Metabolism

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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

- Mono-Amine Oxidase (**MAO**) .

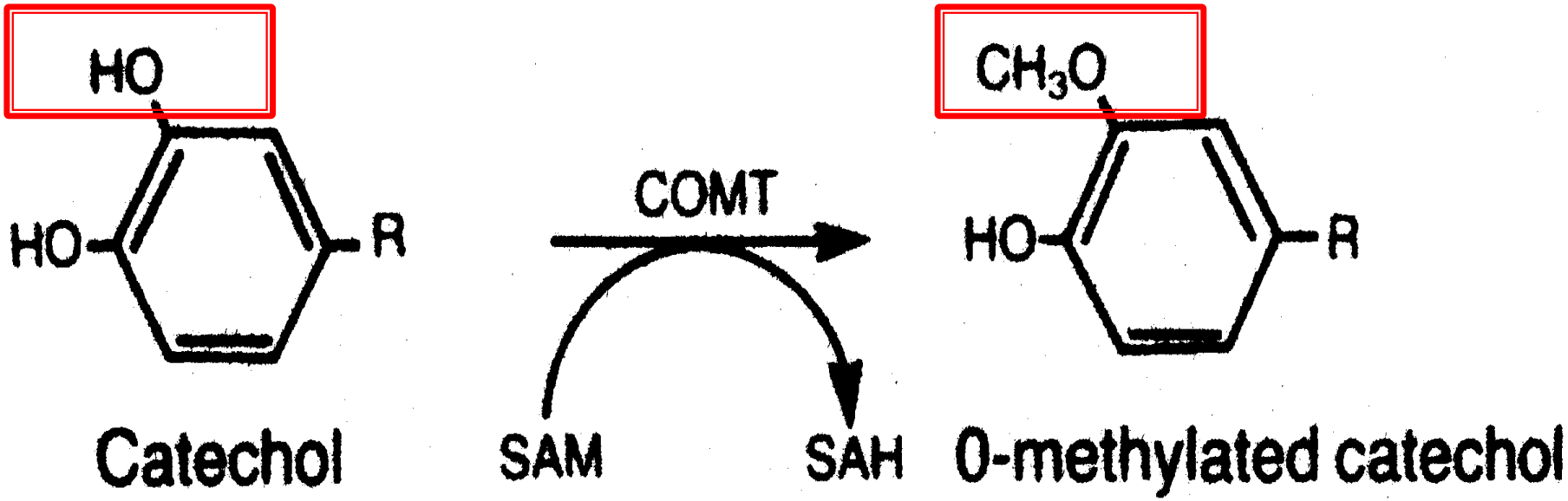
Gut lumen (bacterial flora)

- **Glucouronidase.**

Plasma

Enzymes	substrate
Catechol O-Methyl Transferase (COMT)	catecholamines (e.g. adrenaline)
Esterases	Esters Act on drugs as Local anesthetics
Amidases	amides Act on drugs as local anesthetics

Catechol o-methyl transferase



Cellular sites of drug metabolism

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

Mitochondria

- **N-acetyl transferase:**

  Introduction of acetyl group (CH_3COO^-)

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

  oxidation of catecholamines as adrenaline

Cytoplasm

e.g. Alcohol dehydrogenase: oxidation 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

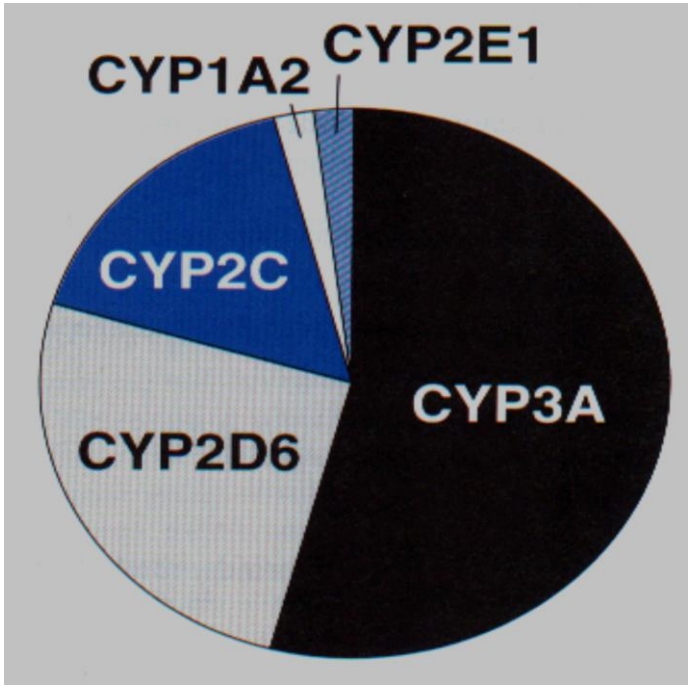
Sub-families are identified as A, B, and C etc.

In human: only 3 isoenzyme families are important

CYP1, CYP2 and CYP3

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 metabolic reactions include:

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

Phase II metabolic reactions include

- **Conjugation reactions**

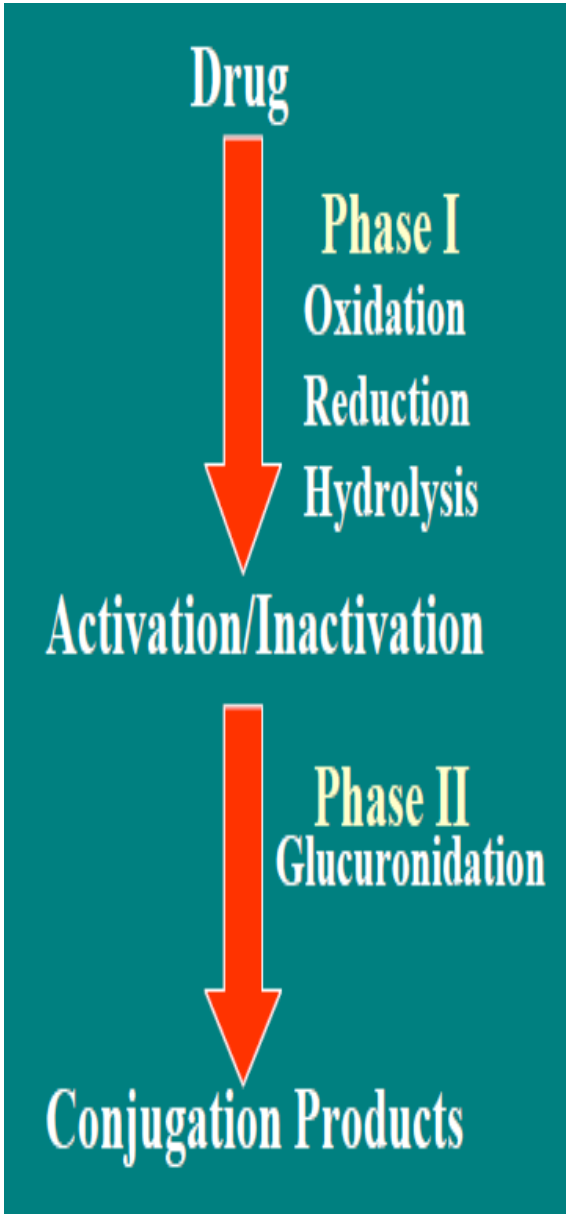
Types of hepatic metabolic reactions

Phase I:

metabolites may be active or inactive.

Phase II:

metabolites are usually 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

These enzymes include **oxidases & dehydrogenases**

Non-microsomal Oxidation

Dehydrogenases

Are required for oxidation of alcohols

e.g. Alcohol dehydrogenase (convert alcohol to aldehyde).

e.g. **Aldehyde dehydrogenase** (convert aldehyde to acid).

Non-microsomal Oxidation

Oxidases

1) Monoamine oxidase (MAO):

- Is responsible for the metabolism of catecholamines as adrenaline and serotonin.
- e.g. **Moclobemide**
  - Is a monoamine oxidase inhibitor.
  - It increases serotonin in the brain.
  - Used as antidepressant drug.

Non-microsomal Oxidation

2) Xanthine oxidase:

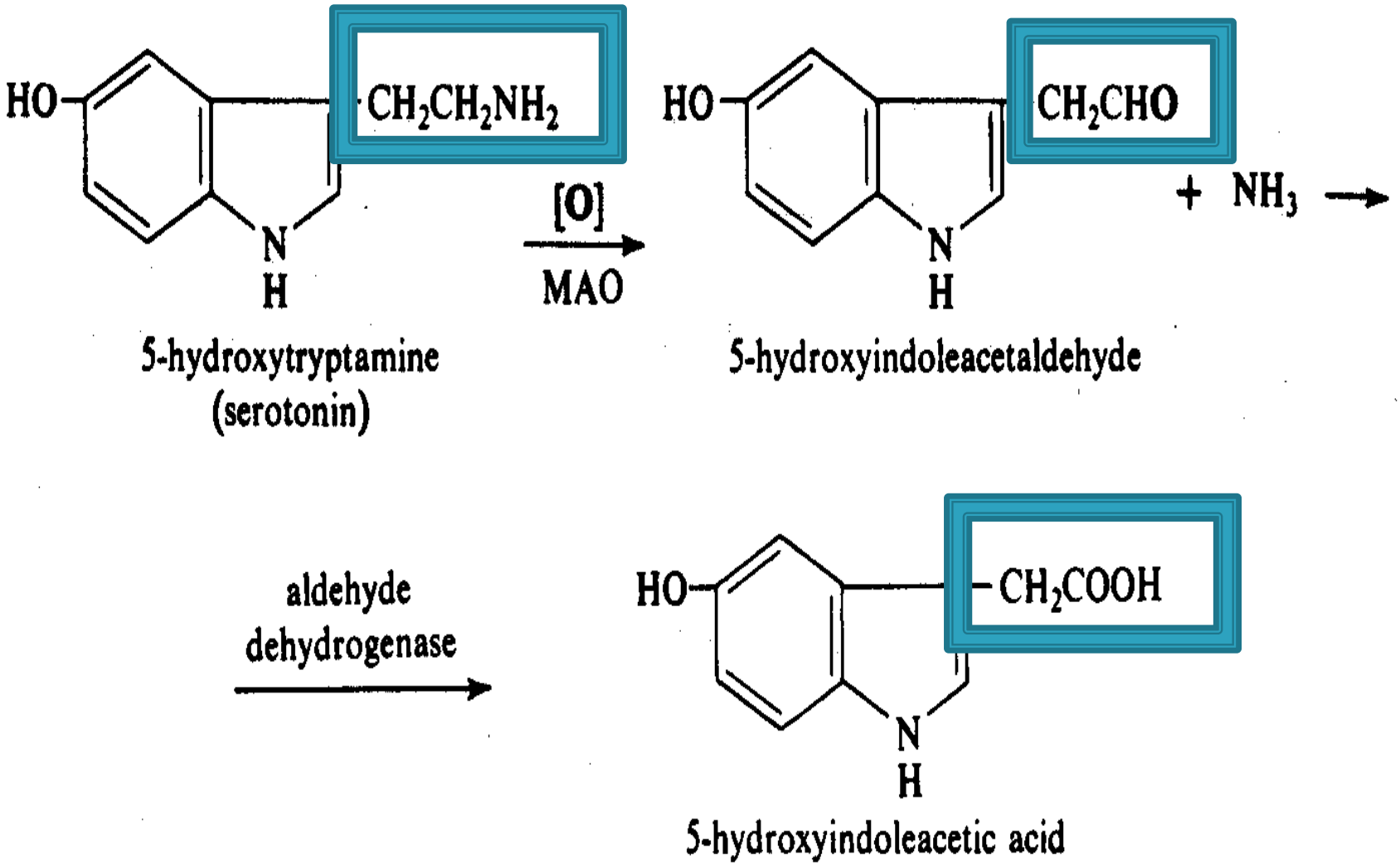
Is required for the oxidation of xanthine

oxidase oxidase

- Hypoxanthine ⟶ xanthine ⟶ uric acid
- uric acid accumulation ⟶ **GOUT**

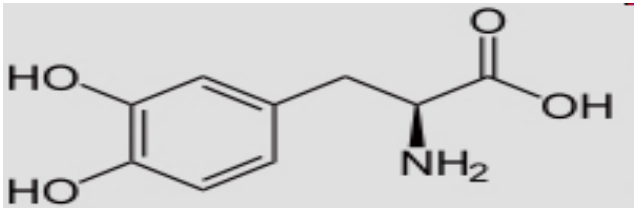
- **Allopurinol**
- is an inhibitor of xanthine oxidase
- used in the treatment of gout.

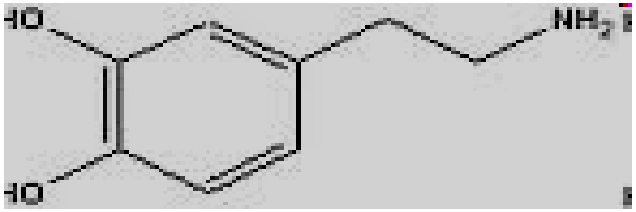
Monoamine oxidase (MAO)



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)**
- **Esterases:** hydrolyze drugs that are **esters**
- **Amidases:** hydrolyze drugs that are **amides**

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 metabolic reactions:

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

Characteristics of Phase II metabolites

Phase II metabolites are:

- **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

- Metabolism may vary from population to another due to the existence of different forms of the metabolic enzymes.
- E.g. metabolism of **isoniazid** (Anti-TB), etc.
- **Slow acetylator phenotype** → results in decrease in isoniazid metabolism & accumulation of isoniazid with risk of **peripheral neuropathy**
- **Rapid acetylator phenotype** → results into excess metabolites produced with risk of **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 taken concurrently.

Enzyme inducers

Alcohol

Cigarette smoking

Phenobarbitone hypnotic

Phenytoin (antiepileptic)

Rifampicin (Anti TB)

Enzyme inhibitors

Grape fruits

Cimetidine

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 continuous or 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 (risk of bleeding).**