Metabolism

Prof. Hanan Hagar
Dr. Ishfaq Bukhari
Pharmacology Department

METABOLISM

By the end of this lecture, students 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.***

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

Intestinal Mucosa and Lumen

Gut Mucosa

- MonoAmine Oxidase (MAO) .

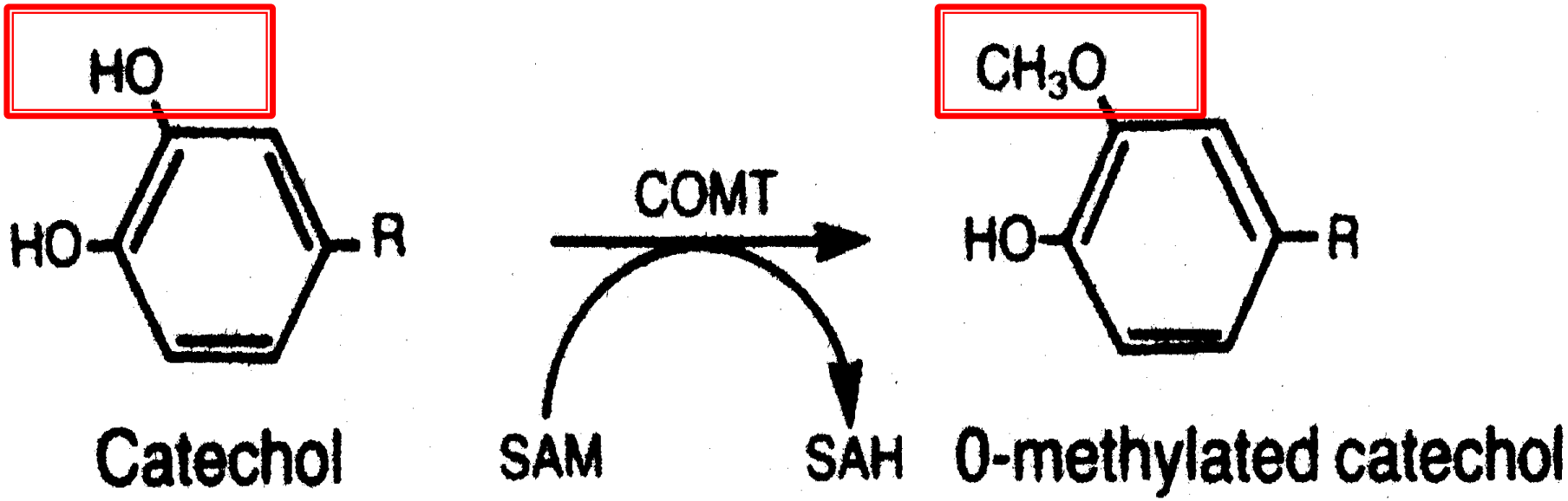
Gut lumen (bacterial flora)

- **Glucouronidase.**

Plasma

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

Catechol o-methyl transferase



Cellular sites of drug metabolism

- **Cytoplasm**
- **Mitochondria**
- **Lysosomes**
- **Microsomes**

Mitochondria

- **Monoamine oxidase enzyme (MAO):**

  oxidation of catecholamines as adrenaline

Cytoplasm

e.g. Alcohol dehydrogenase: reduction of alcohol

Alcohol ⟶ Aldehyde ⟶ Acid

Ethanol ⟶ acetaldehyde ⟶ acetic acid.

$CH_3CH2OH \rightarrow CH_3CHO \rightarrow CH_3COOH$.

Microsomes

Microsomal enzyme system = Cytochrome P-450.

There are more than 20 families CYP1, CYP2, CYP3

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

In human: only 3 isoenzyme families are important

CYP1, CYP2 and CYP3

Types of hepatic metabolic reactions

Two phases of hepatic metabolic reactions:

Phase I reactions include:

- **Oxidation.**
- **Reduction.**
- **Hydrolysis.**

Phase II reactions include

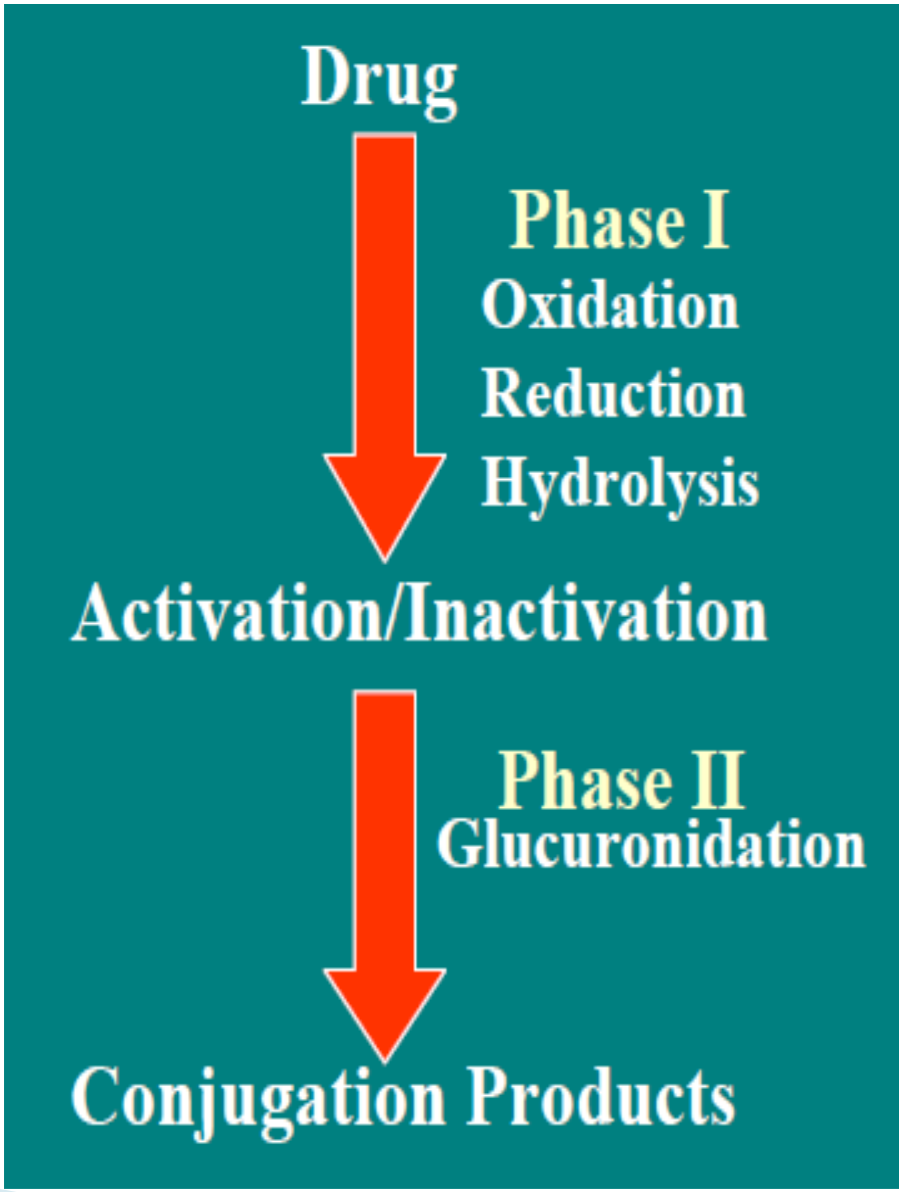
- **Conjugation reactions**

Types of hepatic metabolic reactions

(two) Phases of Biotransformation:

- *Phase I* metabolite may be active or inactive

- *Phase II* metabolites are inactive



Oxidation Reactions

Oxidation

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

Oxidation Reactions

Microsomal oxidation

- occurs in microsomes
- e.g. cytochrome P450 enzymes, NADPH and oxygen

Non microsomal oxidation

- occurs in cytosol or mitochondria
- e.g. oxidases and dehydrogenases.

Non-microsomal Oxidation

- **Dehydrogenases**

Alcohol dehydrogenase & aldehyde dehydrogenase

- **Oxidases**

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.

Non-microsomal Oxidation

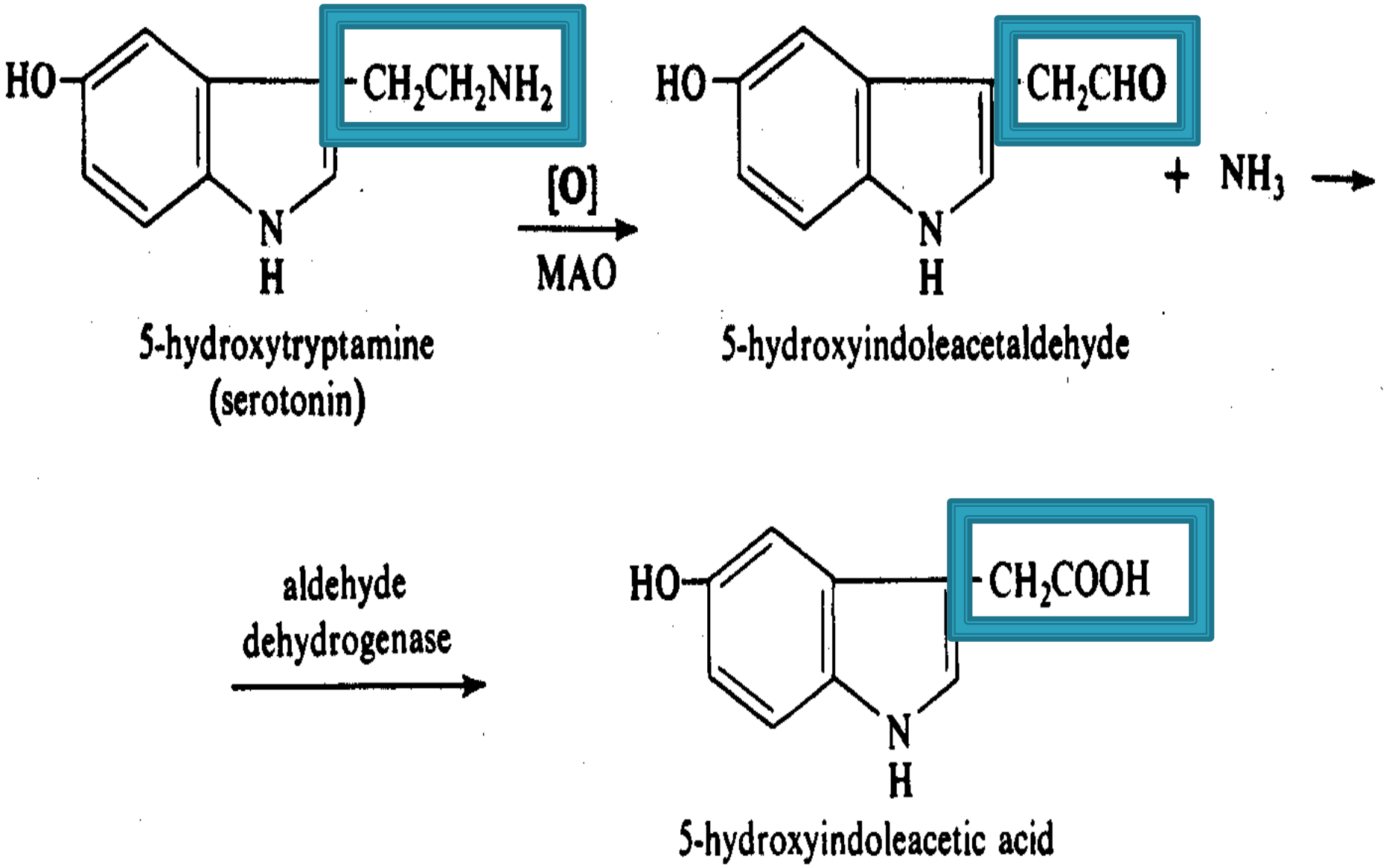
Xanthine oxidase:

metabolism of xanthine

oxidase oxidase

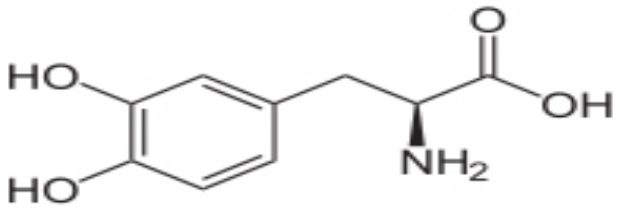
- Hypoxanthine ⟶ xanthine ⟶ uric acid
- uric acid accumulation ⟶ GOUT
- **Allopurinol** is an inhibitor of xanthine oxidase and used in treatment of gout.

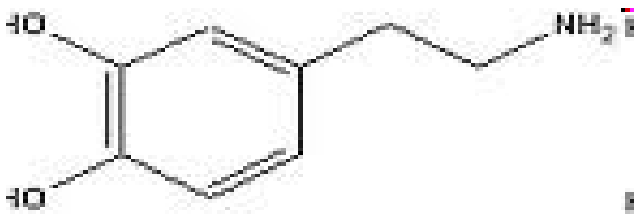
Monoamine oxidase (MAO)



Reduction reactions

- **Removal of oxygen or addition of hydrogen.**
- **may be microsomal or non microsomal.**
- **Examples:** levodopa





DOPA- decarboxylase

Levodopa (DOPA) → Dopamine

Hydrolysis

- **All are *non microsomal***
- **occurs by addition of water molecules in presence of enzymes as (esterases & amidases)**

Hydrolysis

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

$$\text{Ester} + H_2O \longrightarrow \text{Acid} + \text{Alcohol}$$

$$\text{Acetylcholine} \xrightarrow{\text{esterase}} \text{acetate} + \text{choline}.$$

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

$$\text{Amide} + H_2O \longrightarrow \text{Acid} + \text{amine}$$

Phase I reactions can result in

- **Activation of pro-drug**

  e.g. levodopa to dopamine

- **Inactivation of drug (termination of action)**
- **Conversion of active drug to active metabolite**
- **Conversion of nontoxic drug to toxic metabolite**

Paracetamol → hepatotoxic metabolite (hepatic necrosis)

- **Product might undergo phase II**

Phase II Conjugation Reactions

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 conjugation reactions

Conjugation reaction	Enzyme required
glucouronide conjugation	**Glucouronyl transferase**
Acetylation (CH_3COO^-)	**N-acetyl transferase**
Sulphation (SO_4^{--})	**Sulfo transferase**
Methylation (CH_3)	**methyl transferase**
Amino acids conjugation	**Glycine conjugation**

Phase II reactions:

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

Characteristics of Phase II 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
- **Genetic polymorphism**

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 inducers

Alcohol

Cigarette smoking

Phenobarbitone hypnotic

Phenytoin (antiepileptic)

Rifampicin (Anti TB)

Enzyme inhibitors

Grape fruits

Cimetidine (anti-ulcer)

Erythromycin (antibiotic)

Ketoconazole (antifungal)

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.
- **Tolerance may occur**: decrease in the pharmacological action of the drug by repeated administration .

Enzyme induction may result in:

- **Drug interactions may occur:** decrease in action of one drug by administration of another drug
- e.g. oral contraceptives & phenytoin **(inducer).**
- Failure of oral contraceptive may lead to pregnancy if combined with phenytoin**.**

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).**