Pharmacology

Subject : BIOTRANSFORMATION

Lec no : Lecture-5-

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وَقُل رَّبِّ زِدْنِي عِلْمًا

للوصول الى guidance الفارما و تفاريغ المادة كاملة :

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

BIOTRANSFORMATION

(Metabolism)

❖ **These are**: the chemical changes that occur to drugs after absorption until excretion.

- Drug metabolism occurs **mainly in the liver**, also in other organs, e.g. intestinal lumen or wall, lung, plasma, skin and kidney.
- The aim of drug metabolism is **the conversion of the lipophilic drug to a more polar (hydrophilic, ionized)** metabolite which is easily excreted in urine.
- The hydrophilic drugs usually do not undergo metabolism and secreted unchanged in urine

❖ **Types of Biotransformation Reactions**

Phase I (Non-Synthetic)

- Phase I reactions include: **oxidation - reduction - hydrolysis**.
- **The most important reaction is oxidation by cytochrome P450 enzyme system.**
- Phase I reactions result in **unmasking of a polar group** (-OH, -SH, or -NH_2) → **an ionized metabolite** that can be easily excreted.

Phase II (Synthetic)

- An **endogenous substrate**, (e.g. glucuronic acid, glycine, glutathione, sulfate or acetic acid) is **conjugated with the functional group** of the drug or its metabolite → **nontoxic highly polar**, rapidly eliminated **conjugates.**
- **The most important is conjugated with glucuronic acid.**

Phase I reactions

A. Oxidation:

- **The most important is cytochrome P450 oxidases "CYP" (mixed function oxidases) which are hepatic microsomal enzymes**

CYP is further classified by family, subfamily & gene into many isozymes. The name of each one is designated by the term CYP followed by 3 characters e.g. CYP 2C9:

1. The first Arabic numeral represents the family.

2. The alphabetic letter represents the subfamily.

3.The second Arabic numeral represents the individual gene within the subfamily.

- Xanthine oxidase: converts xanthine → uric acid
- Monoamine oxidase (MAO): oxidizes catecholamines & serotonin

B. Reduction:

- Nitroreductase → chloramphenicol
- ~~Carbonyl reductase → naloxone~~

C. Hydrolysis:

- It occurs mainly non-microsomal (in plasma and body fluids)
  - Cholinestrase → Ach.
  - Peptidase → insulin

Consequences of phase I reactions:

- The activity of the drug is modified in one of the following ways:

1- Active drugs → inactive drugs (occurs with most drugs).

2- Inactive drugs (prodrugs) → active drugs, e.g. cortisone to cortisol (hydrocortisone).

3- Active drug → another active one, e.g. codeine to morphine.

4- Active drug → a toxic metabolite e.g. methanol → formaldehyde → retinotoxic & paracetamol → toxic metabolite (NAPQI) → hepatotoxic in case of toxicity

toxic material

جرعات البنادول للي بنوخدها العلاجية عادي لكن لو اخدت جرعات عالية كمية ال toxic material اكبر من ال
glutathione بالتالي رح تتراكم بالجسم وتعمل toxicity وهون الجرعة تحكمت بال metabolism بدل ما تخلصنا من
ال toxic material عن طريق ال conjugation بالتالي toxic dose تكونت

When the hepatic blood increase
رح يوخد معاه drug اكتر بالتالي بصيرله metabolism اكتر

The young and old people have decreased metabolism

بتضل بالجسم فترة اطول Hydrophilic drugs
من ال lipophilic الا لو تدخلت عوامل تانية زي ال
extensive distribution of lipophilic

Phase II reactions

A. Glucuronide conjugation:

- **It is the most common conjugation reaction**
- Glucuronide conjugates secreted in bile may be hydrolyzed by intestinal bacteria and free drug can be reabsorbed again i.e. enterohepatic circulation → prolong duration of drug action e.g. estrogen (so contraceptive pills are given once daily)

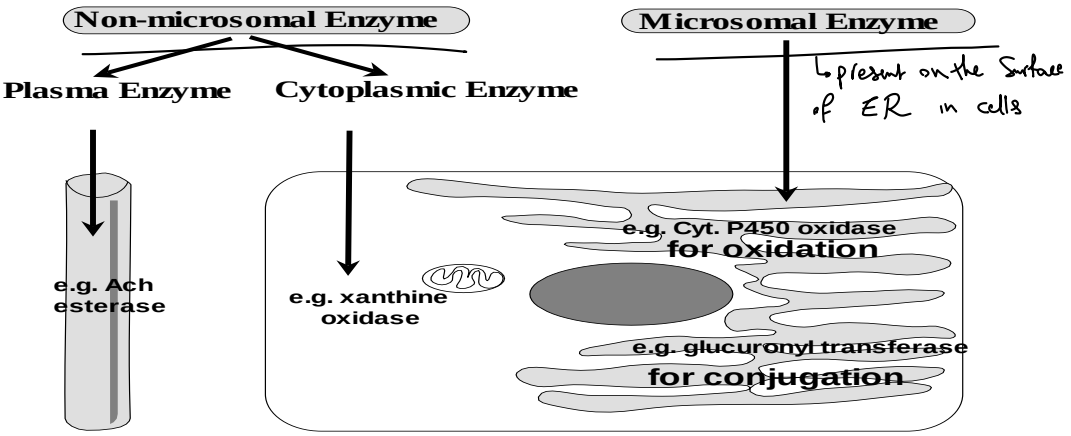
B. Non-Glucuronide conjugation:

- Sulphate formation e.g. steroids
- Glycine conjugation e.g. salicylic acid
- Glutathione conjugation e.g. ethacrynic acid
- Acetyl conjugation (slow & rapid acetylation) e.g. isoniazid

Consequences of phase II reactions:

- Mostly result in drug inactivation
- Some exceptions can occur e.g. morphine is partially converted into morphine-6-glucuronide (active metabolite)

- **Most of drugs is metabolizes by phase-I followed by phase-II reactions**
  - Some drugs is metabolizes firstly by phase-II then by phase-I reactions e.g. isoniazid.
  - Some drugs undergo phase-I or phase-II only
- **Types of enzymes responsible for biotransformation reactions**



very Imp

Microsomal enzymes	Non-microsomal enzymes
Site: in the **liver,** in **microsomes of ER**. So, they are called hepatic microsomal enzymes	Present in **liver**, **GIT**, **lung**, **kidney**, **plasma**, **skin**: in **cytoplasm** and **mitochondria**
Reactions: Phase-I: Oxidation (P450) Reduction Hydrolysis (few reactions) Phase-II: Glucuronic a. conjugation Only	**Reactions:** Phase-I: Oxidation (others than P450) Reduction Hydrolysis (mostly) Phase-II: All Conjugations Except Glucuronic
Substrate: lipophilic drugs & bilirubin	**Lipophilic , hydrophilic drugs** (to terminate action as succinylcholine) & natural body constituents
Affection by drugs: Inducible (Activation)	**Non-inducible**

❖ **Factors Affecting Biotransformation:**

1. **Drugs: (Enzyme induction & enzyme inhibition**).

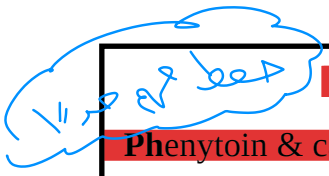
- Some drugs and environmental substances can **induce** ↑ or **inhibit** ↓ the microsomal enzyme activity and lead to undesirable drug interactions

Clinical significance of Enzyme Induction:

❖ Drugs stimulating the microsomal enzyme systems → ↑ activity →

- ↑ their own metabolism → **tolerance** e.g. **phenobaritone.**
- ↑ metabolism of other drugs metabolized by these enzymes and are given at same time→ drug interactions e.g.:
  - **Rifampicin** →↑ **oral contraceptive** metabolism → pregnancy
  - **Phenytoin** →↑ **cyclosporine** metabolism → transplant rejection
  - **Rifampicin** →↑ **warfarin** metabolism → therapeutic failure.
- ↑ metabolism of endogenous substrates e.g. **phenobarbitone** → ↑ elimination of **bilirubin** → used in treatment of neonatal jaundice)
- ↑ metabolism of vitamins e.g. **phenytoin** → ↑ of vit.D, vit.K, folic acid → osteomalacia, bleeding and megaloplastic anemia

- Enzyme induction is reversible. It occurs over a few days-months and passes off over 2-3 weeks after withdrawal of the inducer.



Examples of Enzyme Inducers

Phenytoin & carbamazepine- **ph**enobarbitone – ri**f**ampicin - griseo**f**ulvin - ♂ androgen- nicotine- chronic alcohol ingestion.

Clinical significance of Enzyme Inhibition:

❖ Drugs inhibiting the microsomal enzyme systems → ↓ activity →

- ↓ their <u>own</u> metabolism →↑ drug level**.**
- ↓ metabolism of <u>other drugs</u> metabolized by these enzymes → drug interactions e.g.:
  - **Ciprofloxacin** →↓ **warfarin** metabolism → bleeding
  - **Cimetidine** →↓ **carbamazepine** metabolism → toxicity
- It occurs faster than enzyme induction.

Examples of Enzyme Inhibitors

Cimetidine- **c**hloramphenicol - **c**iprofloxacin- erythromycin - ketocenazol - ♀ **(F)** estrogen, progesterone, contraceptive pills.

2. Pathological factors which affect hepatic activity e.g. liver failure starvation, cancer → ↓ activity of HME → need to adjust dose.

3. Pharmacogenetic variations in metabolizing enzymes e.g. slow & fast acetylators (see pharmacogenetics).

4. Hepatic blood flow: drugs ↓ hepatic blood flow → ↓drug matabolism

5. Age: ↓ enzymatic activity in extremities of age

- Premature babies have ↓ conjugate of chloramphenicol → fatal gray baby syndrome.

6. Sex: female sex hormones are HME inhibitors → receive lower doses than male.