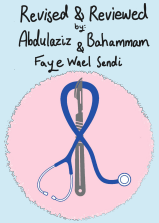


Drug metabolism

Important
Main Text
Male slides
female slides
Extra information
Doctors notes

For any future corrections Editing file

If you didn't understand any part from this lecture Click here

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.

Metabolism

Definition:
Chemical reactions which occur in the body to **change drugs from non polar 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)*

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

The patient takes it in the inactive form, it becomes active after the metabolism

Intestinal Mucosa and Lumen

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

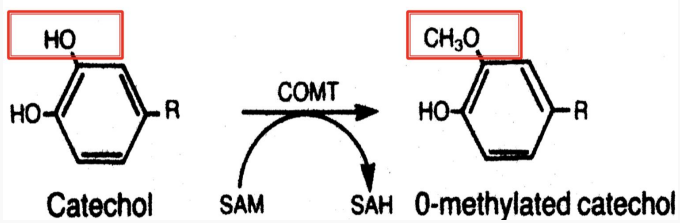
*for drugs with amine groups

Gut lumen (bacterial flora)**
- Glucouronidase

**produced by bacteria

Plasma

Enzyme	Substrate
Catechol O-methyl transferase (COMT)	Catecholamines E.g, adrenaline
Esterase	Esters Act on drugs as local anesthetics
Amidase	Amides Act on drugs as local anesthetics

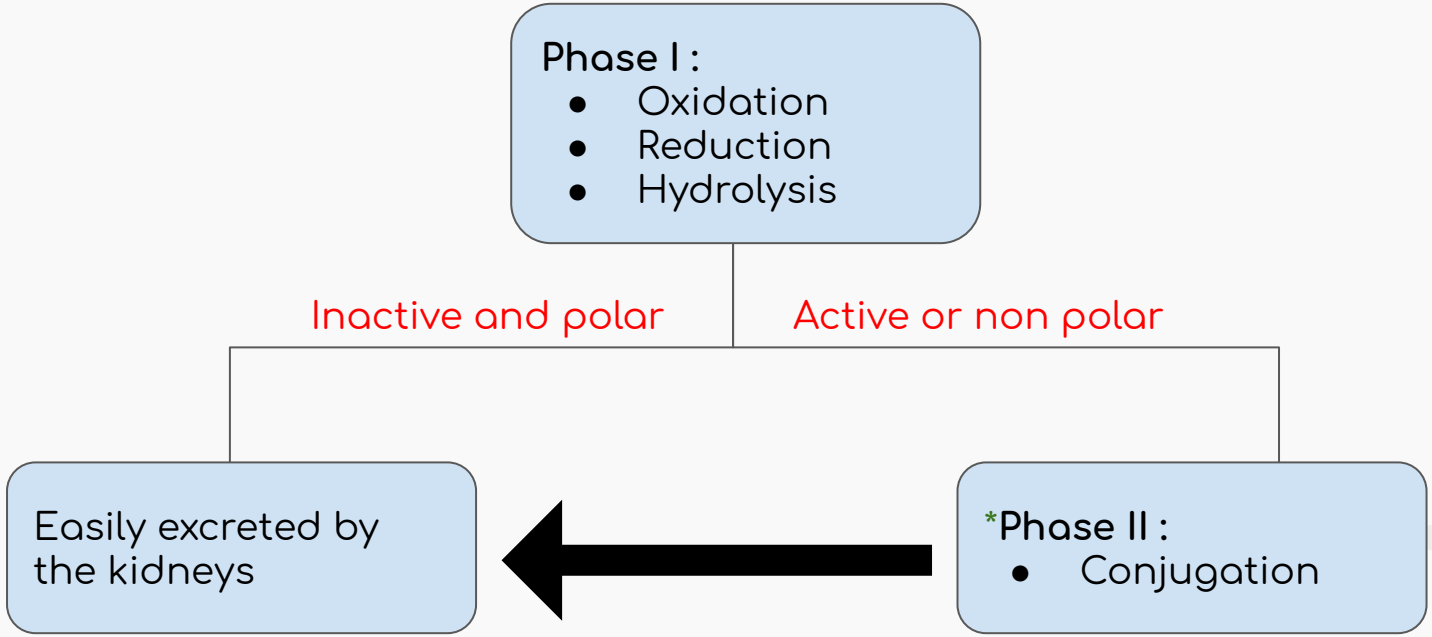


Catechol O-Methyl Transferase
Adds a methyl group to oxygen in catechol

Cellular sites of drug metabolism in liver

Mitochondria	• **N-acetyl transferase:** Introduction of acetyl group (CH_3 COO-) • **Monoamine oxidase enzyme (MAO):** Oxidation of catecholamines as adrenaline
Cytoplasm	**E.g. Alcohol dehydrogenase:** oxidation of alcohol NAD+ → NADH **Alcohol → Aldehyde → Acid** Ethanol → Acetaldehyde → Acetic acid CH3CH2OH → CH3CHO → CH3COOH
Microsomes	Microsomal enzyme system = **Cytochrome P-450** (Oxidation). There are more than 20 families CYP1, CYP2, CYP3 (In humans: only these 3 isoenzyme families are important) Sub-families are identified as A, B, and C etc. 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)
Lysosomes	

Types of hepatic metabolic reactions



Before secretion it has to be:
1- inactive
2- water soluble (polar)

*ياخذ نتائج phase I ويربطه بمركب من الجسم عشان يصير water soluble

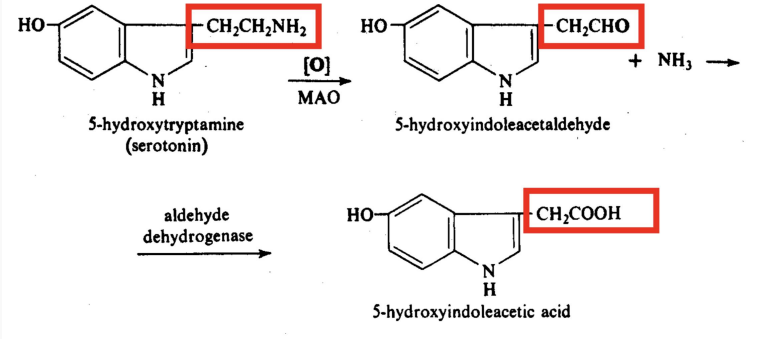
Oxidation

<table>
<tr>
<td rowspan="3">Oxidation
• Addition of O or removal of H
• The most important drug metabolizing reaction</td>
<td>Microsomal
• In microsomes</td>
<td>• E.g. cytochrome P450 enzymes, NADPH and Oxygen</td>
</tr>
<tr>
<td rowspan="2">Non-microsomal
• In cytosol or mitochondria</td>
<td>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</td>
</tr>
<tr>
<td>Dehydrogenases:
• Are required for oxidation of alcohols
e.g. Alcohol dehydrogenase (converts alcohol to aldehyde)
e.g. Aldehyde dehydrogenase (converts aldehyde to acid)</td>
</tr>
</table>

oxidation Non-microsomal oxidases [contd…]

Non-microsomal oxidases e.g:

Serotonin – Monoamine Oxidase (MAO) (Cont.):



3) Xanthine oxidase:

- Is required for the oxidation of xanthine

oxidase oxidase

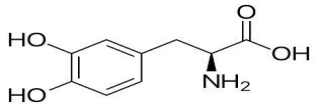
- Hypoxanthine ------> xanthine ------> uric acid
- uric acid accumulation ---> GOUT

- Allopurinol: is an inhibitor of xanthine oxidase, and used in the treatment of Gout.

Reduction Reaction:

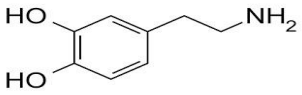
- Removal of oxygen or addition of hydrogen.
- May be microsomal or non-microsomal.

Example:
Levodopa



Levodopa (DOPA)

DOPA-decarboxylase



Dopamine

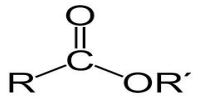
Dopamine deficiency will cause Parkinson's disease

Hydrolysis Reactions:

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

1- **Esterases**: hydrolyze drugs that are **esters**

Ester + H2O → Acid+Alcohol

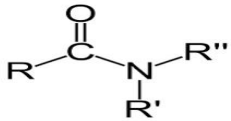


e.g: Acetylcholine (Ach) (Neurotransmitter)

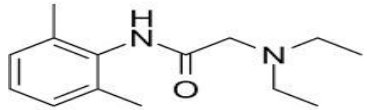
Acetylcholine —Esterase→ acetate + choline.

2- **Amidases**: hydrolyze drugs that are **amides**

Amide + H2O → Acid+Amine



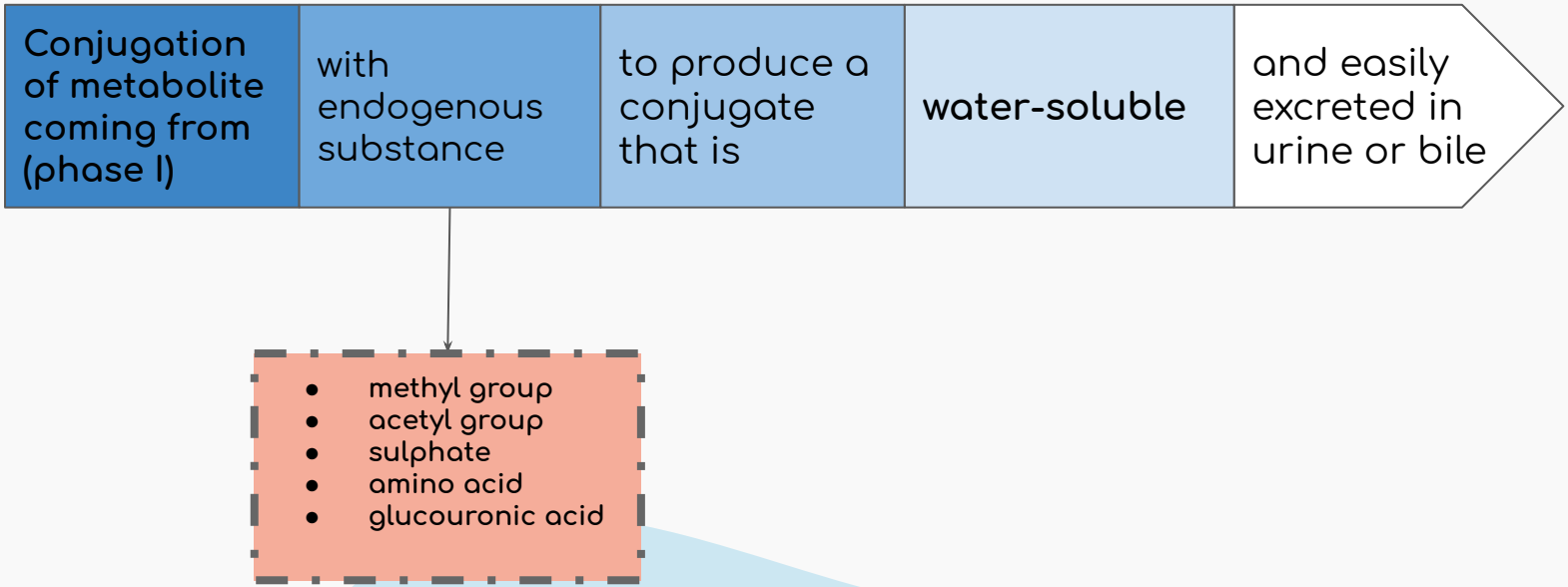
e.g: **Lidocaine** (used as local anesthetic)



Phase I Reactions Results

- 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 (Panadol) to hepatotoxic metabolite (hepatic necrosis)
    - in liver
- Product might undergo phase II

Phase II Conjugation Reactions (example of Phase II Reactions)



Types of conjugation reactions

Conjugation reaction	Enzyme required
Glucuronide conjugation	Glucouronyl transferase
Acetylation (CH_3 COO-)	N-acetyl transferase
Sulphation (SO_4--)	Sulfo transferase
Methylation (CH_3)	Methyl transferase
Amino acids conjugation	Glycine conjugation

helpful video

It is forbidden to give chloramphenicol to children under 2 years

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 glucuronyl transferase enzyme in neonates may result in toxicity with Chloramphenicol (Gray baby syndrome).

Characteristics Phase II metabolites

- Usually pharmacologically inactive
- more water soluble
- Polar
- Easily excreted in urine

Factors affecting metabolism

Age
Decreased metabolism in neonates & elderly. older people have a lower metabolism than young people.

Nutrition
Malnutrition Decreases metabolism Due to less dietary amino acids (proteins) in the body

Diseases
Decreased metabolism in people with liver diseases & kidney diseases

Concurrent use of drugs
Can cause inhibition or induction (in liver microsomal enzyme)

Degree of protein binding
Protein binding increases, metabolism decreases too. E.g: In blood

Factors affecting metabolism (contd...)

Genetic polymorphism:

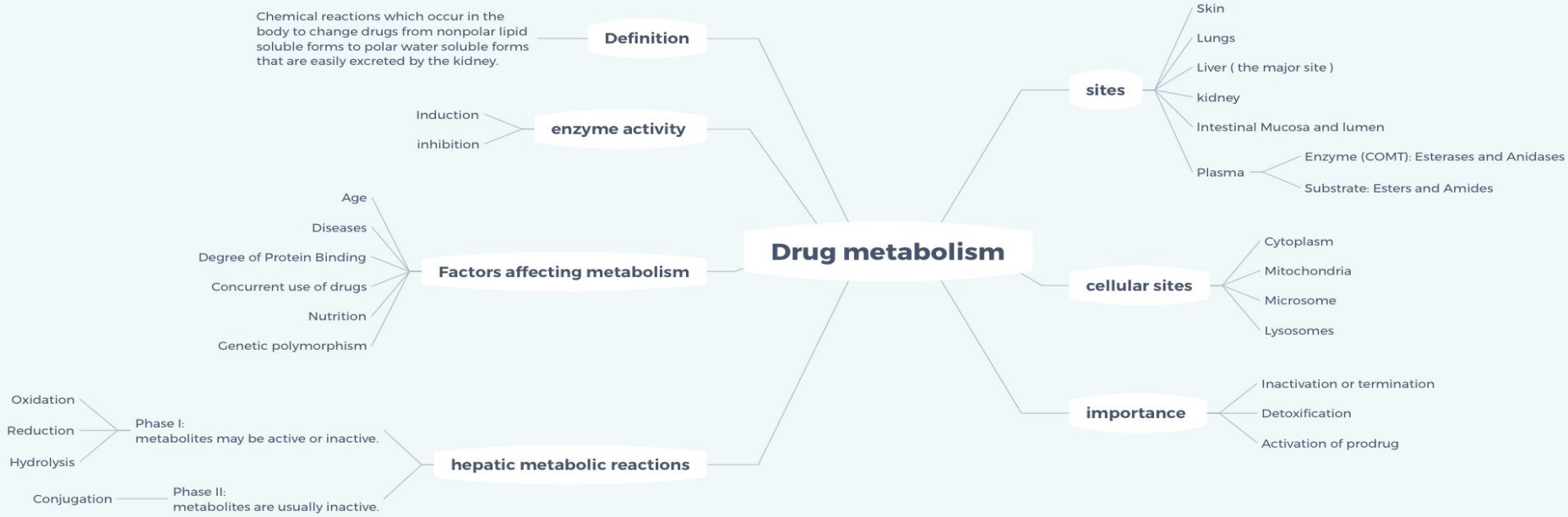
Metabolism may vary from population to another due to the existence of different forms of the metabolic enzymes. E.g.metabolism of **isoniazid** (Anti-TB).

Rapid Acetylator Phenotype	Slow Acetylator Phenotype
Risk of hepatitis.	Risk of peripheral neuropathy
Results into excess metabolites produced	Results in accumulation of isoniazid
Increased isoniazid metabolism	Decrease in isoniazid metabolism

one of side effect

helpful video	Enzyme Induction	Enzyme Inhibition
Liver microsomal enzymes:	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.	Drugs that **decrease activities of liver microsomal enzymes** & decrease the metabolism of the drug itself and other drugs taken concurrently.
examples:	• Alcohol • Cigarette smoking • Phenobarbitone (hypnotic) • Phenytoin (antiepileptic) • Rifampicin (Anti TB)	• Grape fruits • Cimetidine • Erythromycin (antibiotic) • Ketoconazole (antifungal)
Metabolism & excretion of drug itself & co-administered drugs:	Increase	Decrease (Delay)
Action of the drug itself & co-administered drugs:	Decrease	increase (Prolong)

[CONTD...]	Enzyme Induction	Enzyme inhibition
Drug interactions:	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. ملاحظة (team 439): الـphenytoin رح يزيد عمل الإنزيمات اللي تكسر دواء منع الحمل ، فإذا كانت المرأة تأخذ الدوائين مع بعض ، إذن دواء منع الحمل رح يتكسر وما رح يقعد بالجسم وما رح تستفيد المرأة منه ، وبالتالي ممكن يحصل حمل.	e.g. **warfarin** & erythromycin (inhibitor). Inhibition of warfarin metabolism may lead to increase in its anticoagulant effect (risk of bleeding). ملاحظة (team 439): ال erythromycin رح يثبط عمل الإنزيمات اللي تكسر دواء ال warfarin ، إذن الwarfarin رح يقعد بالجسم أطول و يسبب نزيف.
May occur:	Tolerance: decrease in the pharmacological action of the drug by continuous or repeated administration .	


Drug metabolism
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.
enzyme activity
Induction
inhibition
Factors affecting metabolism
Age
Diseases
Degree of Protein Binding
Concurrent use of drugs
Nutrition
Genetic polymorphism
hepatic metabolic reactions
Oxidation
Reduction
Hydrolysis
Phase I:
metabolites may be active or inactive.
Conjugation
Phase II:
metabolites are usually inactive.
sites
Skin
Lungs
Liver (the major site)
kidney
Intestinal Mucosa and lumen
Plasma
Enzyme (COMT): Esterases and Anidases
Substrate: Esters and Amides
cellular sites
Cytoplasm
Mitochondria
Microsome
Lysosomes
importance
Inactivation or termination
Detoxification
Activation of prodrug

MCQ:

1.The addition of glucuronic acid to a drug?			
A. Decreases its water solubility.	B. Usually the drug metabolite is inactive.	C. Is an example of a Phase I reaction.	D. Involves cytochrome P450 enzymes.

2.Which of the following describes the first-pass effect?			
A.Drug given orally is metabolized by the liver before entering the circulation.	B. Absorption of a drug through the duodenum.	C.Drug given IV accumulates quickly in the central nervous system (CNS).	D. Inactivation of a drug as a result of the gastric acids.

3.Which one of these sites is not responsible for drug metabolism?			
A.Skin.	B.Kidney.	C.Spleen.	D.Intestinal lumen.

Answers

1	B
2	A
3	C

MCQ:

4.Hydrolysis reactions are?			
A.non microsomal.	B.none.	C.both.	D.microsomal.

5.How many families are in the microsomal enzyme system ?			
A.3	B.20	C.15	D.10

6.Which of these drugs used for gout treatment ?			
A.rifampicin	B.erythromycin	C.moclobemide	D.allopurinol

7.Which of these drugs used as antidepressant ?			
A.moclobemide	B.phenobarbitone	C.allopurinol	D.ketoconazole

Answers

4	A
5	B
6	D
7	A

SAQ:

A) List the cellular sites of drug metabolism?

B) Where does non-microsomal oxidation occur?

C) Name a monoamine oxidase inhibitor?

A) Mitochondria, cytoplasm, microsomes, lysosomes

B) Mitochondria and cytoplasm

C) Moclobemide

Thank you

Team leaders

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- Abdullah Alghamdi
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