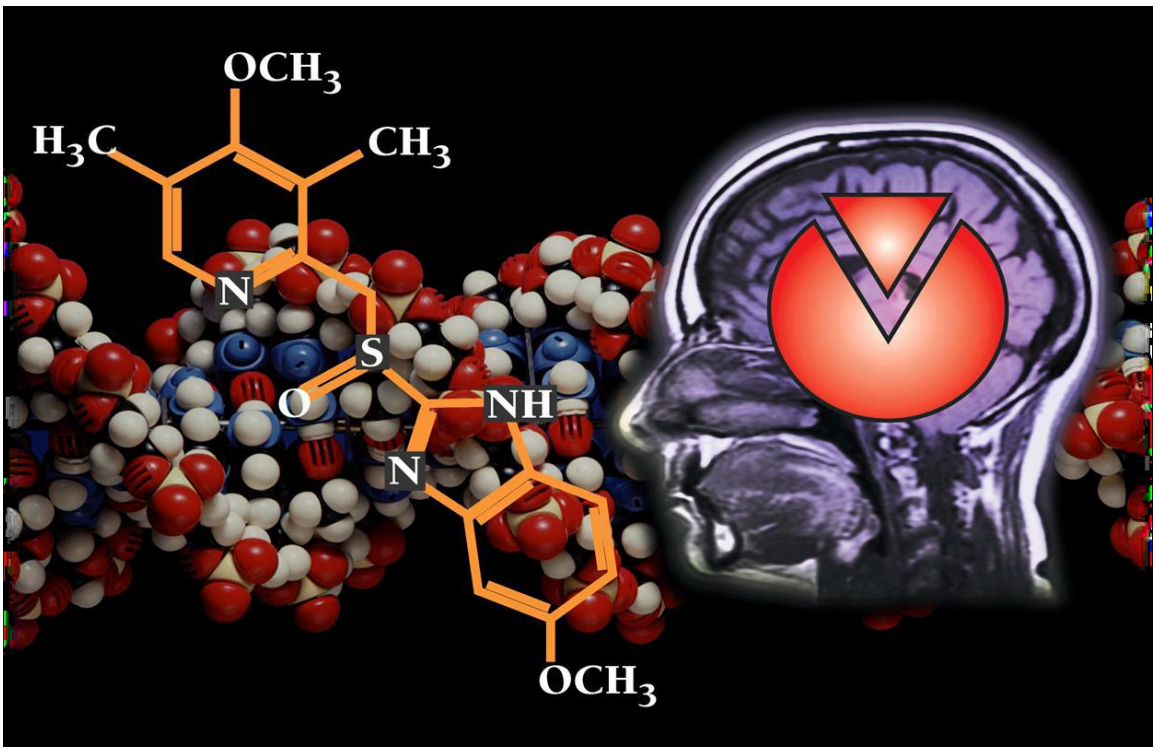
King Saud University
College Of Medicine
Pharmacology Team 430
GIT Block

Drug Metabolism



Note: text colored in red is important information, text colored in green are notes for explanation, and text boxes in maroon margins are additional info.

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Drug metabolism:

Occurs mainly in the "**METABOLIC CLEARING HOUSE" the liver** ➔the drugs are identified as foreign substances that body must get rid of ➔Being mostly lipophilic(having an affinity to lipids) ➔ The liver subjects them to chemical transformation (METABOLISM) ➔ to become inactive & easily EXCRETED (more water soluble).

Note: Most drugs are relatively lipid soluble (lipophilic) which is a characteristic needed for absorption across membranes. The same property would result in a very slow removal from the body because the unchanged molecule would also be readily reabsorbed from the urine in the renal tubule. The body hastens excretion by metabolizing many drugs in the liver to less lipid-soluble (water soluble or polar), less readily reabsorbed forms.

Elimination :

- **If it is polar (water soluble) ➔ renal elimination**
- **If non polar(lipid soluble) ➔ billiary elimination**

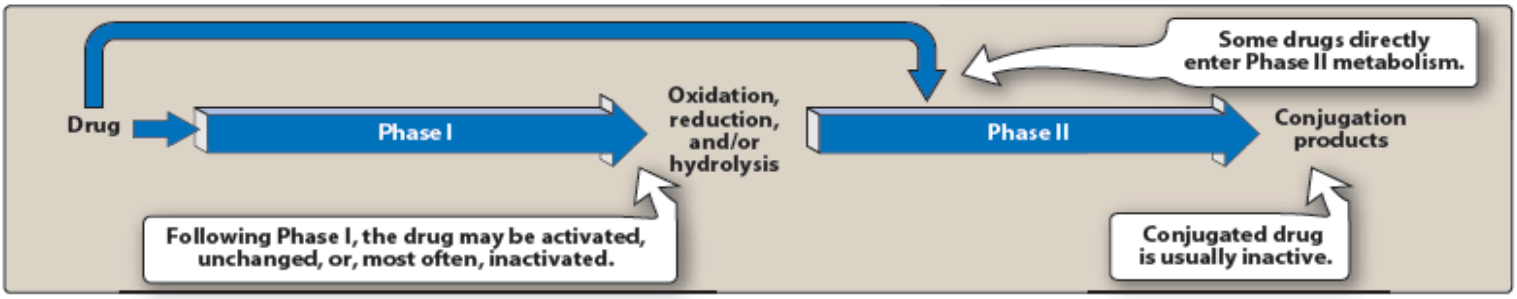
Drug metabolism usually occurs in two phases:

Phase I: OXIDATION /Reduction/Hydrolysis (The " Cytochrome P450" will be in this phase and it is just for oxidation in C-p450)

Note: Phase I reactions include **oxidation** (especially by the **cytochrome P450** group of enzymes, also called **mixed-function oxidases**), reduction, deamination, and hydrolysis. They are *Reactions that convert the parent drug to a more polar (water-soluble) or more reactive product by unmasking or inserting a polar functional group such as* –OH, –SH, or $–NH_2$.

Phase II: CONGUGATION (ADDITION)

Note: Phase II reactions are synthetic reactions that involve **addition (conjugation)** of subgroups to –OH, $–NH_2$, and –SH functions on the drug molecule. The subgroups that are **added** include **glucuronate**, acetate, glutathione, glycine, sulfate, and methyl groups. **Glucuronidation** is the most common and the most important conjugation reaction.



Note: Reversal of order of the phases: Not all drugs undergo Phase I and II reactions in that order. For example**, *isoniazid*** is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

Note: some drugs may be metabolized in phase 2 directly (This means that not all the drugs will be metabolized by the cytochrome system)

The end of metabolism could be:

- Inactive product
- Active metabolite
- A product with different effect
- Toxic metabolite

Cytochrome P450""CYT 450": The Superfamily

Is the terminal rate limiting oxidase of this system (final step)

Its enzymes are part of a cascade ➔ shuttles electrons from molecular oxygen to oxidize the drug

Structure:

They are heme-containing isoenzymes

Distribution:

- **Highly concentrated** in **hepatocytes**
- **Enterocytes** of the **small intestine** present their principal extra-hepatic source
- Very small quantities in **kidneys, lungs, & brain**.

Note: Xenobiotics are chemicals found in organisms, but not expected to be produced or present in them.

Function:

Responsible for most of the **OXIDATIVE METABOLISM** of:

- **Endogenous substances:** steroid hormones, prostaglandins, lipids, & fatty acids
- **Exogenous compounds:** diet (food & beverages) / Drugs/ environmental

} Substrates

Additional info: Cytochrome P450, designated as CYP, is a superfamily of hemecontaining isozymes that are located in most cells but are primarily found in the liver(They are mainly attached to the smooth endoplasmic reticulum (SER) of hepatocytes.),and GI tract.

Nomenclature:

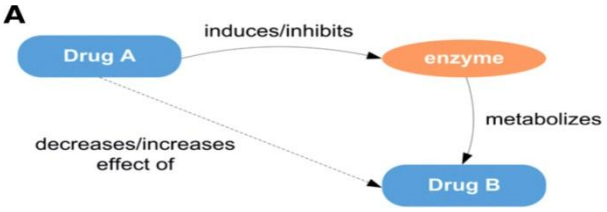
"Cytochrome" **= colored cellsThey color the liver cells dark red as they contain iron**

"P450" **absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.**

Regulation:

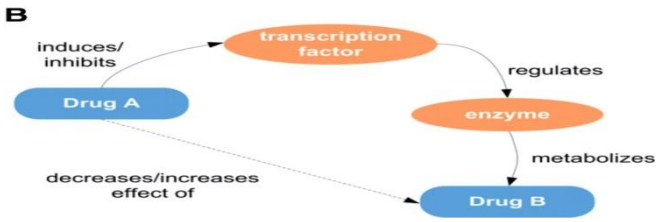
Activation or Inactivation of the CYT P450 can be achieved either:

- **A: Directly**



- **B : Indirectly by expression or repression of its relevant genes by**

(Activation or inhibition of the responsible transcription factors)



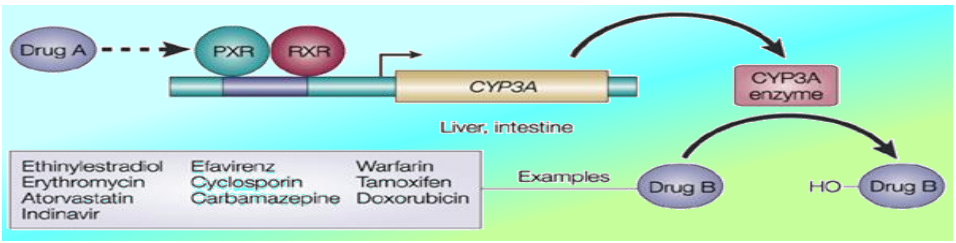
Activation or Inactivation can be processed be any food, intrinsic products or extrinsic xenobiotics as drugs (usually the **lipophylic**) that have to be metabolized.

When drugs play a role in regulation of the CYT P450 ➔they are termed

- Enzyme Inducers if Activate the enzyme
- Enzyme Inhibitors if Inactivate the enzyme

} Pharmacokinetics / Drug – Drug interaction

Molecular Basis of Drug-drug Interaction:



PXR, pregnane X receptor

RXR, retinoid X receptor

The orphan nuclear receptor PXR is a TRANSCRIPTION FACTOR that regulates the expression of the *CYP P450 genes*.

- If Drug A is INDUCER ➔ it binds & activates PXR ➔ which translocates in nucleus➔ **dimerize** with RXR ➔ the heterodiamer PXR / RXR will induce EXPRESSION of CYT P450 isoenzymes to ➔↑metabolism of Drug B
- If Drug A is an INHIBITOR, its binding will prevent activation (PXR will not be activated) ➔ REPRESSION of CYT P450 isoenzymes to ➔↓metabolism of Drug B

Note:(very important): At the gene level: To have the activity of CYP P450 enzymes the drug should combine to TRANSCRIPTION FACTOR (PXR) to induce expression of CYT P450 gene and vice versa.

Outcome of Drug-drug Interactions Mediated By CYT P450:

In relation to enzyme inducers: they decrease the EFFICACY of the drug

- ↑ Metabolism of the inducer + ↓ its pharmacological action. *nullification Tolerance or complete (decrease or absence of the response to the drug)*
- ↑metabolism of co-administered drugs

Note: Consequences of increased drug metabolism include: 1) decreased plasma drug concentrations, 2) decreased drug activity if the metabolite is inactive, 3) increased drug activity if the metabolite is active, and 4) decreased therapeutic drug effect.

IN RELATION TO Enzyme INHIBITORS: they increase the TOXCICITY of the drug

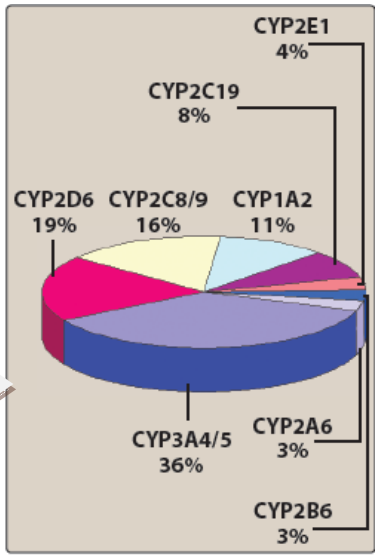
- ↓/ Retard (slow) metabolism & excretion of inhibitor & co-administered drugs.
- ↑ / prolong action of the inhibitor & co-administered drugs.

CYT P450 has been classified into:

- **Families designated by Numbers**
- **Sub families designated by Letters**

The most important one is CYP 3A

Note: Most drugs are metabolized thorough CYP3A isoenzyme.



Major Contributor to Phase I Metabolism is (CYP 3A4)(Very IMP)

Substrates (THE DRUG (A)WHICH WILL BE METABOLIZED BY (CYP 3A))	Inhibitors (The drug –B- that inhibit the enzyme activity)	Inducers(The drug –B- that induce the enzyme activity)
Immunosuppressants : Cyclosporine Azole Antifungals :Fluconazole Antibiotics Erythromycin, Clarithromycin Ca channel blockers Amlodepine, Verapamil Statins; Atorvastatin Antiarrhythmic: Amidarone Cancer Chemotherapy: Cyclophosphamide,Tamoxifen Non-Sedating Antihistaminics : Astamizole Benzodiazipines : Midazolam, Clonazepam	**Note:** Immunosuppressants , Azole Antifungals, and Antibiotics also act as inhibitors. Ritonavir (Protease Inhibitors) Cimetidine Chloramphenicol Nefazadone Grape Fruits	Rifampicin Phenytoin Carbamazepine Barbiturates Dexamethazone Progestins

General basic info. To help you in solving the cases :

If we noticed that the diseased patient is using drug (A) for treating his underlying disease and his symptoms are still occurring (not improving) once he started using other drugs(B) ➔ that means the drug (B) is an (enzyme inducer) ➔ which shortened the drug(A) half life and decreases its plasma levels ➔ the response will be absent or decreased

If we noticed symptoms of **toxicity** (new - unexpected symptoms) ➔ that indicates the **drug (B)** is an (enzyme inhibitor) –➔ inhibit the activity of the enzymes ➔ **drug (A)** will not be metabolized ➔ **Drug A** half-life and plasma level would **increase**➔toxicity

Genetic Variation:

Genetic polymorphisms in CYT P450 isoenzymes have been observed and are reasons behind the ALTERED RESPONSE to drug therapy

CYP2D6

has the most frequent polymorphisms in all CYT P450

When polymorphism occurs ➔ ↓ metabolizing capacity of CYP2D6

i.e those who exhibit the polymorphism become poor metabolizers:

1- Metabolism of some drugs neuroleptics, tricyclic antidepressants, antianginals agent (perihexiline), antiarrhythmics (propafenone & metoprolol) is suppressed ➔ so side effects & toxicity develop. i.e.

- Neuropathy after therapeutic doses of **perihexiline**
- Severe brady arrhythmias ➔heart block on therapeutic dose of **propafenone** or **metoprolol**

Note: In some individual there are mutation or polymorphism for the gene which encodes important enzymes eg: (CYP2D6)so the enzyme will lose its metabolic activity ➔the drug will not be metabolized (you have to memorize the drug which are metabolized by this enzyme)➔toxicity occur

2. The pro-drugs cannot be converted to their therapeutically active metabolite; e.g poor analgesia with **codeine & tramadole** because they are not transformed into active forms

Note: The patient who has genetic polmerphosim in this enzyme, will not get the analgesic effect of codine and tramadole (becouse they have to be metabolized by this enzyme to get it's active form) IMP to know which drug is prodrug which is metaboliate

Summary:

- The liver subjects the drugs to chemical transformation (METABOLISM) ➔ to become inactive & easily EXCRETED

Elimination :

- **If it is polar (water soluble) ➔ renal elimination**
- **If non polar(lipid soluble) ➔ billiary elimination**

- Drug metabolism in the liver usually occurs in two phases, the **CYP 450** (which is responsible for oxidation) is present in the first phase.
- **CYP 450** IS the terminal rate limiting oxidase (FINAL STEP) of the cytochrome system
- **CYP 450** is responsible of oxidization for endogenous substance e.g.; **steroid** and exogenous e.g **Drugs**
- **Activation or Inactivation** of the CYT P450 can be achieved either **Directly , or Indirectly** by expression or repression of its relevant genes by activation or inhibition of the responsible transcription factors
- Indirect **Activation of the CYT P450 ➔ the drug should** (dimerize) two TRANSCRIPTION FACTOR (PXR / RXR)
- **Outcome Of Drug-drug Interactions Mediated By CYT P450** :
  Inducers : decrease EFFICACY by inducing its own metabolism and metabolism of the co-administered drug.
  Inhibitors : ↑TOXCICITY by slowing or decreasing metabolism & excretion of inhibitor & co-administered drugs.

Substrates (THE DRUG (A)WHICH WILL BE METABOLIZED BY (CYP 3A4))	Inhibitors (The drug –B- that inhibit the enzyme activity)	Inducers(The drug –B- that induce the enzyme activity)
Immunosuppressants : Cyclosporine **Azole Antifungals :**Fluconazole **Antibiotics** Erythromycin, Clarithromycin **Ca channel blockers** Amlodepine, Verapamil **Statins;** Atorvastatin **Antiarrhythmic:** Amidarone **Cancer Chemotherapy:** Cyclophosphamide,Tamoxifen **Non-Sedating Antihistaminics :** Astamizole **Benzodiazipines :** Midazolam, Clonazepam	**Note:** Immunosuppressants , Azole Antifungals, and Antibiotics also act as **Ritonavir(Protease Inhibitors)** **Cimetidine** **Chloramphenicol** **Nefazadone** **Grape Fruits**	**Rifampicin** **Phenytoin** **Carbamazepine** **Barbiturates** **Dexamethazone** **Progestins**

- Major Contributor to Phase I Metabolism is **(CYP 3A)**
- **CYP2D6** has the most frequent polymorphisms in all CYT P450 that will supress the Metabolism of some drugs **neuroleptics, tricyclic antidepressants, antianginals agent (perihexiline), antiarrhythmics (propafenone & metoprolol)** → toxicity develop.
- The pro-drugs cannot be converted to their therapeutically active metabolite in CYP2D6 Polymorphisim; e.g poor analgesia with **codeine & tramadole** → ↓ EFFICACY

Review questions

1- Drug metabolisim in humans usually results in a product that is
A) Less lipid soluble than the original drug.
B) More likely to distribute intracelullry
C) More likely to to be reabsorbed by the kidney tubules
D) More lipid soluble than the original drug.

2-If therapy with multiple drugs causes induction of drug metabolisim in your asthma patient, it will
A) Be associated with increased smooth endoplasmic reticulum
B) increased rough endoplasmic reticulum
C) Be associated with decreased CYT p450 enzymes
D) Be irreversible

3-The addition of glucuronic acid to a drug:
A. Decreases its water solubility.
B. Usually leads to inactivation of the drug.
C. Is an example of a Phase I reaction.
D. Occurs at the same rate in adults and newborns.
E. Involves cytochrome P450.

4-Which of the following drugs may inhibit the hepatic microsomal P450 responsible for Clonazepam metabolisim?
A) Rifampin
B) Ethanol
C) Phenorbital
D) Grape Fruits

5- Which of the following drugs inhibits its own metabolism in CYP 3A4 isoenzyme?
A) Grape Fruits
B) Cimetidine
C) Chloramphenicol
D) Nefazadone
E) Fluconazole

Answers: 1-A,2-A,3-B,4-D,5-E

A 50 years old, patient was treated for the last 3 years by the hypocholestrolemic agent; atorvastatin. Yesterday he began to complain of severe muscle pains, weakness and reddish discoloration of urine(be careful to this unexpected symptoms (are not the therpuetic effect of the drug) ➔ toxcity occured)
He receives daily multivitamins and his lab results last week, proved that he has become diabetic, for which he was prescribed metformin. He was also started on a course of fluconazole for a concomitant fungal infection.
From drug history, the diagnosis of his current state was likely rhabdo-myositis (severe muscloskeletal toxicity) and was verified by the lab finding of severe elevation in creatinine phosphokinase. "Which one of the following drug-drug interaction on CYT 3A4 is the likely cause of his current state?

Metformin + Atrovastatin
Atrovastatin + Fluconazole
Metformin + Fluconazole
Fluconazole+ Multivitamin

Note:
In the case you will find 4 drug names so you have to know the **substrate** of the enzyme along with the drugs that is an enzyme **inducer** or **inhibtor**