow RNH_2$	Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions		Metyrapone, methadone, naloxone
Hydrolyses		
Esters	$R_1COOR_2 \rightarrow R_1COOH + R_2OH$	Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides	$RCONHR_1 \rightarrow RCOOH + R_1NH_2$	Procainamide, lidocaine, indomethacin

TABLE 4–1 Phase I reactions. (Continued)

Reaction Class	Structural Change	Drug Substrates
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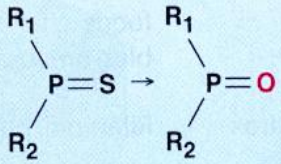
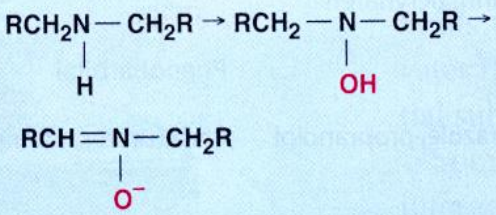
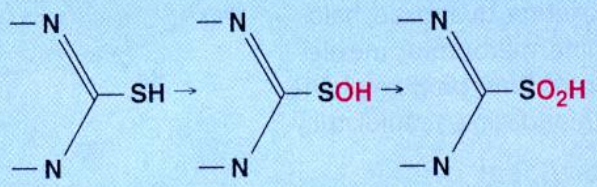
		Parathion
Dechlorination	$CCl_4 \rightarrow [CCl_3^{\cdot}] \rightarrow CHCl_3$	Carbon tetrachloride
Cytochrome P450-independent oxidations:		
Flavin monooxygenase (Ziegler's enzyme)	$R_3N \longrightarrow R_3N^+ \rightarrow O^- \xrightarrow{H^+} R_3N^+OH$	Chlorpromazine, amitriptyline, benzphetamine
		Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases	$RCH_2NH_2 \rightarrow RCHO + NH_3$	Phenylethylamine, epinephrine
Dehydrogenations	$RCH_2OH \rightarrow RCHO$	Ethanol

Reductions		
Azo reductions	$RN=NR_1 \rightarrow RNH-NHR_1 \rightarrow RNH_2 + R_1NH_2$	Prontosil, tartrazine
Nitro reductions	$RNO_2 \rightarrow RNO \rightarrow RNHOH \rightarrow RNH_2$	Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions	$RCR' \rightarrow RCHR'$ (O, OH)	Metyrapone, methadone, naloxone
Hydrolyses		
Esters	$R_1COOR_2 \rightarrow R_1COOH + R_2OH$	Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides	$RCONHR_1 \rightarrow RCOOH + R_1NH_2$	Procainamide, lidocaine, indomethacin

Human Liver 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 account for 15%, 20%, and 30% of the total human liver P450 content, respectively.**

Human Liver P450 Enzymes

- **CYP3A4 alone is responsible for the metabolism of over 50% of prescription drugs metabolized in the liver.**

Enzyme Induction

- **Enhanced rate of enzyme synthesis, or reduced rate of its degradation.**
- **Results in accelerated substrate metabolism, and usually in a decrease in the pharmacological action of the drug.**
- **Toxicity may increase if the drug is metabolized to reactive metabolites.**

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.**
2. **Drugs: Phenobarbital, phenytoin, carbamezepine, rifampin,**

Enzyme Induction

dexamethasone, clofibrate, oral contraceptives, spironolactone.

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

Enzyme Inhibition

- **Some drugs inhibit cytochrome P450 by binding to heme iron and inactivating the enzyme:**

1. **Imidazole-containing drugs such as cimetidine and ketoconazole.**
2. **Macrolide antibiotics metabolites.**
3. **Chloramphenicol metabolite.**
4. **Certain steroids**
5. **Grapefruit furanocoumarines. etc**

Enzyme Inhibition

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

Phase II Biotransformation reactions

- **Conjugation reactions 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 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**

Phase II Biotransformation reactions

acids.

- 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.

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. Methylation Reactions:

- **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, *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-hydroxy-coumarin, 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 mono-substituted 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 (acyl glucuronidation of nonsteroidal antiinflammatory drugs, O-sulfation of N-hydroxyacetylaminofluorine, and N-acetylation of isoniazid) may lead to formation of reactive species and drug toxicities.**

Phase II Biotransformation reactions

- **Sulfation leads to activation of the prodrug minoxidil.**
- **Morphine-6-glucuronide is more potent than morphine.**