MED438

pharmacology
Team 438

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Cytochrome System and Drug Metabolism

Objectives:

By the end of the lecture , you should know:

- Revise the aim & phases of drug metabolism
- 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 molecular mechanism of interactions by CYT P450
- Classify its different isoforms, their substrates, inducers& inhibitors
- Delineate some of its genetic variations.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Drug Metabolism

- Identified as foreign substances that body must get rid of.
- Occurs mainly in the liver " metabolic clearing house".
- Being mostly lipophilic ➔ The liver subjects them to chemical transformation (Metabolism) to become inactive & easily **excreted,** by either transforming them into:
  - **Polar product** and excreted by Renal elimination
  - Or **Non-Polar product** and excreted by Biliary elimination.

Cytochrome P450 "CYT P450"

What does it mean?

"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 located mainly attached to the smooth endoplasmic reticulum (SER) of hepatocytes, they are isolated in the subcellular fraction termed the **microsomes**

=

Liver Microsomal Enzymes\ CYT P450

What are they?

1 CYT P450 superfamily is the terminal rate limiting oxidase of this system

2 Its enzymes are part of a cascade to transfers electrons from molecular oxygen to oxidize the drugs

3 Structure: they are heme-containing isoenzymes attached to O2, N3, Su, Fe

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

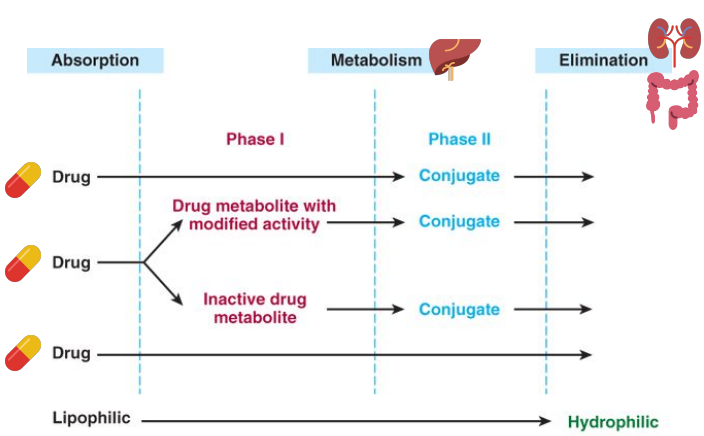
5 Responsible for most of the oxidative metabolism of:
Endogenous substances: steroid hormones, prostaglandins, lipids & fatty acids
Exogenous compounds: diet (food & beverages), Drugs, environmental xenobiotics.

There are two phases of drug metabolism:

Phase I
Oxidation\Reduction\Hydrolysis

Phase II
Conjugation

Result in:
- Inactive product
- Active metabolite
- Similar to parent
- More active than parent
- A product with different effect
- Toxic metabolite



Cycle of CYT P450 in Drug Oxidations

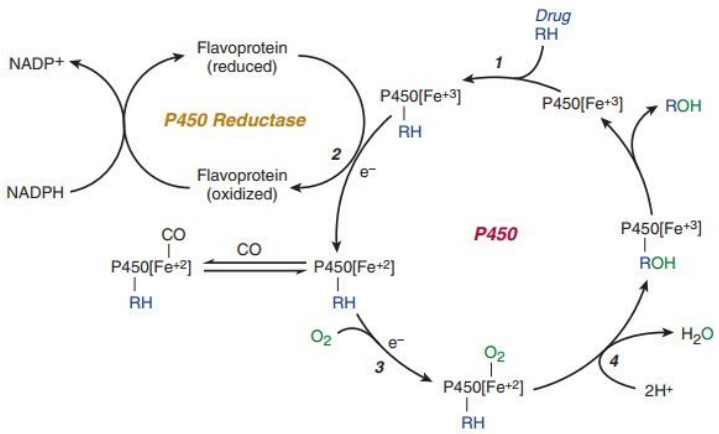
Microsomal drug oxidations require P450, P450 reductase, NADPH, & molecular oxygen

Step 1 oxidized (Fe3+) P450 combines with drug substrate to form a binary complex

Step 2 NADPH donates an electron to the flavoprotein P450 reductase, which in turn reduces the (oxidized P450 drug complex)

Step 3 A second electron is introduced from NADPH via the same P450 reductase, which serves to reduce molecular oxygen & to form (an activated oxygen – P450-substrate complex)

Step 4 This complex in turn transfers activated oxygen to the drug substrate to form the oxidized product



Regulation of CYPs

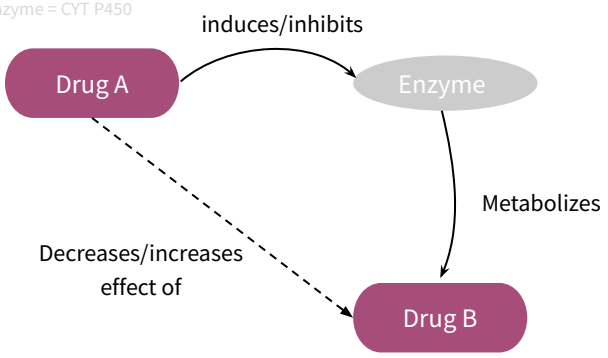
- Activation or Inactivation can be processed by any food, intrinsic products or extrinsic xenobiotics as drugs (usually the lipophilic) that have to be metabolized

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

Directly

The drug activates/inhibits the CYT p450 system directly

Drug A = Substrate
Drug B = Affected
Enzyme = CYT P450

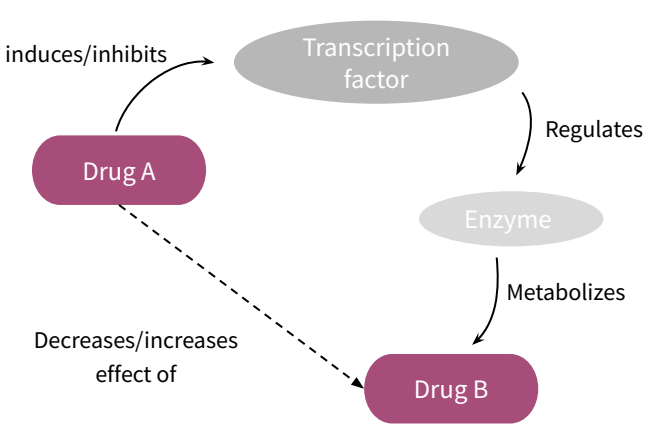


Drug A acts directly on CYT P450 by either induces or inhibits it, this eventually affect the metabolization of Drug B and alter its efficacy

VS

Indirectly

By **expression or repression** of its relevant genes by activation or inhibition of the responsible **transcription factors**



Drug A acts on the genes that regulate CYT P450 by activates or inhibits their transcription, this eventually affect the metabolization of Drug B and alter its efficacy

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

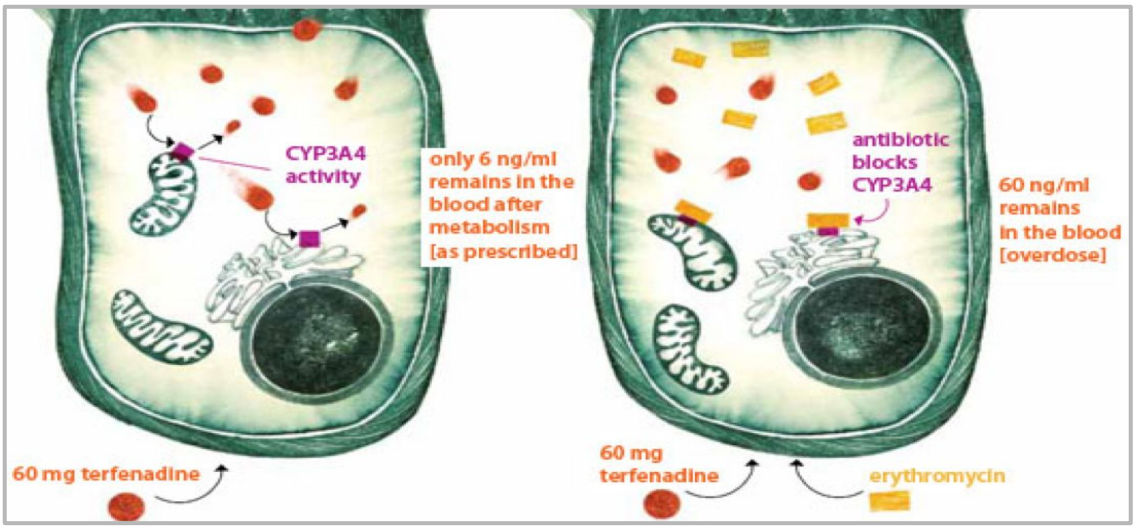
Enzyme Inducers
If they activate the enzyme

Enzyme Inhibitors
If they inactivate the enzyme

This causes drug-drug interactions (pharmacokinetics)

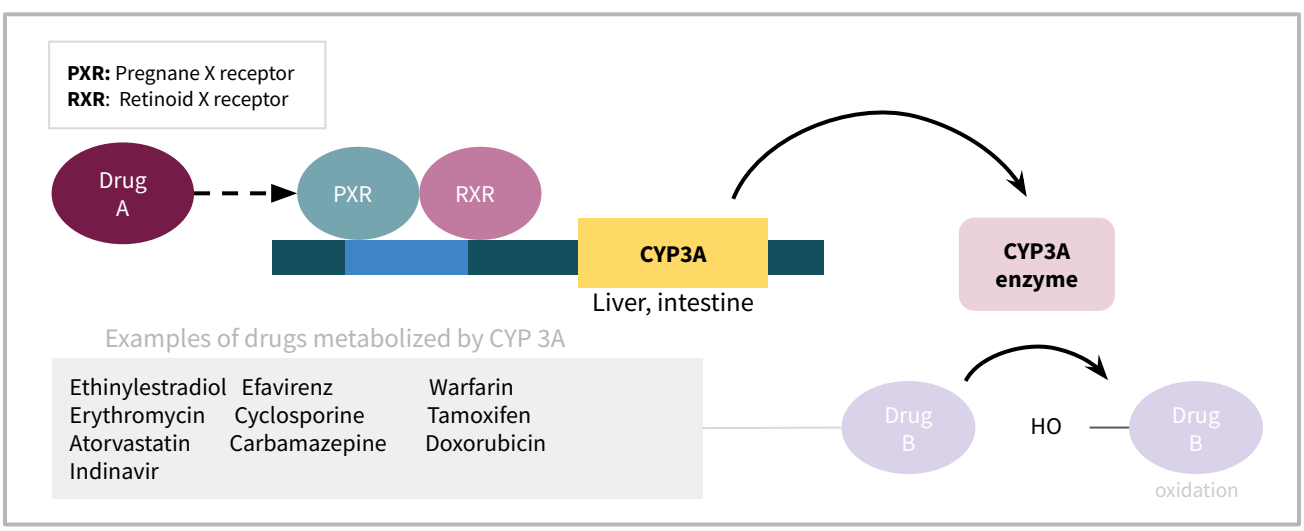
Examples for Regulation of CYPs

A) Direct Regulation:



- **Normally:** Terfenadine (Anti-histaminic drug) after its metabolization, 6 ng\ml remains to reach the blood and produce the desired effect.
- **In case of co-administration with Erythromycin:** Erythromycin is an enzyme inhibitor, decreases the metabolization of Terfenadine to 60 ng\ml causing toxicity

B) Indirect Regulation
" Molecular Basis of drug-drug interaction":



- The orphan nuclear receptor **PXR** is a Transcription factor that **regulates the expression of the CYP P450 genes.**

1. **If Drug A is INDUCER:** it binds & activates PXR, which translocates in nucleus → dimerize with RXR → the hetero-diamer PXR / RXR will induce the expression of CYT P450 isoenzymes to increase metabolism of Drug B.
2. **If Drug A is an INHIBITOR:** its binding will prevent the activation of PXR → repression of CYT P450 isoenzymes to decrease metabolism of Drug B

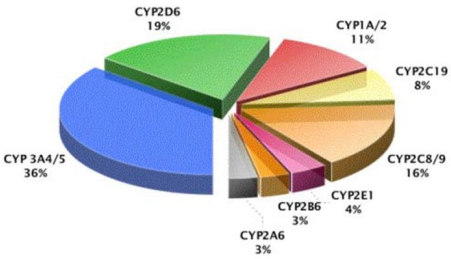
Outcome Of Drug-drug Interactions Mediated By CYT P450

Enzyme Inducers	↑metabolism of the inducer (it self) and the co-administered drugs →↓ their pharmacological action = Tolerance or complete nullification \ ↓Efficacy
Enzyme Inhibitors	↓ or retard metabolism & excretion of the inhibitor and the co-administered drugs →↑or prolong their pharmacological action = ↑ toxicity

Classification of CYT P450

It has been classified into:
Families designated by numbers & **Sub families** designated by letters

Distribution of different CYP isoforms in the liver:
- CYP3A4/5 : 36%
- CYP2D6: 19%
- CYP2C9: 16%
- CYP1A/2 : 11%
- CYP2C19: 8%



Genetic Variation

Genetic polymorphisms in CYT P450 isoenzymes have been observed & are reasons behind the altered response to drug therapy

CYT P450 3A4

- Most calcium channel blockers
- Most benzodiazepines
- Most HIV protease inhibitors
- Most HMG-CoA- reductase inhibitors (statins)
- Cyclosporine
- Most non-sedating antihistamines
- Cisapride

Substrates	Inducers	Inhibitors

• Ca^{+2} channel blocker
  ○ Amlodipine
  ○ Verapamil
• Benzodiazepines
  ○ Midazolam
  ○ Clonazepam
• HMG-CoA- reductase inhibitors (statins)
  ○ Atorvastatin
• Immunosuppressants
  ○ Cyclosporine
• Azole Antifungals
  ○ Fluconazole
• Antibiotics
  ○ Erythromycin
  ○ Clarithromycin
• Cancer Chemotherapy
  ○ Cyclophosphamide
  ○ Tamoxifen
• Non-Sedating Antihistamines
  ○ Astemizole
	• Rifampicin\Rifampin
	• Phenytoin
	• Carbamazepine
	• Barbiturates
	• Dexamethasone
	• Progestins
	• Rifabutin
		• Grapefruits
		• Nefazodone
		• H2 Blocker
		  ○ Cimetidine
		• Immunosuppressant
		  ○ Cyclosporine
		• Azole Antifungals
		  ○ Fluconazole
		  ○ Ketoconazole
		  ○ Itraconazole
		• Antibiotics
		  ○ Erythromycin
		  ○ Clarithromycin
		  ○ Troleandomycin
		  ○ Chloramphenicol
		• Protease Inhibitors
		  ○ Ritonavir

CYT P450 2D6

Substrates	Inducers	Inhibitors

• Codeine
• Many B-blockers
  ○ Propranolol
  ○ Metoprolol
  ○ Timolol
  ○ Bupranolol
• Many tricyclic antidepressants
	• Rifampicin	• Fluoxetine
		• Haloperidol
		• Paroxetine
		• Quinidine

Genetic Variation

This isoenzyme has **the most frequent polymorphisms** in all CYT P450 and 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 (perhexiline), antiarrhythmics (propafenone & metoprolol) **are suppressed** , so side effects & **toxicity** develop. i.e.:

- Neuropathy after therapeutic doses of perhexiline
- Bradycardias & arrhythmias 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 & tramadol because they are not transformed into active forms.

- It is Absent in 7% of Caucasians, 1-2% non-Caucasians.
- Hyperactive in up to 30% of East Africans.

CYT P450 1A2

Substrates	Inducer	Inhibitors
• Theophylline • Imipramine • Propranolol • Clozapine	• smoking tobacco	• Many fluoroquinolone antibiotics • Fluvoxamine • Cimetidine

CYT P450 2C9

Substrates	Inducers	Inhibitors

• Most NSAIDs (including COX-2)
  ○ Celecoxib
  ○ Diclofenac
  ○ Ibuprofen
  ○ Tolbutamide
• S-warfarin (the active form)
• Phenytoin
	• Rifampicin
	• Barbiturates
		• Fluconazole

Genetic Variation

- 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
- Absent in 1% Caucasians and African-Americans

CYT P450 2C19

Substrates	Inducers	Inhibitors
• Diazepam • Omeprazol • Phenytoin	• Rifampicin • Barbiturates	• Omeprazole • Isoniazid • Ketoconazole

Genetic Variation

- Polymorphism in CYP2C19 shows increased & prolonged action of its substrates as omeprazole.
- This has been an **advantage as in those variants there is↑ cure rates in peptic ulcer** patient with Helicobacter pylori **(beneficial effect)** .
- Absent in 20-30% of Asians, 3-5% Caucasians.

Case from Dr. Slides

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 & reddish discoloration of urine. He receives daily multivitamins & 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 musculoskeletal toxicity) & 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?

A) Metformin + Atorvastatin B) Atorvastatin + Fluconazole
C) Metformin + Fluconazole C) Fluconazole+ Multivitamins

Correct answer: B

Quiz

MCQ

1- Which of the following is a CYP2C19 inhibitor?
(A)Omeprazole (B)Itraconazole (C)Grapefruit (D)Erythromycin

2- Which of the following is a CYP450 inducer?
(A)Ritonavir (B)Paroxetine (C)Rifampin (D)Cimetidine

3- CYP2D6 catalyzes the metabolism of:
(A)Haloperidol (B)Quinidine (C)Fluoxetine (D)Amoxapine

4- Which of the following is induced by smoking tobacco?
(A)CYP2C9 (B)CYP2C19 (C)CYP1A2 (D)CYP2D6

5- Which of the following is characteristic of enzyme inducers?
(A)Increase metabolism and prolong the duration of action
(B)Decrease metabolism and prolong the duration of action
(C)Increase Efficacy
(D)Decrease Efficacy

6- A 34-year-old female insists on drinking a cup of grapefruit juice every morning for "body cleansing." Grapefruit juice is known to interfere with the cytochrome P450 system, disrupting levels of certain drugs. The cytochrome P450 system includes dozens of enzymes. Which is the most abundant CYP enzyme in human livers?
(A) CYP1A2 (B) CYP2A6 (C) CYP2D6 (D)CYP3A4

Answers:

MCQ

Q1	A	Q2	C	Q3	D	Q4	C	Q5	D	Q6	D

Share with us your ideas !

Good Luck , Future Doctors!

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