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.

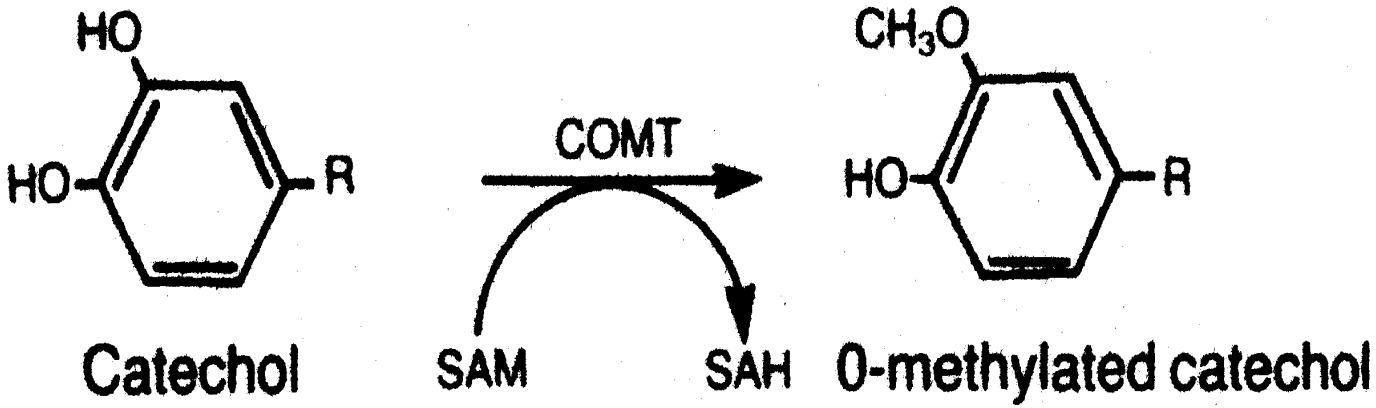
Organ sites of drug metabolism

- 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: $NAD^+ \longrightarrow NADH$

Alcohol $\longrightarrow$ Aldehyde $\longrightarrow$ Acid

Ethanol $\longrightarrow$ acetaldehyde $\longrightarrow$ acetic acid.

$CH_3CH_2OH \rightarrow \quad CH_3CHO \rightarrow \quad CH_3COOH.$

Organ sites of drug metabolism

- Cellular sites of drug metabolism
  - Mitochondria
    - N-acetyl transferase:
      - Introduction of acetyl group (CH3COO-)
    - 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

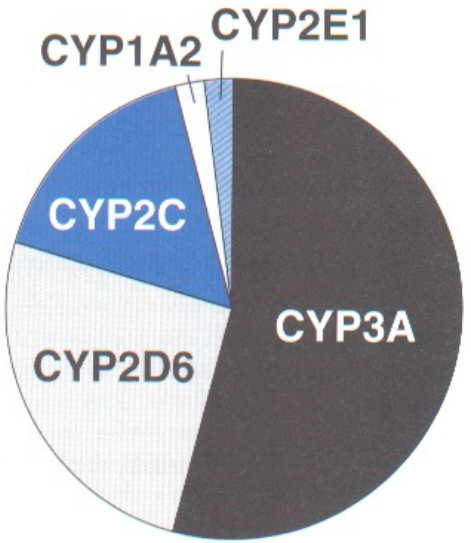
Sub-families are identified as A, B, and C etc.

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

Oxidation - Cytochrome P-450

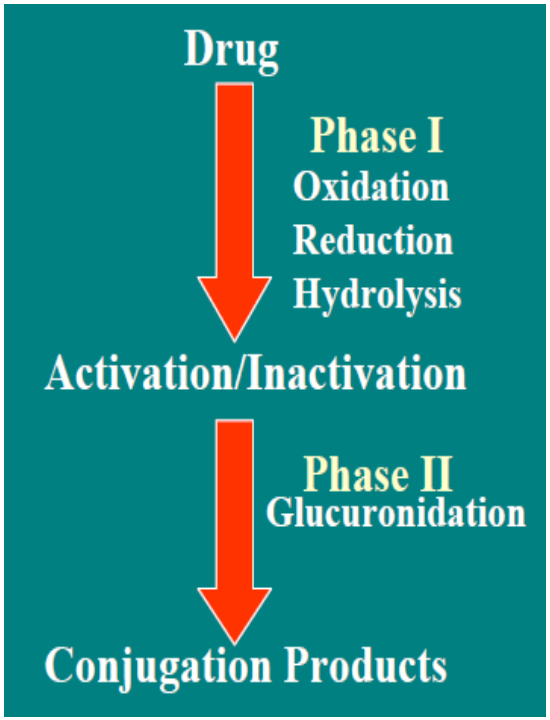
- CYP 3A4/5 carry out biotransformation of the largest number (30–50%) of drugs.

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

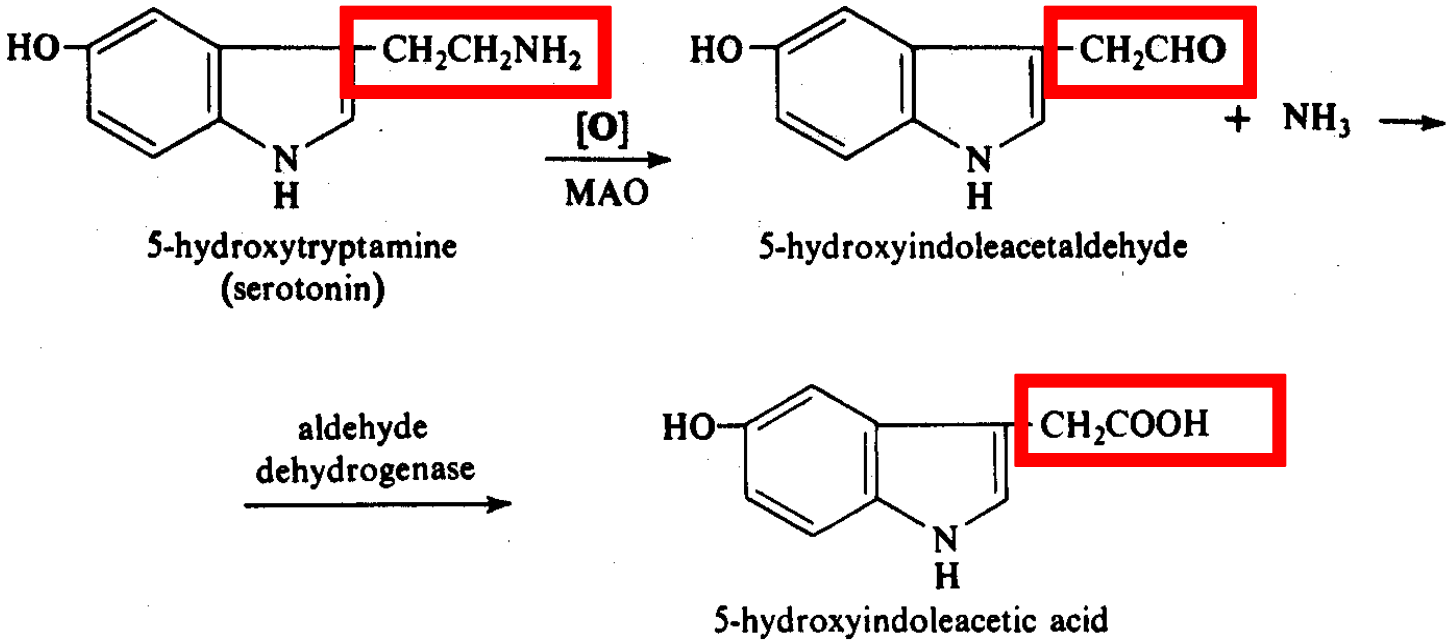
- **Phase I reactions :**
  - Oxidation
    - **Non-microsomal** occurs in cytosol or mitochondria,e.g.
      - Alcohol – Dehydrogenase
        - Alcohol dehydrogenase & aldehyde dehydrogenase

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):



5-hydroxytryptamine (serotonin)

5-hydroxyindoleacetaldehyde

5-hydroxyindoleacetic acid

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.

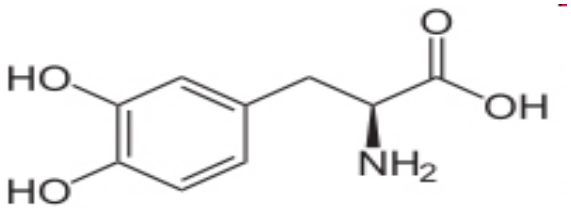
$$\text{Hypoxanthine} \xrightarrow{\text{oxidase}} \text{xanthine} \xrightarrow{\text{oxidase}} \text{uric acid}$$

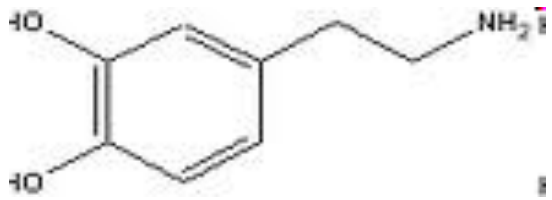
$$\text{uric acid accumulation} \longrightarrow \text{GOUT}$$

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



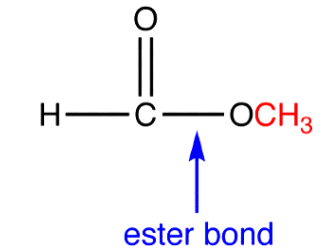


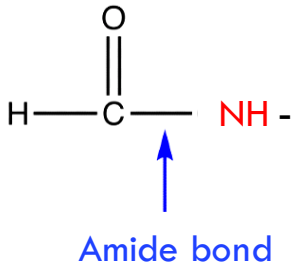
DOPA- decarboxylase

Levodopa (DOPA) → 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

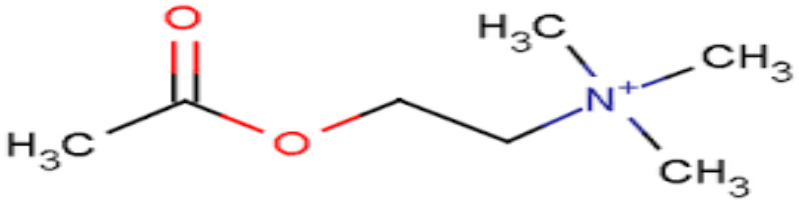
Acetylcholine ⟶ acetate + choline.

- Amides as lidocaine (used as local anesthetic)

Types of hepatic metabolic reactions

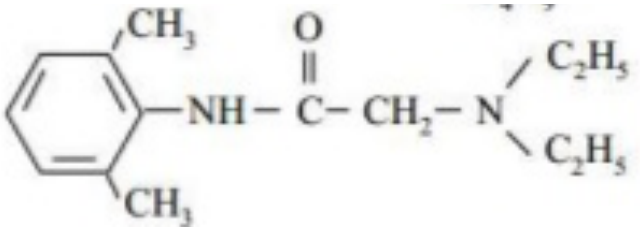
- **Phase I reactions :**
  - Hydrolysis
    - Esters as acetylcholine (neurotransmitter).

Acetylcholine



    - Amides as lidocaine (used as local anesthetic)

Lidocaine



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	**Glucouronyl transferase**
Acetylation (CH_3COO^-)	**N-acetyl transferase**
Sulphation (SO_4^{--})	**Sulfo transferase**
Methylation (CH_3)	**methyl transferase**
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).
- Deficieny 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).