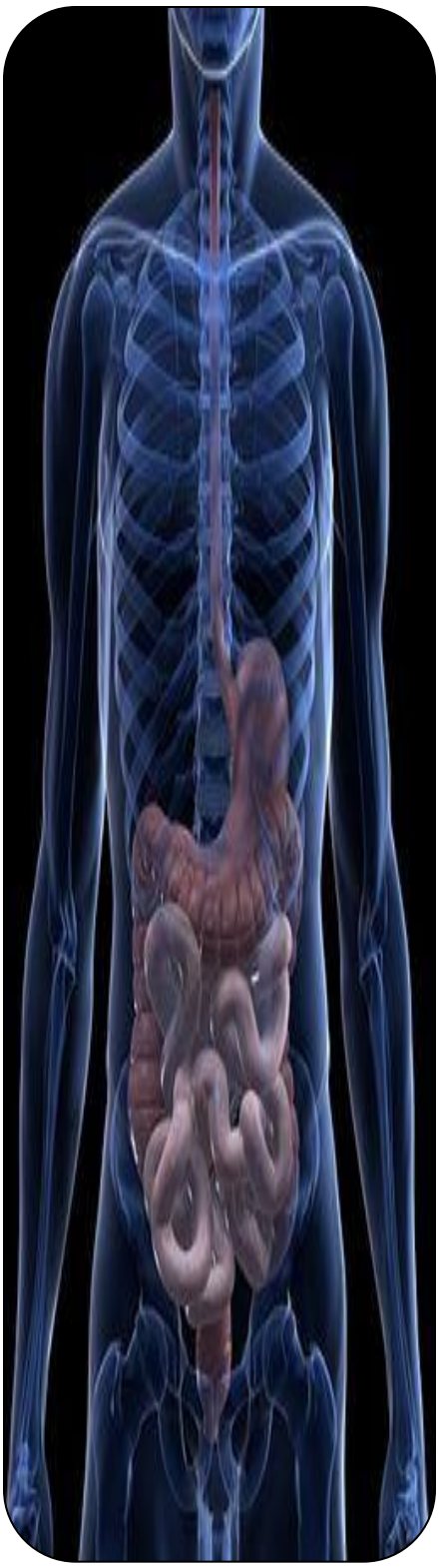


Pharmacology Team

CYTOCHROME SYSTEM & DRUG METABOLISM

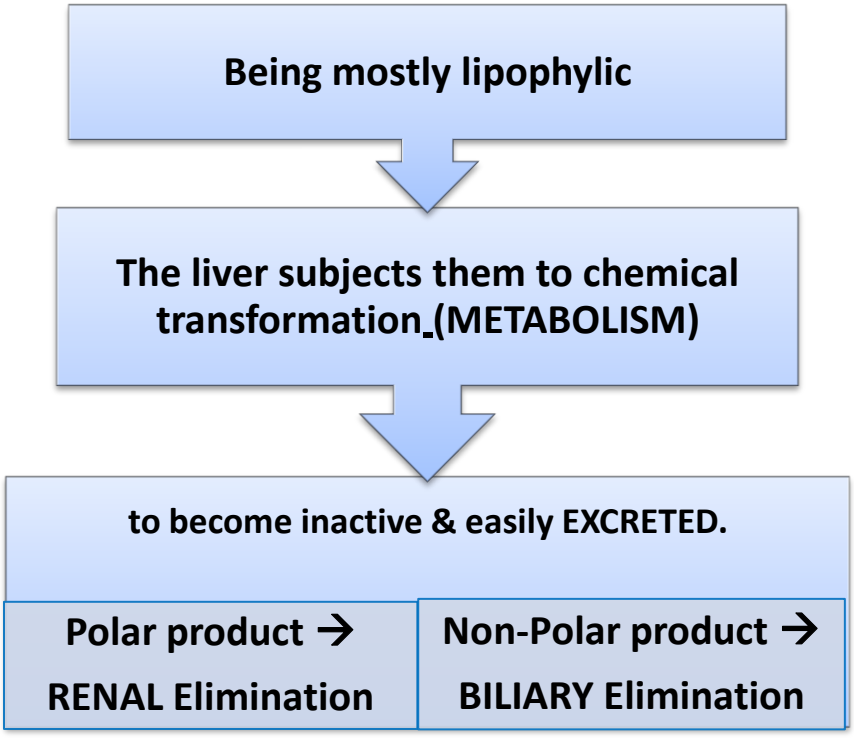
Objectives:

- Revise the intent of drug metabolism and its different phases
- Define the role of cytochrome system in relation to drug metabolism
- Expand on the nature, location, nomenclature, structure, distribution & function of CYT P450
- Focus on its regulation; directly & indirectly, its induction & inhibition in relevance to drug interactions
- Interpret the molecular mechanism of interactions by CYT P450
- Classify its different isoforms, their substrates, inducers & inhibitors
- Delineate some of its genetic variations

Done by:
*Alaa Alanazi
*Mohammed Alangari

Drug Metabolism:

Occurs mainly in the "METABOLIC CLEARING HOUSE" (Liver).Identified as foreign substances that body must get rid of.



Drug Metabolism:

Phase I
OXIDATION /Reduction/Hydrolysis

Create a conjugation site

Phase II
CONGUGATION

Drug metabolism may start phase 1 then phase 2 or directly start with phase 2

Our aim of the metabolism is:

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

CYTOCHROME SYSTEM :
Its enzymes are part of a cascade
➔ shuttles electrons from molecular oxygen to oxidize the drugs

" Cytochrome P450" " CYT 450" superfamily is the terminal rate limiting oxidase of this system.

CYTOCHROME P450 FAMILY OF ENZYMES:

They are located mainly attached to the smooth endoplasmic reticulum (SER) of hepatocytes.

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

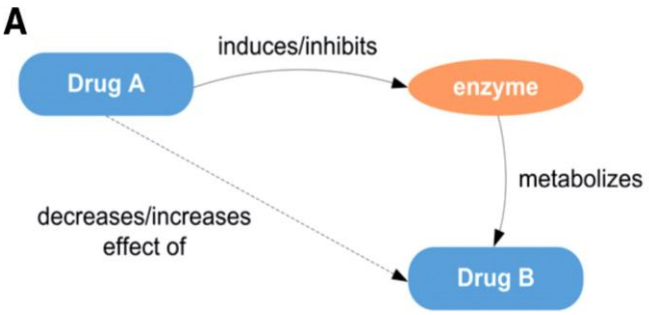
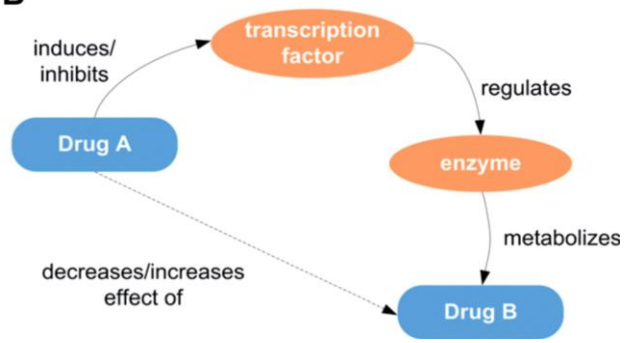
"P450" absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide**.**

They are isolated in the subcellular fraction termed the **MICROSOMES**
➔ **Liver microsomal enzymes**

STRUCTURE	DISTRIBUTION	Function
They are heme-containing isoenzymes	➢ Highly concentrated in hepatocytes ➢ Enterocytes of the small intestine present their principal extra-hepatic source ➢ Very small quantities in kidneys, lungs, & brain	Responsible for most of the OXIDATIVE METABOLISM of: Substrates • Endogenous substances: steroid hormones, prostaglandins, lipids, & fatty acids • Exogenous compounds: diet(food & beverages) / Drugs/ environmental xenobiotics.

Regulation

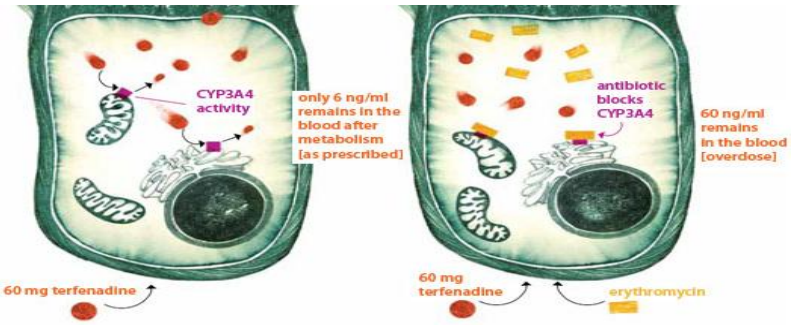
<u>Activation</u> or <u>Inactivation</u> of the CYT P450 can be achieved either

Directly	Indirectly
A 	by expression or repression of its relevant genes by activation or inhibition of the responsible transcription factors B 

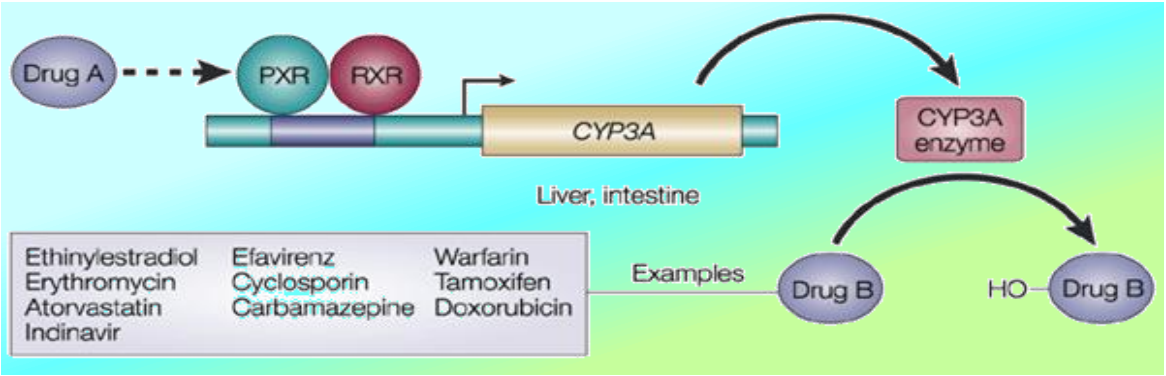
<u>Activation</u> or <u>Inactivation</u> can be processed be any food, intrinsic products or extrinsic xenobiotics as drugs (usually the lipophylic) that have to be metabolized

When drugs play a role in regulation of the CYT P450 ➔they are termed
<u>Enzyme Inducers</u> if Activate the enzyme
<u>Enzyme Inhibitors</u> if Inactivate the enzyme

→ PHARMACOKINETIC DRUG-DRUG INTERACTION



Molecular Basis Of Drug–drug Interaction



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 → REPRESSION of CYT P450 isoenzymes to →↓metabolism of Drug B

PXR, pregnane X receptor
RXR, retinoid X receptor.

Outcome Of Drug-drug Interactions Mediated By CYT P450 :

IN RELATION TO ENZ INDUCERS
↑→metabolism of the inducer + ↓→ its pharmacological action.
Tolerance or complete nullification
↑ →metabolism of co-administered drugs ↓ EFFICACY

IN RELATION TO ENZ INHIBITORS
↓/ Retard metabolism & excretion of inhibitor & co-administered drugs.
↑ / prolong action of the inhibitor & co-administered drugs ↑TOXCICITY

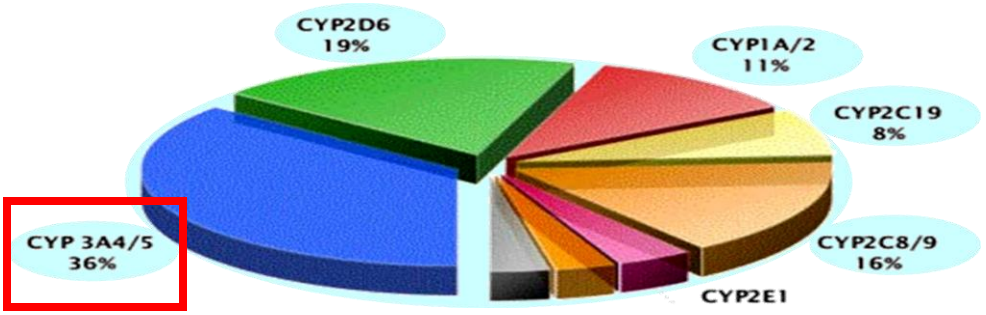
Classification

CYT P450 has been classified into

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

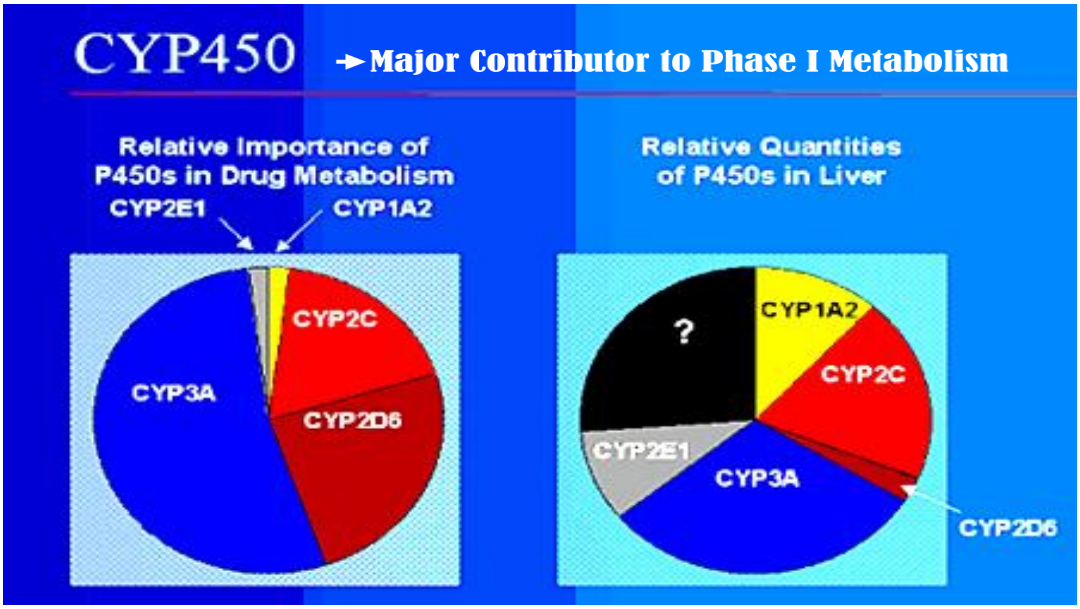
Distribution of different CYPs isoforms in the liver.

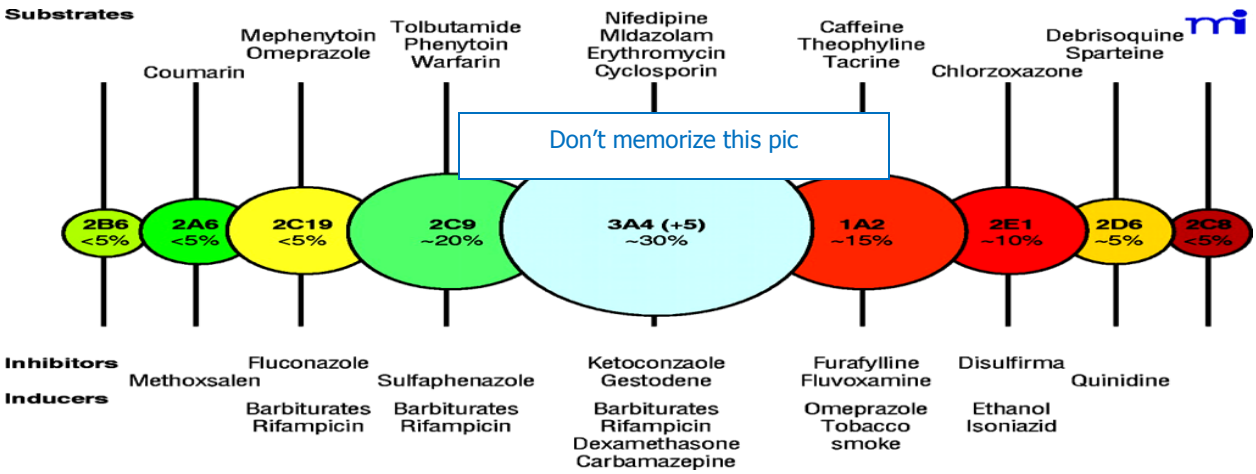
You should memorize them



Don't memorize the parentages

Important ..!!





CYT P450 3A4

Substrates	Inhibitors	Inducers
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**	• They are inhibitors..!! • Don't give them with any of inhibitors coz they already inhibit their own metabolism→ lead to sever toxicity **Protease Inhibitors** **Ritonavir** **Cimetidine** **Chloramphenicol** **Nefazadone** **Grape Fruits**	**Rifampicin** **Phenytoin** **Carbamazepine** **Barbiturates** **Dexamethazone** **Progestins**

Genetic Variation:

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

CYP2D6:

This isoenzyme 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**

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 .

CYP2C9:

Warfarin, phenytoin, & tolbutamide are examples of drugs with narrow therapeutic index that are metabolized by CYP2C9.
Clearance of these drugs is impaired in genetic variation of the enzyme

CYP2C19: Benefit

Polymorphism in CYP2C19 showes increased & prolonged action of its substrates as omeprazole
This has been an advantage as in those variants → ↑ cure rates in peptic ulcer patient with H*elicobacter pylori*

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.

Questions:

1-"***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***
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?

1-**Metformin + Atrovastatin**
2-Atrovastatin + Fluconazole
3-Metformin + Fluconazole
4-Fluconazole+ Multivitamins

Answer : 2

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

Answer: A

3-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

Answer: A

4-**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.
Answer: B

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

Answer: D

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

Answer :E