Lecture (3)

Metabolism

pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

- Red : important
- Black : in male / female slides
- Pink : in girls slides only
- Blue : in male slides only
- Green : notes, Extra

Editing File:

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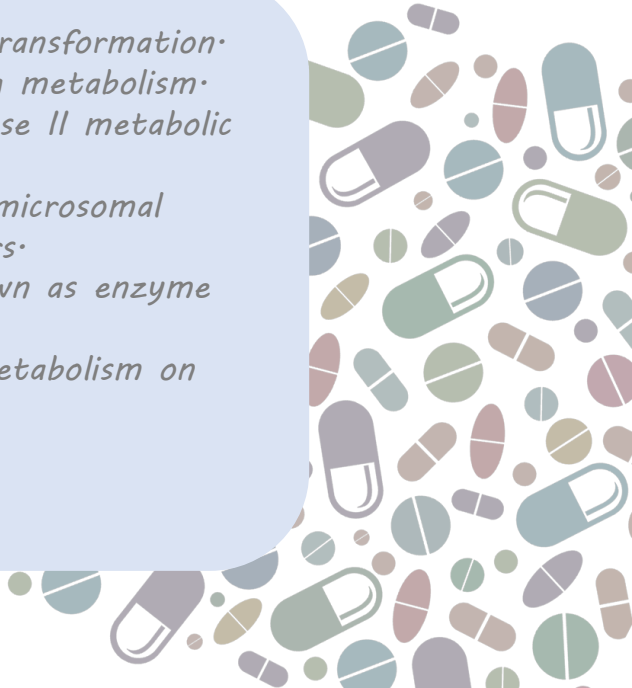
Objectives:

- 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)

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:

- 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

a pro drug is a drug that's taken in the inactive form to be activated inside the body

Organ sites of drug metabolism:

1) Liver (major site) **2) Kidney** **3) Skin** **4) Lung**

5) Intestinal Mucosa and Lumen:
Gut Mucosa: MonoAmine Oxidase (MAO)
Gut Lumen (bacterial flora): Glucouronidase

6) Plasma:

Enzymes	Substrates
Catechol o-methyl transferase (COMT)	Catecholamines (adrenaline)
Esterases	Esters (Local Anesthetics)
Amidases	Amides (Local Anesthetics)

Cellular sites of drug metabolism:

1) Cytoplasm:

e.g. Alcohol dehydrogenase: oxidation of alcohol NAD^+ → NADH

Alcohol → Aldehyde → Acid

Ethanol → Acetaldehyde → Acetic Acid

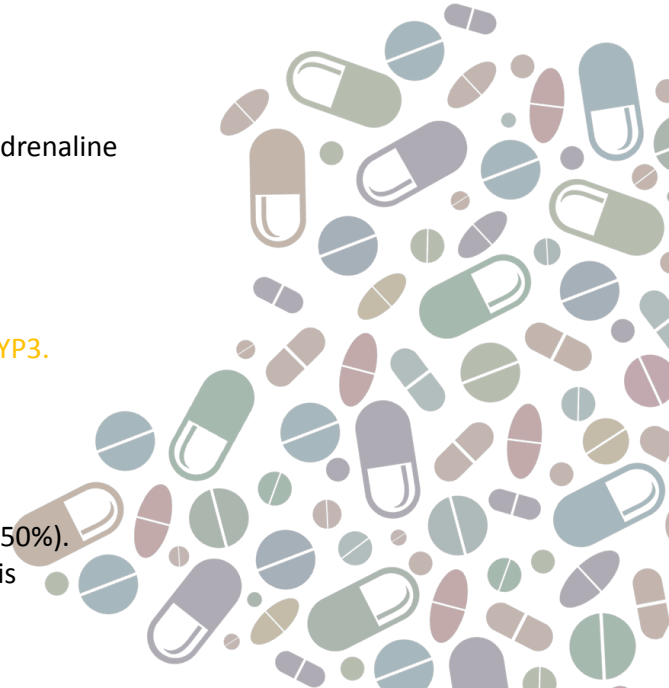
2) Mitochondria:

- N-acetyl transferase: introduction of acetyl group (CH_3COO)
- MonoAmine Oxidase enzyme (MAO): oxidation of catecholamines as adrenaline

3) 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 humans: only 3 isoenzyme families are important: CYP1, CYP2, and CYP3.

4) Lysosomes



Oxidation – Cytochrome P-450

CYP 3A4/5 carry out biotransformation of the largest number of drugs (30-50%). Expressed in liver and intestine (responsible for first pass metabolism at this site).

Types of hepatic metabolic reaction

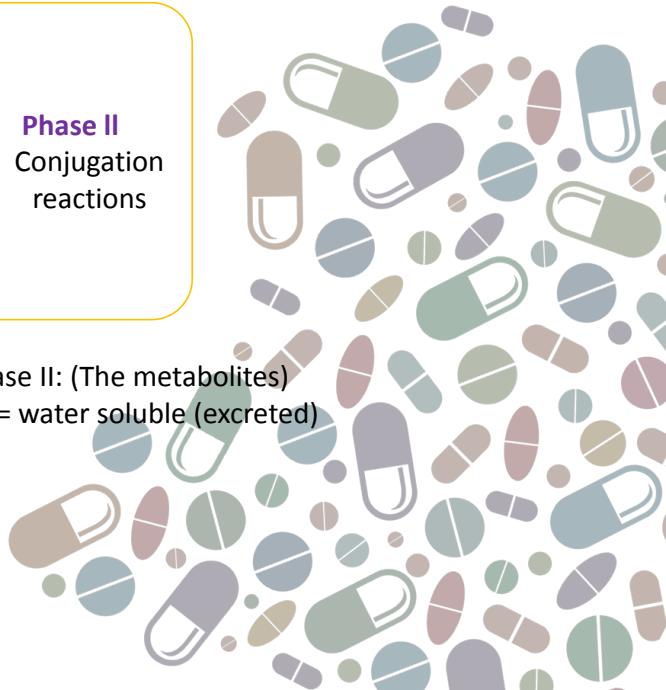
Two phases of hepatic metabolism reactions

Metabolism → **Phase I**
- Oxidation
- Reduction
- Hydrolysis

→ **Phase II**
- Conjugation reactions

After Phase I: (The metabolites)
1.Active
or
2.Inactive

After Phase II: (The metabolites)
Inactive = water soluble (excreted)



Oxidation

-Addition of oxygen or removal of hydrogen
-Most important drug metabolizing reaction

Microsomal

Occurs in microsomes
E.g. ***cytochrome P450 enzyme, NADPH, and oxygen***

Non-microsomal

Occurs in cytosol
or mitochondria

Dehydrogenases

Are required for oxidation of alcohols.
E.g *Alcohol dehydrogenase* (alcohol → aldehyde)
E.g. *Aldehyde dehydrogenase* (aldehyde → acid)

Oxidase

Mono amine Oxidase (MAO)

Responsible for the metabolism of catecholamines as adrenaline and serotonin
E.g. ***Moclobemide*** (MAO inhibitor used as an antidepressant drug by increasing serotonin in the brain)

Xanthine Oxidase

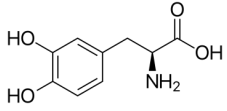
Required for the oxidation of xanthine.
-Hypoxanthine → xanthine → uric acid →
-accumulation of uric acid → GOUT
E.g. ***Allopurinol*** (inhibitor of xanthine oxidase used in treatment of gout)

Reduction:

Removal of oxygen or addition of hydrogen.

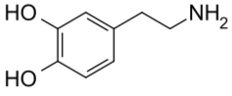
- May be microsomal or non-microsomal

E.g.: levodopa



Levodopa (DOPA)

DOPA- decarboxylase

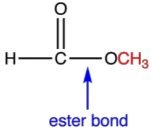


Dopamine

Hydrolysis

occurs by addition of water molecules in presence of enzymes

All are non-microsomal



Esterases

hydrolyze drugs that are esters

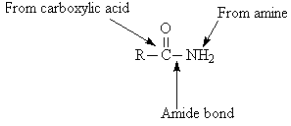
Ester + H_20 → Acid + Alcohol

e.g. Esters as **acetylcholine** (neurotransmitter).

Acetylcholine → acetate + choline.

Amidases

hydrolyze drugs that are amides



Amide + H20 → Acid + amine

e.g. Amides as **lidocaine** (used as local anesthetic)

Phase I 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

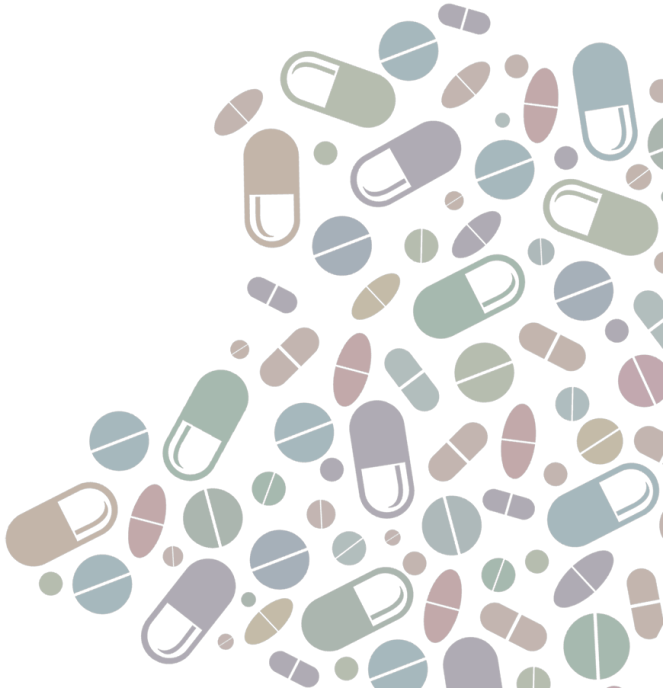
Phase II Conjugation reaction:

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 reaction:

Most important one →

Conjugation reaction	Enzyme required
glucouronide conjugation	Glucouronyl transferase
Acetylation (CH_3COO^-)	N-acetyl transferase
Sulphation (SO_4^{2-})	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).

-Deficiency of glucouronyl transferase enzyme in neonates may result into toxicity with **chloramphenicol** (Gray baby syndrome).

اسم الدواء مهم

Characteristics of Phase II product:

- 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**: Existence of different forms of metabolic enzymes.

E.g. metabolism of **Isoniazid** (anti- TB)

Slow acetylator phenotype: decrease in metabolism of isoniazid → accumulation of isoniazid → risk of **peripheral neuropathy**

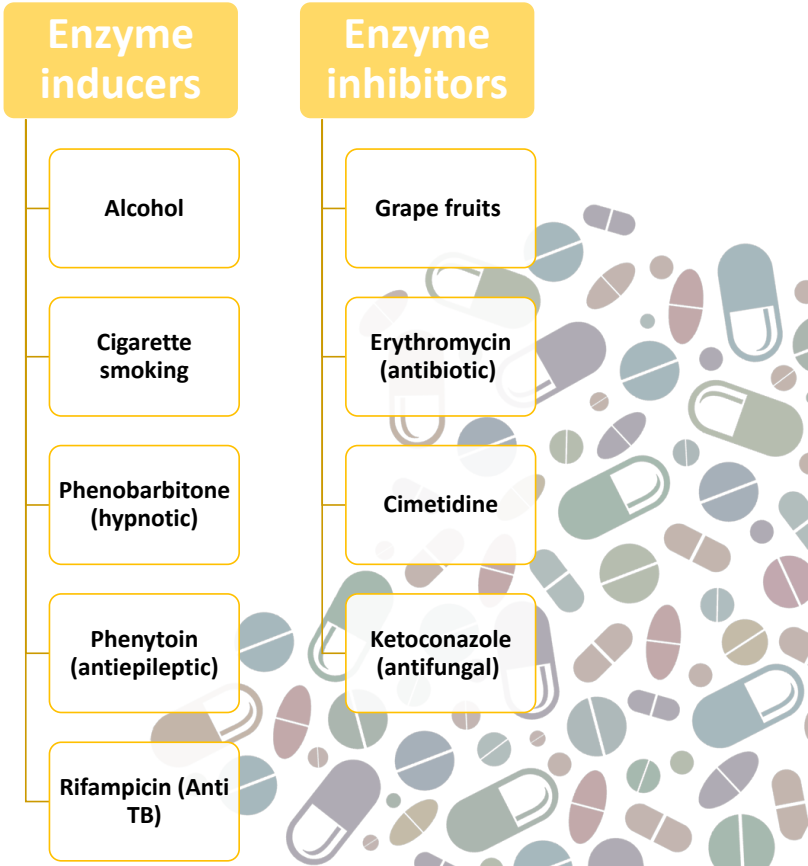
Rapid acetylator phenotype: excess metabolites → risk of **Hepatitis**

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.

اسماء الادوية هنا مهم حفظها

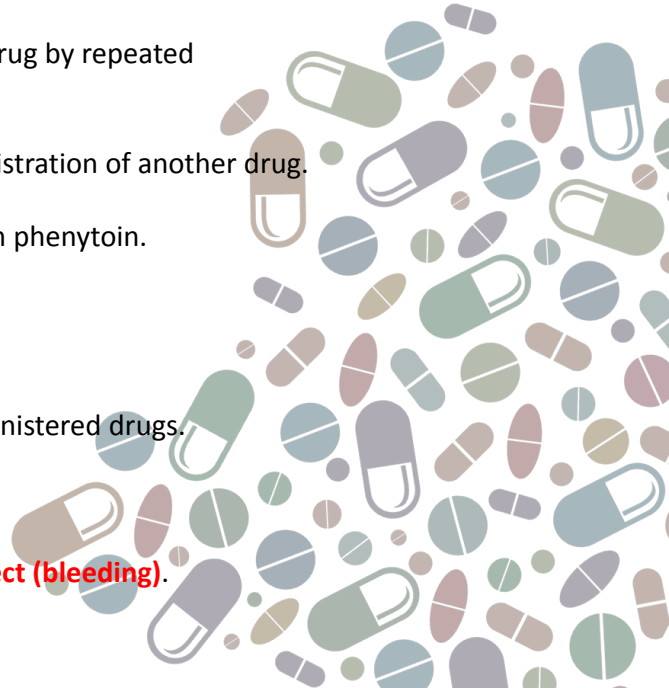


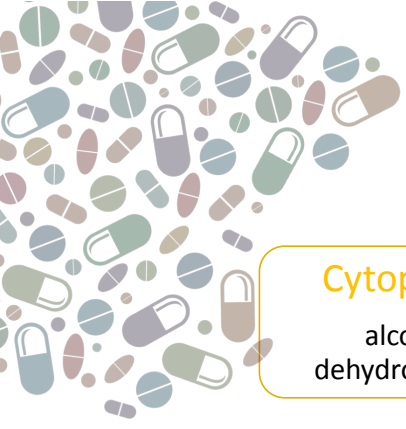
Enzyme induction may result in:

- ↑ 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 .
- **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 result in:

- ↓ 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 increase its **anticoagulant effect (bleeding)**.





Cellular metabolism site

Cytoplasm
alcohol dehydrogenase

Microsomes
Cytochrome P-450
(CYP1, CYP2, CYP3)

Mitochondria
MAO

Lysosomes

Oxidation
- **Microsomal** → Cytochrome, NADHP, & O2
- **Non-microsomal**
  - Dehydrogenases
  - Oxidase
    - Mono amine Oxidase (*Moclobemide*)
    - Xanthine Oxidase (*Allopurinol*)

Reduction
(microsomal or non)
- levodopa

Hydrolysis
(Non-microsomal)
- Esterases (*acetylcholine*)
- Amidases (*lidocaine*)

Conjugation reaction	Enzyme required
Glucouronide conjugation	Glucouronyl transferase
Acetylation (CH_3COO^-)	N-acetyl transferase
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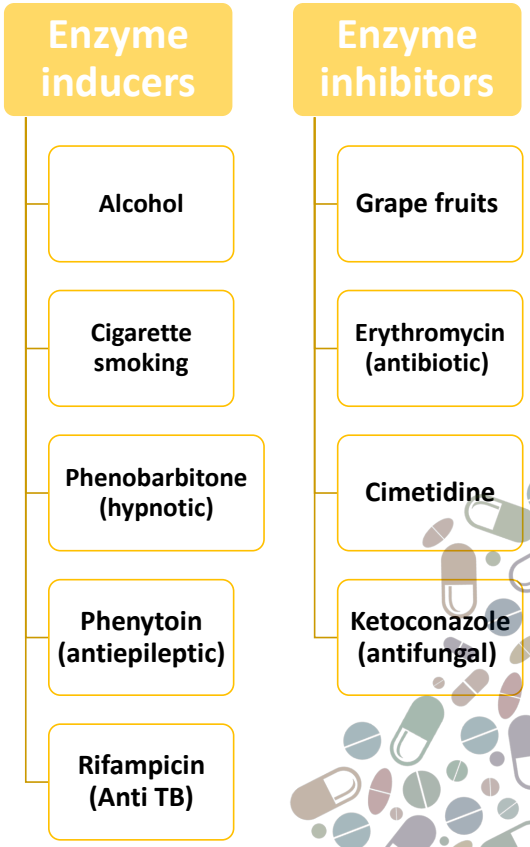

Which of these is an enzyme inhibitor?			
Allopurinol	Ketoconazole	Rifampicin	Phenobarbitone
Which of these affect metabolism?			
Age	Metabolism of Isoniazid	Erythromycin	All of the above
Where is MAO metabolized?			
Cytoplasm	Mitochondria	Microsomes	Lysosomes
Example of a pro drug			
Moclobemide	Warfarin	Prednisone	None of the above

What is the name of Xanthine oxidase inhibitor?

What is an example of a an antiepileptic?

B	D	B	C	Allopurinol	Phenytoin

Good luck

Thanks to the pharma team 435

PHARMACOLOGY 435

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