Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Metabolism

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.

Titles Very important Terms Extra informations

Success Doesn't Come To You, You Go To It!

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.

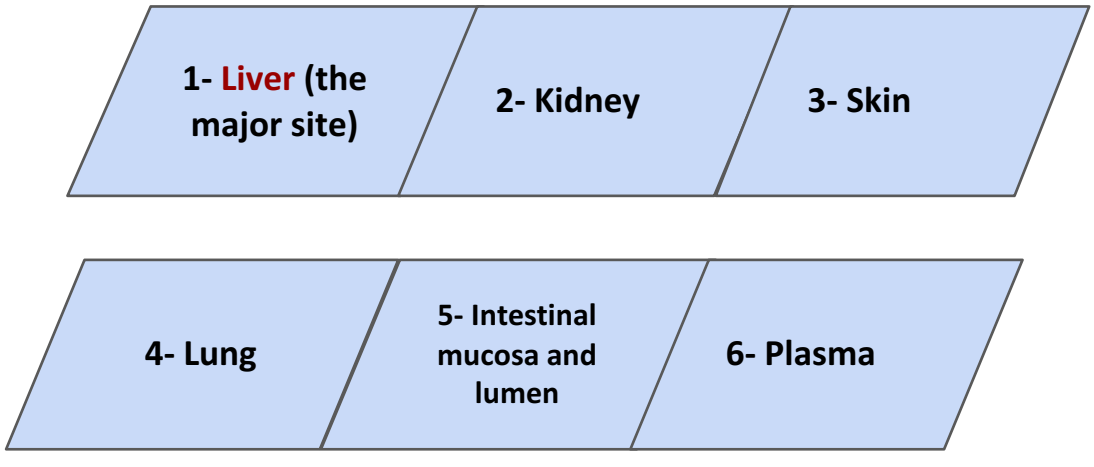
-Importance of metabolism :

Inactivation or termination of drug action (most drugs). To stop the **effect** of the drug. Patients may take several doses of a drug, so the old doses must be inactivated to prevent drug accumulation.

-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 Prodrug is inactive form of drug which should be active after administration, e.g.levodopa is converted to dopamine after activation.

Organ sites of drug metabolism:

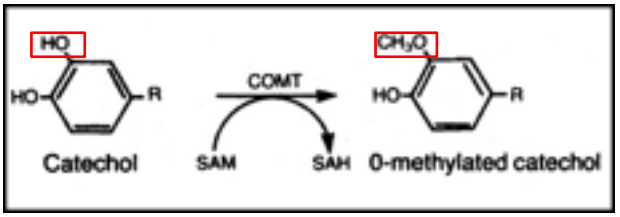


Anything ends with (ase) is an enzyme.
substrate comes before the name of the enzyme , e.g. Mono-Amine Oxidase *the Amine group is affected by the enzyme so it is the substrate, **Oxidase** is the name of enzyme , **mono** means adding one oxygen to Amine group.

5- Intestinal mucosa and lumen:

1- Gut mucosa: Mono- **A**mine **O**xidase **(MAO)** it breaks the adrenaline*.

2- Gut lumen(bacterial flora): Glucouronidase.



*Catechol O-Methyl Transferase
Adding methyl to the oxygen.

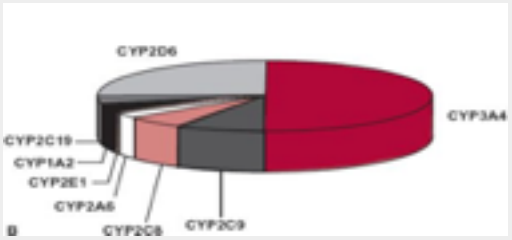
6- Plasma

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

Eters=acid-alcohol.
Amides=acid-amine.

Adrenaline يتأثر بأنزيمين:
1-MAO.
2-COMT.

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)



Cellular sites of drug metabolism

1- Cytoplasm	2- Mitochondria	3- Lysosome	4- Microsome(Main site)
e.g. Alcohol dehydrogenase: oxidation of alcohol Alcohol (by Alcohol dehydrogenase)→ Aldehyde (by Aldehyde dehydrogenase) → Acid. (eg. Ethanol → acetaldehyde → acetic acid). (CH3CH2OH→ CH3CHO → CH3COOH).	➢N-acetyl transferase: Introduction of acetyl group (CH3COO-). ➢Monoamine oxidase enzyme (MAO): oxidation of catecholamines as adrenaline.	--------	Microsomal enzyme system = Cytochrome P-450 (450 type of enzymes). 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

*metabolite has to be water soluble

Phase I — May be active or inactive

Phase II — Usually inactive

Conjugation reactions

*Combination or التحام

1- Oxidation — Addition of O, or removal of H

The most important drug metabolizing reaction

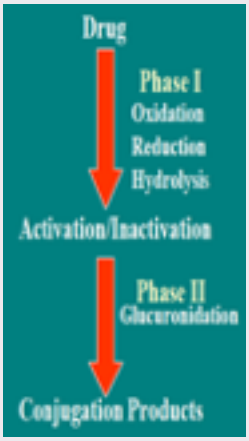
2- Reduction

3- Hydrolysis

A- Microsomal oxidation

لما يخلص الدواء من المرحلة الاولى عشان يدخل المرحلة الثانية يكون اسمه biproduct or metabolite.

- Occurs in microsomes
- E.g. Cytochrome P450 enzymes, NADPH & oxygen



B- Non microsomal oxidation

- Occurs in cytosol or mitochondria
- These enzymes include **oxidases** & **dehydrogenases**

Oxidenases

1) Monoamine oxidase (MAO)

Responsible for metabolism of catecholamines as adrenaline & serotonin

E.g. **Moclobemide** *MAO inhibitor*
- A monoamine oxidase inhibitor.
- increases serotonin in the brain.
- used as antidepressant drug

الناس اللي فيهم مرض الاكتئاب عندهم serotonin قليل في CNS .
فعالجهم بأدوية تزيد تركيز serotonin ال.
How? by decreasing the metabolism of serotonin , so this drug (Moclobemide) inhibits the MAO enzyme that metabolise serotonin.

2) Xanthine oxidase

Required for the oxidation of xanthine

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

*Xanthine exists in coffee, tea, meat.

Hypoxanthine —(oxidase)→ xanthine —(oxidase)→ uric acid

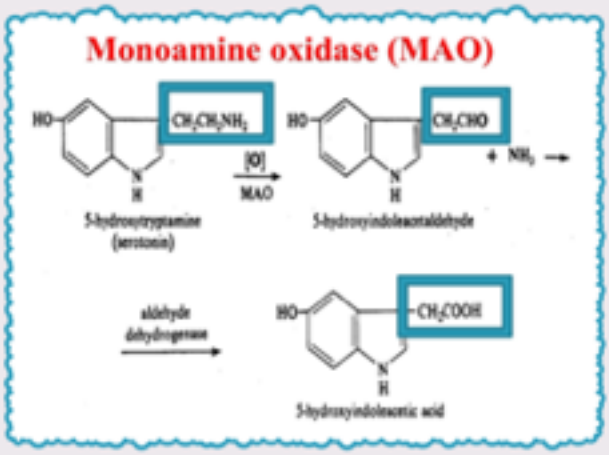
uric acid accumulation → GOUT

Dehydrogenases

Required for oxidation of alcohols

E.g. **Alcohol dehaydrogenase**
- convert alcohol to aldehyde.

E.g. **Aldehyde dehydrogenase**
- convert aldehyde to acid.



Continue : Types of hepatic metabolic reactions

2- Reduction

Removal of O, or addition of H.

May be microsomal or non microsomal.

Levodopa (DOPA) → Dopamine

E.g. **Levodopa** *Treatment of parkinson's

3- Hydrolysis

Non microsomal

Occurs by addition of H_2O in presence of enzymes as (**esterases** & **amidases**)

Hydrolysis

- Esters as acetylcholine (neurotransmitter).

Ester + H_2O → Acid + Alcohol

esterase

Acetylcholine → acetate + choline.

- Amides as lidocaine (used as local anesthetic)

Amide + H_2O → Acid + amine

Esterases : hydrolyze drugs that are esters.
Amidases : hydrolyze drugs that are amides.

Phase I can result in :

1- Activation of pro-drug e.g. Levodopa to dopamine.
2- Inactivation of drug (termination of action).
3- Conversion of active drug to active metabolite. *Long duration of action.
4- Conversion of nontoxic drug to toxic metabolite.
Paracetamol --> hepatotoxic metabolite (hepatic necrosis)
5- Product might undergo phase II

*Paracetamol is the panadol.

The drug that comes from phase 1 has a little lipid solubility it starts phase 2 to be water soluble.

Phase II — Usually inactive

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 & easily excreted in urine or bile.

All are non microsomal **except** glucouronidation is a microsomal process (the most common of phase II reactions).

Deficiency of glucouronyl transferase enzyme in neonates may result into toxicity with chloramphenicol (Grey baby syndrome)

*Leads to accumulation of the drug.

*The transforming of the first metabolite from Phase I to a more soluble form by combining it with an endogenous group that makes it more soluble.

Characteristics of Phase II metabolites:

- Usually pharmacologically inactive.
- Polar
- More water soluble
- Easily excreted in urine.

Conjugation reaction	Enzyme required
مهم most common 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

Factors affecting metabolism

The factor	The rate of metabolism
1-Age	Decrease in neonates & elderly.
2-Diseases	Decrease in liver disease.
3-Degree of Protein Binding	Decrease in binding protein. *with plasma proteins*
4-Concurrent use of drugs	• increase in the induction. • decrease in the inhibition.
5-Nutrition	decrease in malnutrition * مايأكلون بروتين بالتالي مافيه امينو اسيدز تكون الانزايمس*

6-Genetic polymorphism: metabolism may vary from population to another due to the existence of different forms of the metabolic enzyme. E.g isoniazid (anti-tuberculosis drug) .

*slow acetylator phenotype: results in decrease in isoniazid metabolism & accumulation of isoniazid with risk of peripheral neuropathy

"The enzyme which will metabolize the drug (isoniazid) has genetic problem so the rate of metabolism is slow that will lead to accumulation of the drug and causes diseases (peripheral neuropathy)"

*rapid acetylator phenotype: results into excess metabolites produced with risk of hepatitis

"The enzyme which will metabolize the drug (isoniazid) has genetic problem so the rate of metabolism is high which will accumulate the metabolites in the liver and toxics the liver then causes 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.

Short duration of action

Liver microsomal enzymes inhibitors:

drugs that decrease activities of liver microsomal enzymes & decrease the metabolism of the drug itself and other drugs taken concurrently.

Long duration of action

Enzyme Inducers

- **Alcohol**
- **Cigarette smoking**

Alcoholics and smokers require larger doses of drugs.

- **Phenobarbitone** hypnotic (Sleeping Pills)
- **Phenytoin** (antiepileptic) treatment of epilepsy
- **Rifampicin** (anti TB) treatment of tuberculosis

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 continuous or repeated administration (possibility of addiction).
- **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 lead to increase its anticoagulant effect (risk of bleeding).

Summary


Metabolism
Definition
Change drugs from nonpolar soluble form TO polar water soluble form
Importance of Metabolism
Inactivation or Termination of drug action
Detoxification
Activation of prodrug
Convert inactive form Active form
Levodopa
Carbidopa
Prednisone
Prednisolone
Ex: Adrenaline
Catecholamines
Esters
Amides
Esterases
Amidases
Catechol-O-methyl Transferase
Plasma
Liver (major site)
Organ Sites
Skin
Lung
Kidney
Intestinal mucosa and Lumen
Gut Lumen
Gut Mucosa
Glucuronidase
Mono-Amine Oxidase (MAO)
Cellular sites
Mitochondria
Cytoplasm
Microsomes
N-acetyl transferase
Alcohol dehydrogenase
Cytochrome P-450
Monoamine oxidase enzyme
Oxidation
CYP 3A4/5
Enzyme Induction and Inhibitions
Enzyme inducers
Enzyme inhibitors
Alcohol
Cigarette smoking
Phenobarbitone hypnotic
Phenytoin
Rifampicin
Grape fruits
Cimetidine
Erythromycin
Ketoconazole
Types of hepatic metabolic reaction
Phase II
Usually inactive
Conjugation reaction
Types
Methylation
Glucuronide conjugation
Sulphation
Acetylation
Amino acid conjugation
Phase I
Active or inactive
Include
Hydrolysis
Non microsomal
Reduction
Microsomal or Non microsomal
Ex: levodopa
Presence of enzymes as
Esterases
Esters are Acetylcholine
Amides
Amides are lidocaine
Oxidation
Microsomal
Cytochrome P450
Oxygen
NADPH
Non microsomal
Dehydrogenase
Alcohol dehydrogenase
Aldehyde dehydrogenase
Oxidase
Monoamine oxidase
Xanthine oxidase
Allopurinol
Nucleoside
Factors affecting metabolism
Age
Diseases
Concurrent use of drug
Genetic polymorphism
Nutrition
Degree of protein binding

MCQs

1-Drugs excreted by the kidney should be:
A- polar lipid soluble
B- nonpolar water soluble
C-nonpolar lipid soluble
D-polar water soluble

2-Chemical reactions change drugs from nonpolar lipid soluble forms to polar water soluble forms called:
A- excretion
B- absorption
C- metabolism
D- distribution

3- which of the following Organs is the major sites of drug metabolism:
A- plasma
B- kidney
C- liver
D- skin

4-Microsomal enzyme system:
A- Cytochrome P-450
B-Cytochrome C-455
C-Cytochrome B-450
D-Cytochrome P-540

5-In human only 3 isoenzyme families are important one of them is:
A-CPY2
B-CYP1
C-PCY3
D-YCP2

6-Phase I metabolic reactions:
A-usually inactive.
B-usually active.
C-may be active or inactive.
D-must be active

7-All are non microsomal except:
A-Amino acids conjugation
B-Methylation
C-Acetylation
D-glucouronidation

8-which of the following is correct:
A-Age decrease rate of metabolism
B-Diseases increase rate of metabolism in liver diseases
C-Protein Binding increase rate of metabolism
D-malnutrition increase rate of metabolism

Useful video

https://youtu.be/oCPRi5JFMdg

Answers: 1-D 2-C 3-C 4-A 5-B 6-C 7-D 8-A

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