PHARMACOLOGY
TEAM 439

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MED439
KING SAUD UNIVERSITY

Drug Metabolism

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

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information

Objectives

Any Future corrections will be posted on the editing file.
make sure to check it **frequently**

Click Here

- 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)

Importance

Detoxification Biotransformation is required for protection of body from toxic metabolites

Activation of prodrug (convert inactive form of drug to active form)

prodrug: the inactive drug that was in a pharmaceutical form (tablet, capsule...etc). But after metabolism to water soluble form, it got activated.

- **Levodopa** ⬇ **Dopamine**
- **Prednisone** ⬇ **Prednisolone**

Inactivation or termination of drug action (most drugs).

team #437: 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.

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.

sites

- kidney
- Intestinal Mucosa and Lumen
- Liver (the major site)
- plasma
- lungs
- skin

Note: Remember that urine is basically made of water. So for the drug to be excreted from the body, it has to change to a water soluble form in order to dissolve in urine. (and this is the main goal of metabolism)

Intestinal Mucosa and Lumen

Gut Mucosa

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

Gut lumen (bacterial flora)

Glucuronidase

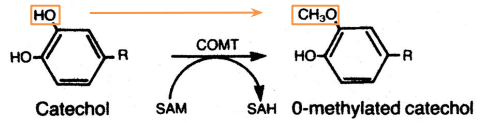
Glucuronidase: an enzyme that acts on the substrate " glucuronic acid"

ملاحظة : اعرفوا الإنزيمات ، وإيش وظيفتها وتعمل على أي substrate

Note: If the word ends with (-ase) then this is an enzyme. To know the function of the enzyme look at the root word. E.g. Oxidase is responsible for oxidation.

#437 :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 .

Plasma

Enzyme	Substrate
Catechol O-Methyl Transferase (**COMT**) **Catechol O-Methyl transferase** **(Adding methyl to the oxygen)**  Note: the function of this enzyme is to transfer a methyl group. The enzyme takes a methyl molecule and sticks it next to an oxygen. this happens in a catechol ring.	**catecholamines (e.g. adrenaline, serotonin)** catechol: is a benzene ring that has two (OH) groups attached to it. If catechol ring has an amine then the structure is called catecholamine.
Esterases This enzyme acts on esters E.g. acetylcholinase acts on acetylcholine	**Esters** (Act on drugs as Local anesthetics)
Amidases **e.g. Lidocaine**	**Amides** (local anesthetic)

Cellular sites of drug metabolism	**Cytoplasm**	• **e.g Alcohol dehydrogenase: oxidation of alcohol (NAD+ ⟶ NADH)** Alcohol ⟶ Aldehyde ⟶ Acid Ethanol ⟶ acetaldehyde ⟶ Acetic acid CH_3CH_2OH ⟶ CH_3CHO ⟶ CH_3COOH
	Mitochondria	• **N-acetyl transferase:** **Introduction of acetyl group (CH3COO-)** • **MonoAmine Oxidase enzymes (MAO):** **Oxidation of catecholamines** such as adrenaline
	Microsome	• 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, CYP3** • **Oxidation - CYP 3A4** 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

Two phases of hepatic metabolic reactions:

*Metabolites are a substance formed in or necessary for metabolism (e.g. the drug after metabolism)

Phase I include :

metabolites may be :

active or inactive .

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

The drug that cannot be metabolized in phase I **(active)**, will move to phase II

Phase II include :

metabolites are usually inactive (polar -water soluble).

- **conjugation**

Oxidation Reaction:

- Is **addition of oxygen or removal of hydrogen**.
- Is the most important drug metabolizing reaction.
- May be **microsomal** or **non-microsomal**.

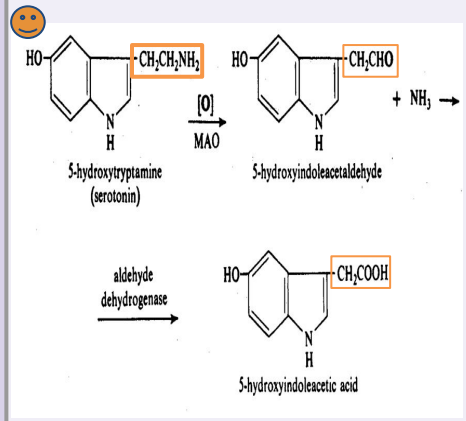
Microsomal Oxidation :

- occurs in microsomes
- e.g. cytochrome P450 enzymes, NADPH and oxygen

Non-microsomal Oxidation :

- occurs in cytosol or mitochondria
- These enzymes include oxidases & dehydrogenases

Oxidases



1) Monoamine oxidase (MAO):

- Is responsible for the metabolism of catecholamines as adrenaline and serotonin.
- **Moclobemide**: Is a Monoamine Oxidase(MAO) inhibitor. It **increases serotonin** in the brain. Used as **antidepressant drug.**

2) Xanthine oxidase:

- Is required for the oxidation of xanthine
- Hypoxanthine ---> xanthine ---> uric acid
- uric acid accumulation ---> GOUT
- **Allopurinol**: is an inhibitor of xanthine oxidase, and used in the **treatment of gout**.

Dehydrogenases

- **Are required for oxidation of alcohols**
- e.g. Alcohol dehydrogenase (convert alcohol to aldehyde).
- e.g. Aldehyde dehydrogenase (convert aldehyde to acid).

Reduction Reaction:

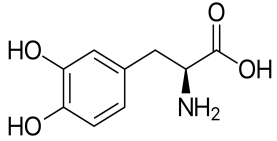
- Removal of oxygen or addition of hydrogen
- Can be microsomal or non microsomal

Example:
Levodopa

Levodopa (inactive) convert into dopamine (active)

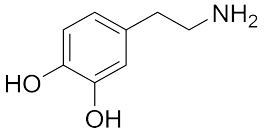
*Parkinson's disease is treated with levodopa

Levodopa (DOPA) → Dopamine



DOPA- decarboxylase

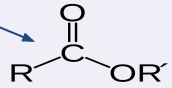
=Carboxyl removal



Hydrolysis Reactions:

- all are **non microsomal**
- occurs by **addition of water molecules** in presence of enzymes such as:

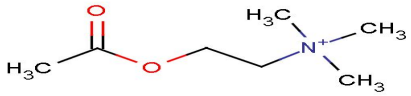
1- **Esterases**: hydrolyze drugs that are **esters**



Ester+ H2O → Acid + Alcohol

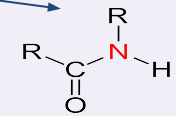
e.g. **acetylcholine** (neurotransmitter))

Acetylcholine —estrases→ acetate + choline

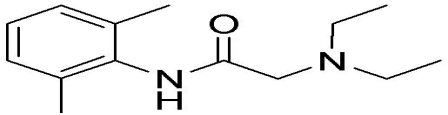


2- **Amidases**: hydrolyze drugs that are **amides**

Amide + H2O→ Acid + amine



e.g.**lidocaine** (Used as local anesthetic)



Phase I Reactions Results

- Conversion of non toxic drug to toxic metabolite
  - Paracetamol→ Hepatotoxic metabolite (hepatic necrosis)
- Activation of pro drug
  - E.g. levodopa to dopamine
- Conversion of active drug to Active metabolite
- Products might undergo phase II
- Inactivation of drug (termination of action)

Extra note:large amounts of non toxic metabolite makes it toxic

Phase II Reactions

E.g

Conjugation Reactions

Phase II Metabolic Reactions
All are **non microsomal** except **glucuronidation**.
Glucuronide conjugation is a microsomal Process (**the most common of phase II reactions**).
Deficiency of **glucuronyl transferase** enzyme in neonates→ toxicity with chloramphenicol (Gray baby syndrome).

Characteristics of phase II products

- polar
- More water soluble
- Easily excreted in urine
- Usually pharmacologically inactive

Metabolite coming from Phase I → **With endogenous substance** → **To produce conjugate that is** → **Water soluble** → **and easily excreted in urine or bile**

- Amino acid
- Glucuronic acid
- Methyl
- Acetyl
- Sulphate

Conjugation reaction	Enzyme Required
Glucuronide Conjugation	Glucuronyl Transferase
Acetylation (CH3 COO-)	N-acetyl Transferase
Sulphation (SO4--)	Sulfo Transferase
Methylation (CH3)	Methyl Transferase
Amino Acids Conjugation	Glycine Conjugation

Factors affecting metabolism

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

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

Diseases
Decreased metabolism in people with liver diseases & kidney diseases

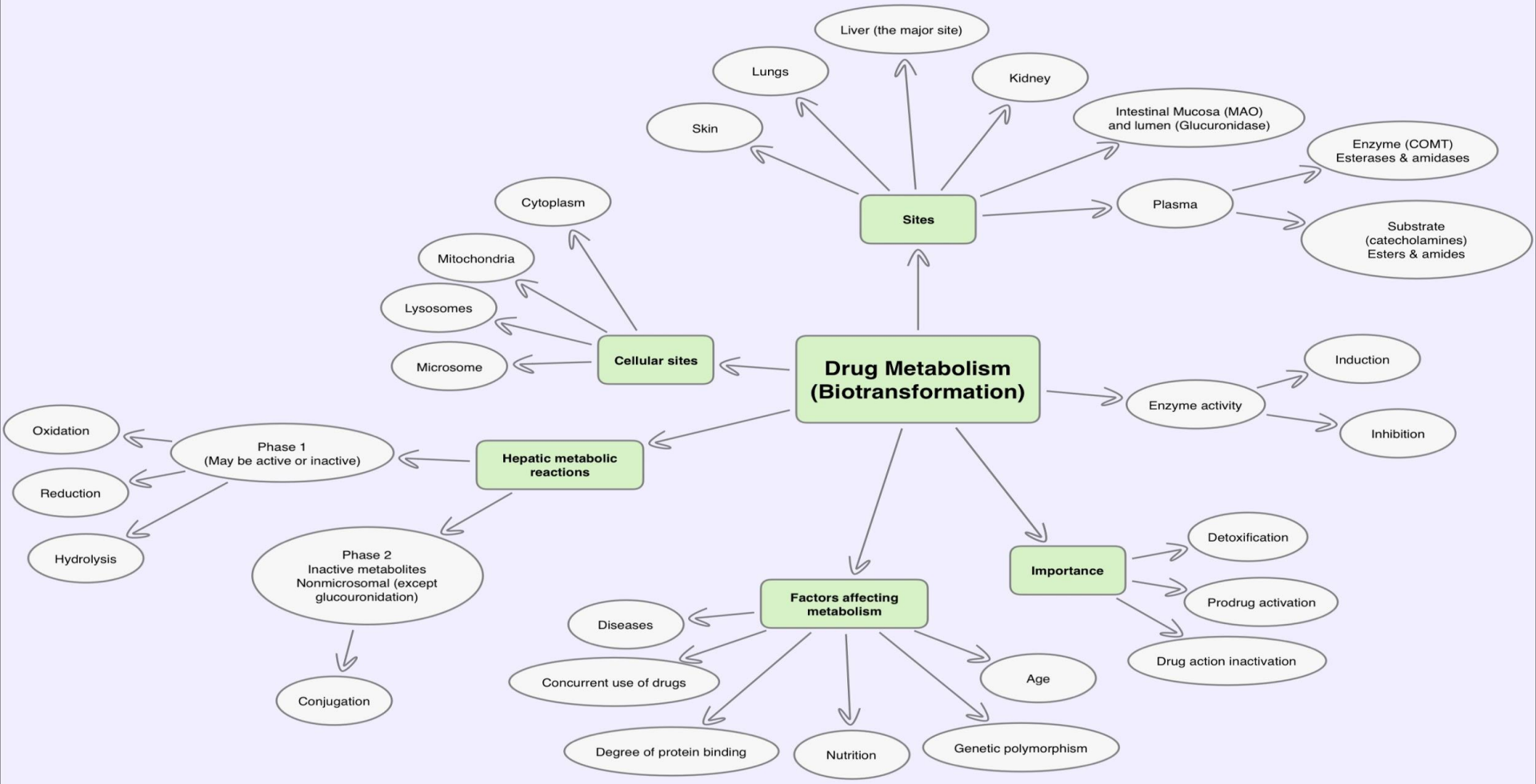
Concurrent use of drugs
Can cause **inhibition** or **induction**

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

Genetic Polymorphism
Metabolism vary from a population to an another due to the existence of different forms of the metabolic enzymes.

E.g: Metabolism of **isoniazid (anti-TB)**	**Rapid Acetylator Phenotype**	Risk of **hepatitis**	Results into excess metabolites produced	Increased isoniazid metabolism
	Slow Acetylator Phenotype	Risk of **peripheral neuropathy**	Accumulation of isoniazid	Decreased isoniazid metabolism

	Enzyme induction	Enzyme inhibition
Metabolism & excretion of drug itself & co-administered drugs	Increase	Decrease (delay)
Action of the drug itself & co-administered drugs.	Decrease	Increase (prolong)
Activities of liver microsomal enzymes	Increase	Decrease
Examples of inducers & inhibitors	• Alcohol • Cigarette smoking • Phenobarbitone hypnotic • Phenytoin (antiepileptic) • Rifampicin (Anti TB)	• Grape fruit • Cimetidine • Eryhthromycin (antibiotic) • Ketoconazole (antifungal)
Drug interactions	- oral contraceptives (birth control) & phenytoin (inducer) Oral contraceptive + phenytoin= failure of oral contraceptive(pregnancy) ملاحظة : الـphenytoin رح يزيد عمل الإنزيمات اللي تكسر دواء منع الحمل ، فإذا كانت المرأة تاخذ الدوائين مع بعض ، إذن دواء منع الحمل رح يتكسر وما رح يقعد بالجسم وما رح تستفيد المرأة منه ، وبالتالي ممكن يحصل حمل .	- Warfarin & erythromycin (inhibitor) Inhibition of warfarin metabolism → Increased anticoagulant effect (risk of bleeding). ملاحظة : ال erythromycin رح يثبط عمل الإنزيمات للي تكسر دواء الwarfarin ، إذن الwarfarin رح يقعد بالجسم أطول ويسبب نزيف .
May occur to:	**Tolerance**: **decrease** in the pharmacological **action** of the drug by continuous or repeated administration *Large doses of inducers will cause greater effect (increased metabolism)	


Drug Metabolism (Biotransformation)
Sites
Liver (the major site)
Lungs
Kidney
Skin
Intestinal Mucosa (MAO) and lumen (Glucuronidase)
Plasma
Enzyme (COMT) Esterases & amidases
Substrate (catecholamines) Esters & amides
Cellular sites
Cytoplasm
Mitochondria
Lysosomes
Microsome
Hepatic metabolic reactions
Phase 1 (May be active or inactive)
Oxidation
Reduction
Hydrolysis
Phase 2 Inactive metabolites Nonmicrosomal (except glucouronidation)
Conjugation
Enzyme activity
Induction
Inhibition
Factors affecting metabolism
Diseases
Concurrent use of drugs
Degree of protein binding
Nutrition
Genetic polymorphism
Age
Importance
Detoxification
Prodrug activation
Drug action inactivation

MCQ

1) which one of these sites is not responsible for drug metabolism?			
A) Skin	B) Kidney	C) Intestinal lumen	D) Spleen

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

3) Most of drugs...			
A) inactivate and terminate	B) detoxify	C) activate prodrugs	D) none of them

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

ANSWERS

1	D
2	D
3	A
4	B

MCQ

5) The enzyme required for glucoronide conjugation?

A) Glyciene conjugation	B) Methyl transferase	C) Sulfo transferase	D) Glucouronyl transferase

6) Slow acetylator phenotype leads to?

A) Hepatitis	B) Peripheral neuropathy	C) Excess metabolites produced	D) Increased isoniazid metabolism

7) Which of these drugs used for gout treatment ?

A) moclobemide	B) allopurinol	C) erythromycin	D) rifampicin

8) Which of these drugs used as antidepressant ?

A) allopurinol	B) moclobemide	C) phenobarbitone	D) ketoconazole

ANSWERS

5	D
6	B
7	B
8	B

SAQ

1) List 4 sites in the body that metabolise drugs.

2) What does Allopurinol do?

3) Where does the Non-microsomal oxidation occur ?

4) What is the difference between Phase 1 and Phase 2 reactions in terms of activity ?

ANSWERS

A1) ~~Liver (Major site), Kidney, Skin, and intestinal mucosa~~

A2) ~~it is an inhibitor for xanthine oxidase, and it is used to treat GOUT~~

A3 ~~Cytosol or mitochondria~~

A4) ~~Phase 1 metabolite may be active or inactive, while Phase 2 metabolite are inactive~~

GOOD LUCK!

this lecture was done by :

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نورة الدخيل
اسيل الشهري
الجوهرة البنيان
شادن العبيد
سديم آل زايد
روان باقادر
ميس العجمي
نورة السالم
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فهد البواردي
فيصل العتيبي
محمد القهيدان
يزيد القحطاني