METABOLISM OR BIOTRANSFORMATION

- It is the enzymatic conversion from one chemical form of a substance to another.
- **Metabolism** is an essential pharmacokinetic process, which converts lipid soluble and non-polar compounds to water soluble and polar compounds so that they are excreted by various processes.
- This is because only water-soluble substances undergo excretion, whereas lipid soluble substances are passively reabsorbed from renal or extra renal excretory sites into the blood by virtue of their lipophilicity.

- **Biotransformation**: It is a specific term used for chemical transformation of xenobiotics in the body/living organism.

- **Xenobiotics** : These are all chemical substances that are not nutrient for body (foreign to body) and which enter the body through ingestion, inhalation or dermal exposure.

- They include :
  drugs, industrial chemicals, pesticides, pollutants, plant and animal toxins, etc.

Biotransformation results in...

- It causes conversion of an active drug to inactive or less active metabolite(s) called as **pharmacological inactivation**.

Phenobarbitone	p-Hydroxyphenobarbitone
Phenytoin	p-Hydroxyphenytoin
Procaine	p-Aminobenzoic acid
Griseofulvin	6-Demethylgriseofulvin

- It causes conversion of an active to more active metabolite(s) called as **bioactivation** or **toxicological activation**.

Codeine	Morphine
Paracetamol	Imidoquinone of N-hydroxylate metabolite
Sulphonamides	Acetyl derivatives
Malathion	Malaoxon
Halothane	Trifluoroacetic acid

- It causes conversion of an inactive drug (pro-drug) to active metabolite(s) called as **pharmacological activation**

Phenacetin	Paracetamol
Enalapril	Enalaprilat
Pivampicillin	Ampicillin
Sulphasalazine	5-Aminosalicylic acid
Levodopa	Dopamine

- It causes conversion of an active drug to equally active metabolite(s) (**no change** in pharmacological activity)

Digitoxin	Digoxin
Diazepam	Nordiazepam
Amitriptyline	Nortriptyline
Phenylbutazone	Oxyphenbutazone

Site/Organs of drug metabolism

The **major site** of drug metabolism is the **liver** (microsomal enzyme systems of hepatocytes)

Secondary organs of biotransformation

- kidney (proximal tubule)
- lungs
- testes (Sertoli cells)
- skin (epithelial cells); **plasma. nervous tissue (brain);** intestines

Metabolic enzymes:

- Microsomal enzymes

Non-Microsomal enzymes

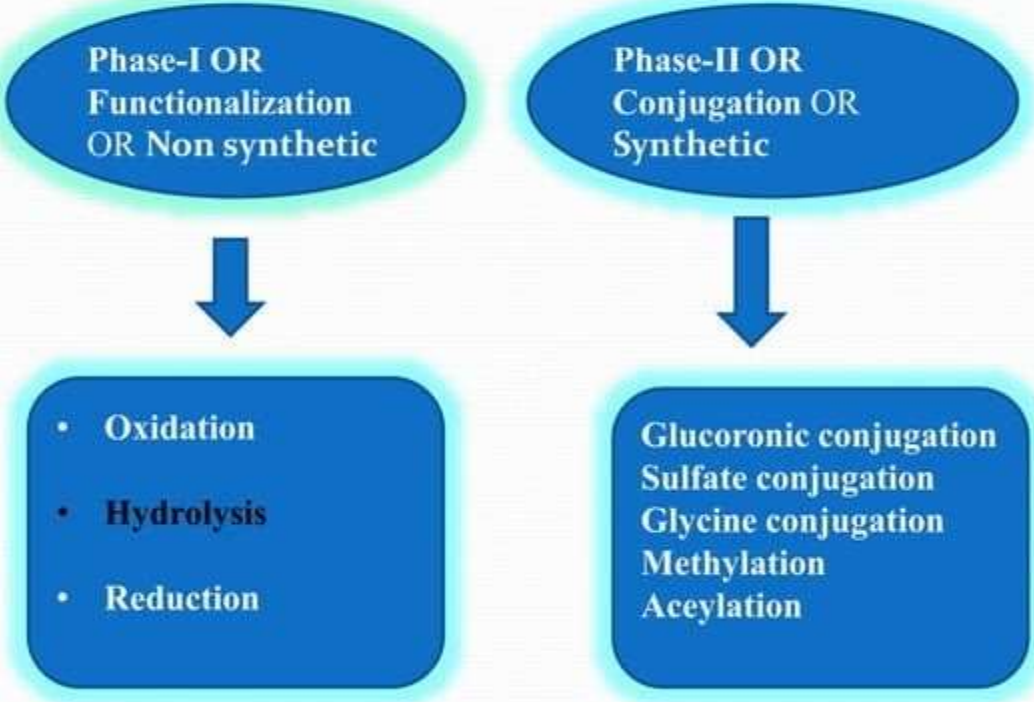
Found in smooth ER of liver cells

Found in cytoplasm & mitochondria of liver cells

CYP-450, mono oxygenase, flavin mono oxygenase

Alcohol dehydrogenase, aldehyde dehydrogenase, MAO

Types of biotransformation



Phase-I /Functionalization / Non synthetic reactions:

- Attechment of functional groups (OH, COOH, NH_2 etc)
- Metabolite- active or Inactivate
- Convert to more hydrophilic in nature

- Examples:
- Oxidation-phenytoin, barbiturates

- Hydrolysis-aspirin

- Reduction- benzodiazepines

Phase-II / Conjugation / Synthetic reactions:

Detoxification reactions and almost **always results in loss of biological activity of a compound**.

- Endogenous polar molecule is conjugated(as carbohydrates and amino acids like glucoronic acid, methyl gp, sulphate, glycine)

- Converted to hydrophilic & pharmacologically inactive
- Examples:

Glucoronic conjugation- paracetamol, chloramphenicol

1.Oxidation

- Addition of oxygen OR removal of hydrogen.
- Oxidation by cytochrome P450 enzymes (microsomal mixed-function oxidases).

- Oxidation by enzymes other than cytochrome P450 is—most of these
- (a) oxidation of alcohol by alcohol dehydrogenase,
- (b) oxidation of aldehyde by aldehyde dehydrogenase,
- (c) N-dealkylation by monoamineoxidase.

- Eg. phenytoin, barbiturates, propranolol, imipramine etc.

- **PHASE I ENZYMES**
  Cytochrome P450 Monooxygenase (Cytochrome P450, P450, or CYP)
- Flavin-Containing Monooxygenase (FMO)
- Esterase
- Alcohol Dehydrogenase (ADH)
- Aldehyde Dehydrogenase (ALDH)
- Monoamine Oxidase (MAO)

PHASE II ENZYMES

- Uridine Diphosphate-Glucuronosyl transferase (UDPGT)
- Sulfo transferase (ST)
- N-Acetyl transferase (NAT)
- Glutathione S-Transferase (GST)
- Methyl Transferase
- Amino Acid Conjugation

2. Reduction :

- Addition of hydrogen
- Substrates for reductive reactions include azo- or nitro compounds, epoxides, heterocyclic compounds, and halogenated hydrocarbons:

(a) Azo or nitro gp reduction by cytochrome P450;

(b) Carbonyl (aldehyde or ketone) reduction by aldehyde reductase, aldose reductase, carbonyl reductase, quinone reductase

Eg. Chloramphenicol, warfarin, halothane, chloral hydrate etc.

3. Hydrolysis

- involve the cleavage of drug molecule by taking up a molecule of water.
- Ester + H_2O ⟶ acid + alcohol
- A **number of drugs with ester, ether, amide and hydrazide linkages undergo hydrolysis.**
- Examples: procaine, procainamide, aspirin and pethidine etc.

PHASE II REACTIONS

- Phase II or conjugation reactions involve combination of the drug or its phase I metabolite with an endogenous substance to form a highly polar product, which can be efficiently excreted from the body.

1. Conjugation with glucuronic a./ Glucuronidation

- Conjugation with glucuronic acid (glucuronide conjugation or glucuronidation) is the most common and most important phase II reaction.

- The biochemical donor (cofactor) of glucuronic acid is uridine diphosphate«-D-glucuronicacid (UDPGA) and the reaction is carried out by enzyme uridine diphosphate-glucuronyl transferase (UDP-glucuronyl transferase).

- Glucuronyl transferase is present most tissues but liver is the most active site of glucuronide synthesis.

- Eg. Paracetamol, diazepam, chloramphenicol, lorazepam, metronidazol, morphine etc.

2. Conjugation with methyl group/ Methylation :

- Conjugation with methyl group (methyl conjugation or methylation) involves transfer of a methyl group ($-CH_3$) from the cofactor S-adenosyl methionine (SAM) to the acceptor substrate by various methyl transferase enzymes.

- Eg. Nicotinic acid, adrenaline, histamine etc.

3. **Conjugation with acetyl group/ Acetylation :**

- Compounds having amino or hydrazine gps are conjugated with the help of acetyl coenzyme-A
- Eg. Sulfonamides, clonazepam ets.

4. **Conjugation with sulphate/ Sulphation**:

- Steroids and phenolic compounds are undergoes to this reaction.
- Eg. Sex steroids, methyldopa etc

Drug metabolism

Factors affecting drug metabolism:

- Age
- Sex
- Genetic differences
- Nutrition
- Pathological conditions
- Route of administration
- Effect of drug on metabolism

- Enzyme induction: eg barbiturates, phenytoin , rifampin etc

- Enzyme inhibition: eg. Cemetidine, ketoconazole, erythromycine etc.