

METABOLISM

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Metabolism



By the end of this lecture, you should:

- Recognize the importance of biotransformation
- Know the different sites for drug metabolism
- Define the major phase I and phase II metabolic reactions.
- Describe the modulation of liver microsomal enzymes by inducers and inhibitors
- Mention two drugs that are known as enzyme inducers and inhibitors.
- Know the impact of first pass metabolism on drug bioavailability Question

Drug Metabolism (Biotransformation)

□ Definition

- Chemical reactions which occur in the body to change drugs from nonpolar lipid soluble forms to polar water soluble forms that are easily excreted by the kidney.

Importance of Metabolism



- Inactivation or termination of drug action (most drugs).
- Detoxification Biotransformation is required for protection of body from toxic metabolites
- Activation of prodrug (**convert inactive form of drug to active form**)
 - e.g. levodopa - carbidopa, prednisone – prednisolone

Organ sites of drug metabolism



- Liver (the major site).
- Intestinal Mucosa and Lumen
- Plasma
- Kidney
- Skin
- Lung

Organ sites of drug metabolism

- Intestinal Mucosa and Lumen
 - ▣ **Gut Mucosa**
 - MonoAmine Oxidase (MAO).
 - ▣ **Gut lumen (bacterial flora)**
 - Glucouronidase.

Organ sites of drug metabolism

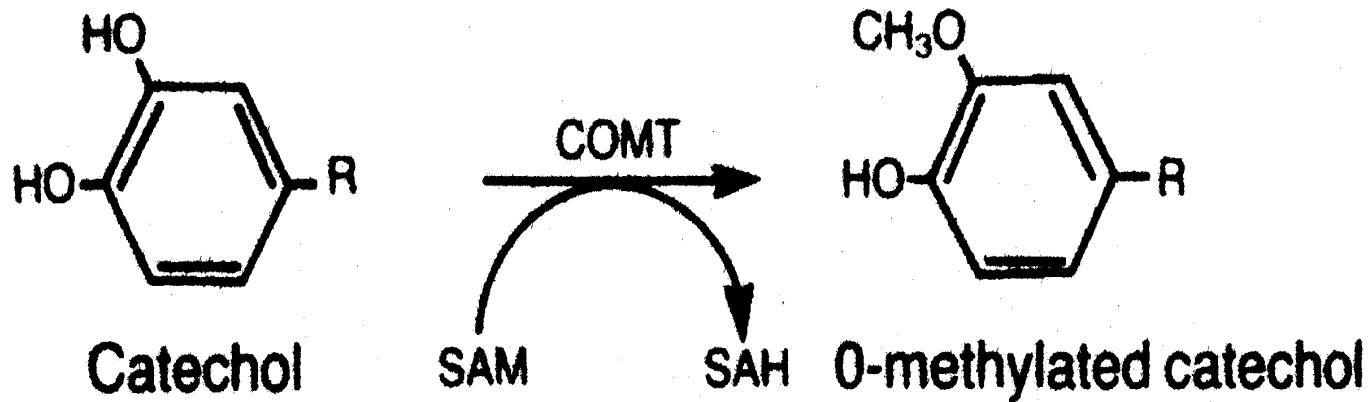
□ Plasma

Enzymes	substrate
Catechol o - methyl transferase (COMT)	catecholamines (adrenaline)
Esterases	Esters Local anesthetics
Amidases	amides Local anesthetics

Organ sites of drug metabolism

- Plasma

- Catechol o-methyl transferase (COMT)



Organ sites of drug metabolism



- Cellular sites of drug metabolism
 - Cytoplasm
 - Mitochondria
 - Lysosomes
 - Microsomes

Organ sites of drug metabolism

- Cellular sites of drug metabolism

- ▣ Cytoplasm

e.g. Alcohol dehydrogenase: $\text{NAD}^+ \longrightarrow \text{NADH}$

Alcohol \longrightarrow Aldehyde \longrightarrow Acid

Ethanol \longrightarrow acetaldehyde \longrightarrow acetic acid.

$\text{CH}_3\text{CH}_2\text{OH} \longrightarrow \text{CH}_3\text{CHO} \longrightarrow \text{CH}_3\text{COOH}.$

Organ sites of drug metabolism

- Cellular sites of drug metabolism
 - ▣ Mitochondria
 - N-acetyl transferase:
 - Introduction of acetyl group (CH_3COO^-)
 - Monoamine oxidase enzyme (MAO):
 - Oxidation of catecholamines as adrenaline

Organ sites of drug metabolism

- Cellular sites of drug metabolism

- ▣ Microsomes

Microsomal enzyme system = Cytochrome P-450.

There are more than 20 families

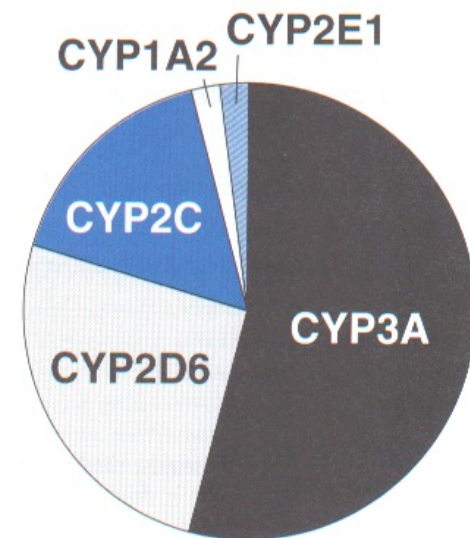
Sub-families are identified as A, B, and C etc.

In human: only 3 isoenzyme families are important CYP1, CYP2
and CYP3

Oxidation - Cytochrome P-450

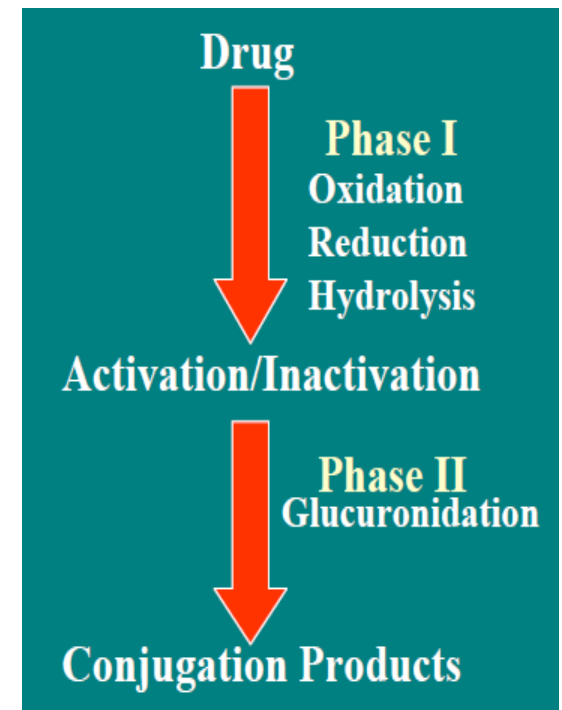
□ **CYP 3A4/5** carry out biotransformation of the largest number (30–50%) of drugs.

Expressed in liver and intestine (responsible for first pass metabolism at this site).



Types of hepatic metabolic reactions

- **Two phases of hepatic metabolic reactions**
 - ▣ **Phase I**: *Phase I* metabolite may be active or inactive
 - Oxidation.
 - Reduction.
 - Hydrolysis.
 - ▣ **Phase II**: metabolites are inactive
 - Conjugation reactions



Types of hepatic metabolic reactions

□ Phase I reactions :

□ Oxidation

- Is addition of oxygen or removal of hydrogen.
- Is the most important drug metabolizing reaction.
- May be **microsomal** or **non-microsomal**

Types of hepatic metabolic reactions

□ Phase I reactions :

□ Oxidation

- **Microsomal** occurs in microsomes, e.g. cytochrome P450 enzymes, NADPH and oxygen
- **Non-microsomal** occurs in cytosol or mitochondria, e.g.
 - Alcohol – Dehydrogenase
 - Adrenaline – Monoamine Oxidase
 - Xanthine – Xanthine oxidase

Types of hepatic metabolic reactions

- **Phase I reactions :**

- Oxidation

- **Non-microsomal** occurs in cytosol or mitochondria, e.g.

- Alcohol – Dehydrogenase

- Alcohol dehydrogenase & aldehyde dehydrogenase

Types of hepatic metabolic reactions

□ Phase I reactions :

□ Oxidation

■ **Non-microsomal** occurs in cytosol or mitochondria, e.g.

■ Serotonin and Adrenaline – Monoamine Oxidase (MAO):

■ Metabolism of catecholamines as adrenaline and serotonin

■ e.g. Moclobemide is MAO inhibitor and used as antidepressant since it increases serotonin in brain.

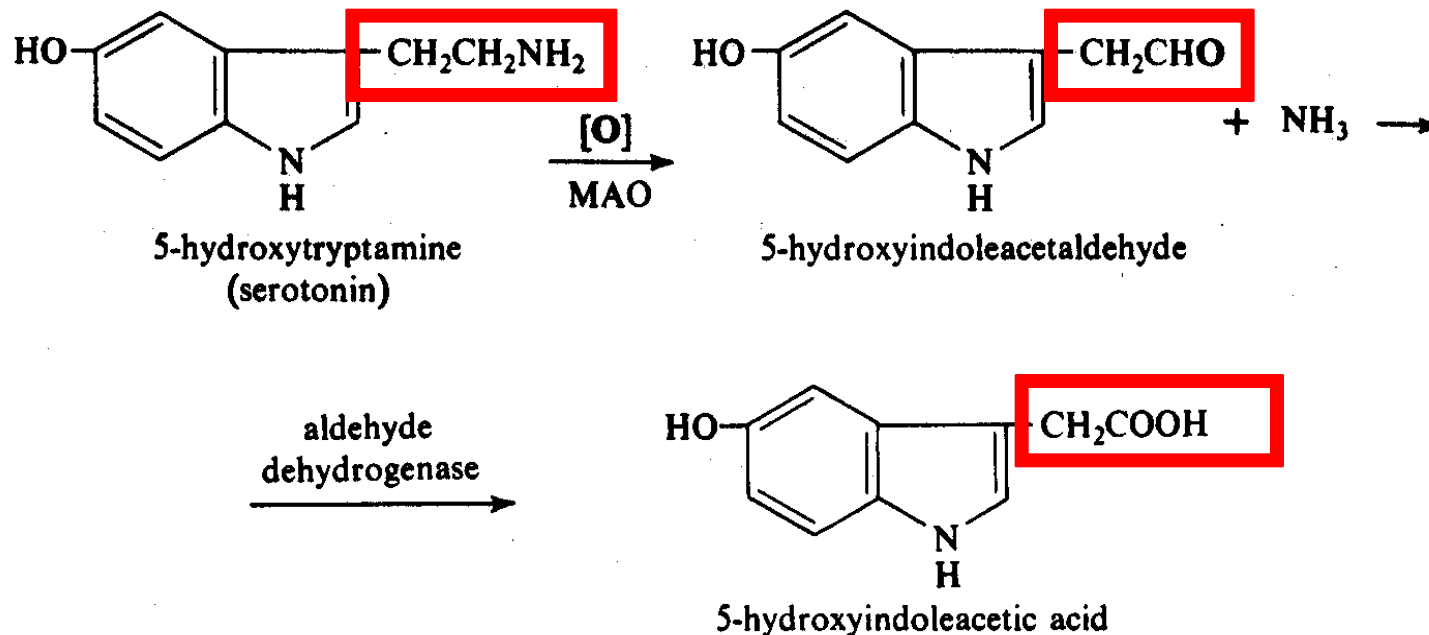
Types of hepatic metabolic reactions

□ Phase I reactions :

□ Oxidation

■ **Non-microsomal** occurs in cytosol or mitochondria, e.g.

■ Serotonin – Monoamine Oxidase (MAO):



Types of hepatic metabolic reactions

□ Phase I reactions :

▣ Oxidation

■ **Non-microsomal** occurs in cytosol or mitochondria, e.g.

■ Xanthine – Xanthine oxidase

■ Metabolism of xanthine , e.g.

Hypoxanthine $\xrightarrow{\text{oxidase}}$ xanthine $\xrightarrow{\text{oxidase}}$ uric acid

uric acid accumulation \longrightarrow GOUT

Allopurinol is an inhibitor of xanthine oxidase and used in treatment of gout.

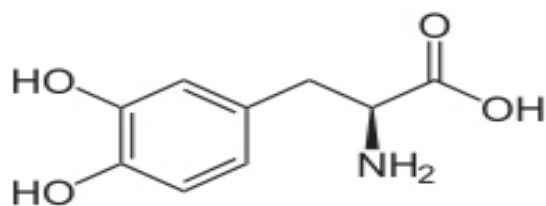
Types of hepatic metabolic reactions

□ Phase I reactions :

▣ Reduction

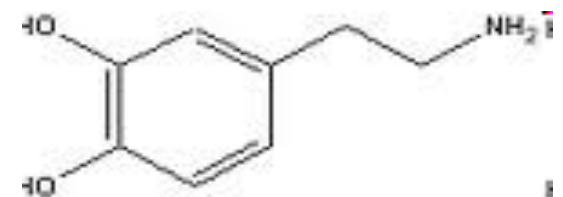
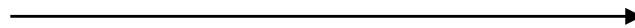
- Removal of oxygen or addition of hydrogen.
- may be microsomal or non microsomal.

■ Examples: levodopa



Levodopa (DOPA)

DOPA- decarboxylase



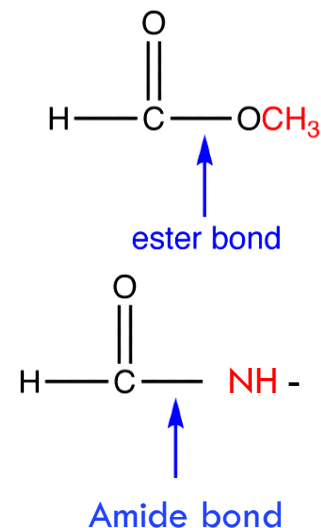
Dopamine

Types of hepatic metabolic reactions

□ Phase I reactions :

□ Hydrolysis

- All are non microsomal
- occurs by addition of water molecules in presence of enzymes as (**esterases & amidases**)
- Esterases: hydrolyze drugs that are **esters**
- Amidases: hydrolyze drugs that are **amides**



Types of hepatic metabolic reactions

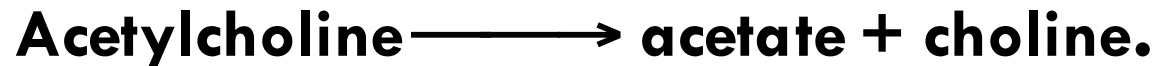
□ Phase I reactions :

□ Hydrolysis

- Esters as **acetylcholine** (neurotransmitter).



esterase



- Amides as **lidocaine** (used as local anesthetic)

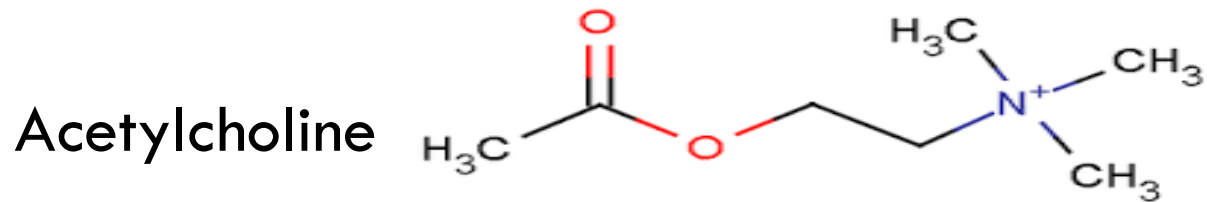


Types of hepatic metabolic reactions

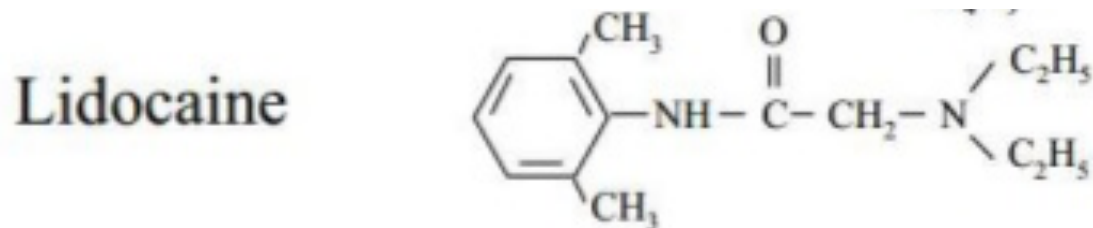
□ Phase I reactions :

□ Hydrolysis

- Esters as **acetylcholine** (neurotransmitter).



- Amides as **lidocaine** (used as local anesthetic)



Types of hepatic metabolic reactions

- **Phase I reactions can result in :**
 - Inactivation of drug (termination of action)
 - Activation of pro-drug
 - e.g. levodopa to dopamine
 - Conversion of active drug to active metabolite
 - Conversion of nontoxic drug to toxic metabolite
 - Paracetamol → hepatotoxic metabolite (hepatic necrosis)
 - Product might undergo phase II

Types of hepatic metabolic reactions

- **Phase II reactions :**

- Conjugation

Conjugation of metabolite coming from (**phase I**) with endogenous substance as methyl group, acetyl group, sulphate, amino acid or glucouronic acid to produce conjugate that is **water soluble** and **easily excreted in urine or bile**.

Types of hepatic metabolic reactions

□ Phase II reactions :

▣ Conjugation

Conjugation reaction	Enzyme required
glucouronide conjugation	<u>Glucouronyl transferase</u>
Acetylation (CH₃ COO⁻)	<u>N-acetyl transferase</u>
Sulphation (SO₄⁻⁻)	<u>Sulfo transferase</u>
Methylation (CH₃)	<u>methyl transferase</u>
Amino acids conjugation	Glycine conjugation

Types of hepatic metabolic reactions

- **Phase II reactions :**
- All are non microsomal except glucouronidation
- Glucouronide conjugation is a microsomal process (**the most common**).
- Deficiency of **glucouronyl transferase** enzyme in neonates may result into toxicity with chloramphenicol (**Gray baby syndrome**).

Types of hepatic metabolic reactions

- **Phase II reactions :**

- Characteristics of its Products

- Usually pharmacologically inactive.
 - Polar
 - More water soluble.
 - Easily excreted in urine

Factors affecting metabolism

- Age: ↓ rate of metabolism in neonates & elderly
- Diseases: ↓ rate of metabolism in liver diseases
- Degree of Protein Binding: ↓ rate of metabolism
- Concurrent use of drugs: Induction & inhibition
- Nutrition: malnutrition ↓ rate of metabolism

Factors affecting metabolism



- Genetic polymorphism
 - Isoniazid (Anti-TB), etc.
 - **Slow acetylator** phenotype → peripheral neuropathy
 - **Rapid acetylator** phenotype → hepatitis

Enzyme Induction & inhibition



- **Liver microsomal enzymes inducers:** drugs that increase activities of liver microsomal enzymes & increase the metabolism of drug itself and other drugs taken with the inducer at the same time.
- **Liver microsomal enzymes inhibitors:** drugs that decrease activities of liver microsomal enzymes & decrease the metabolism of the drug itself and other drugs.

Enzyme Induction & inhibition

Enzyme inducers

Alcohol

Cigarette smoking

Phenobarbitone **hypnotic**

Phenytoin **(antiepileptic)**

Rifampicin **(Anti TB)**

Enzyme inhibitors

Grape fruits

Cimetidine

Erythromycin **(antibiotic)**

Ketoconazole **(antifungal)**

Enzyme Induction & inhibition

□ Enzyme induction may result in:

- ↑ the metabolism and excretion of the inducer drug itself and co-administered drugs.
- ↓ the action of the inducer drug itself & co-administered drugs.
 - e.g. oral contraceptives & phenytoin (**inducer**).
 - Failure of oral contraceptive may lead to pregnancy if combined with phenytoin.
- Tolerance may occur: decrease in the pharmacological action of the drug by repeated administration .

Enzyme Induction & inhibition

□ Enzyme inhibition may

- ↓ Delay the metabolism and excretion of the inhibitor drug and co-administered drugs.
- ↑ Prolong the action of the inhibitor drug & co-administered drugs.
 - e.g. warfarin & erythromycin (inhibitor).
 - Inhibition of warfarin metabolism may lead to increase its anticoagulant effect (bleeding).