Lecture 6

Cytochrome system and drug metabolism

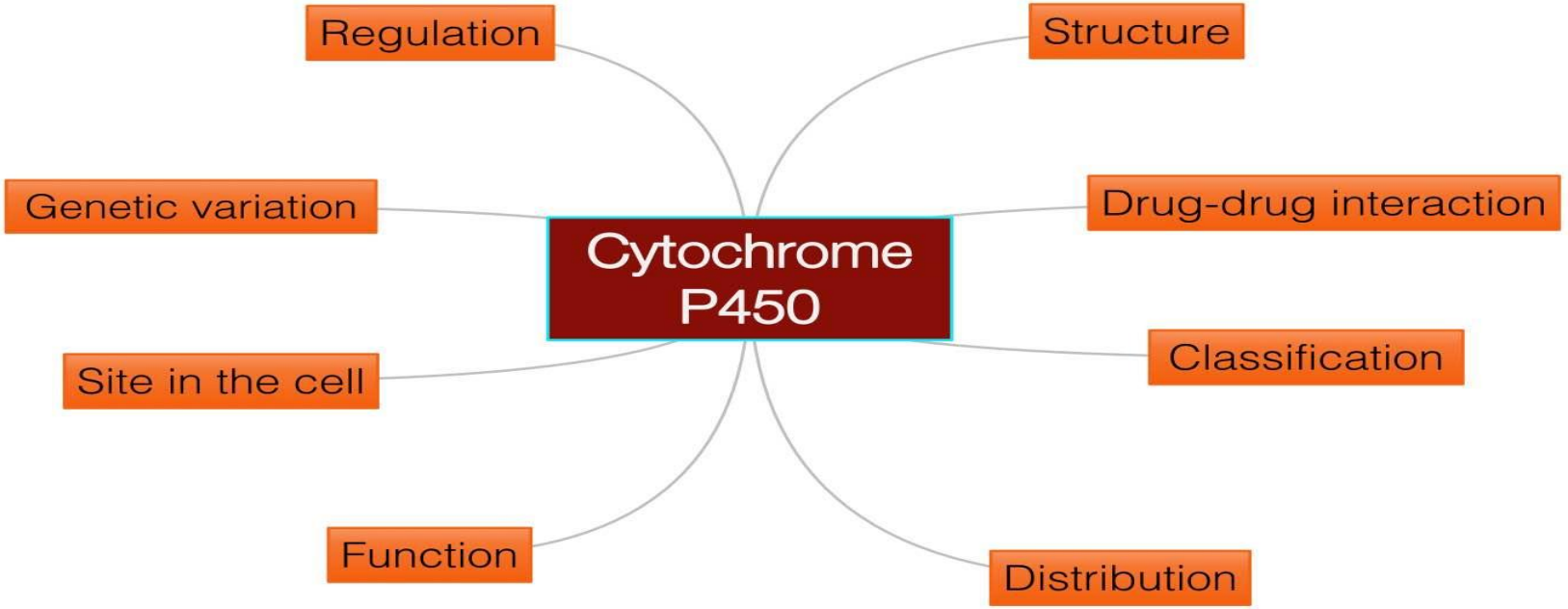
Objectives:

- ★ 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

- Additional Notes
- Important
- Explanation –Extra-

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com

mind map



before starting, please check our **GIT block correction**

drug metabolism

- Drugs metabolism occurs *mainly* in the *liver* (metabolic clearance house).
- Once a drug enters the body it is identified as a foreign substance that the body must get rid of it.
- As most of drugs are *lipophilic*, the liver subjects them to **chemical transformation** to become easily excreted by :

1. *Renal* elimination of polar (hydrophilic) products.
2. *Biliary* elimination of non-polar (lipophilic) products.

There are two phases of drug metabolism :

1. **Phase I :**

Definition : modification of drug molecule via **oxidation**, **reduction** or **hydrolysis**.

- *Cytochrome system* is the major system involved in **phase I** reactions.

2. **Phase II :**

Definition : **conjugation** with endogenous compounds via activity of **transferases**.

drug metabolism

Note :

1. *Not* all drugs undergo **Phase I** and **Phase II** in order.
2. *Some* drugs directly enters Phase II metabolism.

End product of drug metabolism :

1. Inactive metabolite (*most drugs*).
2. Active metabolite (*prodrugs*).
3. A product with different effect.
4. Toxic metabolite.

Cytochrome P450 (CYT P450)

superfamily is the terminal rate of limiting oxidise of this system.Its enzymes are part of cascade, shuttles electrons from molecular oxygen to oxidize the drugs.(cyt-p450 is the last stage before drug become ready to get conjugated).

- **Cytochrome = colored cells :** They color liver cells dark red as they contain *iron*.
- **P450 =** absorbed a very characteristic wavelength(450nm) of *ultraviolet* light when it exposed to *carbon monoxide*(*CO*).

Cytochrome P450 (CYT P450)

Location	located mainly attach to smooth endoplasmic reticulum of hepatocytes. They are isolated in the Microsomes (liver microsomal enzymes).
Structure	They are heme-containing isoenzymes.
Distribution	❖ **Highly** concentrated in **hepatocytes**. ❖ Enterocytes of small intestine present their extra-hepatic source. ❖ Very **small** quantities in kidneys, lungs and brain.
Function	responsible for most of **Oxidative Metabolism** of : ❖ **Endogenous substances** : steroid hormones, prostaglandins, lipids and fatty acids. ❖ **Exogenous substances** : diet, drugs and environmental xenobiotics.

Regulation of CYT P450

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

- ❖ **Directly**. (the drug activate the system directly)
- ❖ **Indirectly** : by *expression* or *repression* of **relevant genes** by or inhibition of the responsible transcription factors.
- ❖ Activation or inactivation can be processed by any *food*, *intrinsic products* *extrinsic xenobiotics* as *drugs* (usually lipophilic) that have to be metabolized.

- ❖ When drugs play a role in regulation of **CYT P450** , they are termed :
  1. **Enzyme Inducers** if **Activate** the enzyme.
  2. **Enzyme Inhibitors** if **Inactivate** the enzyme.

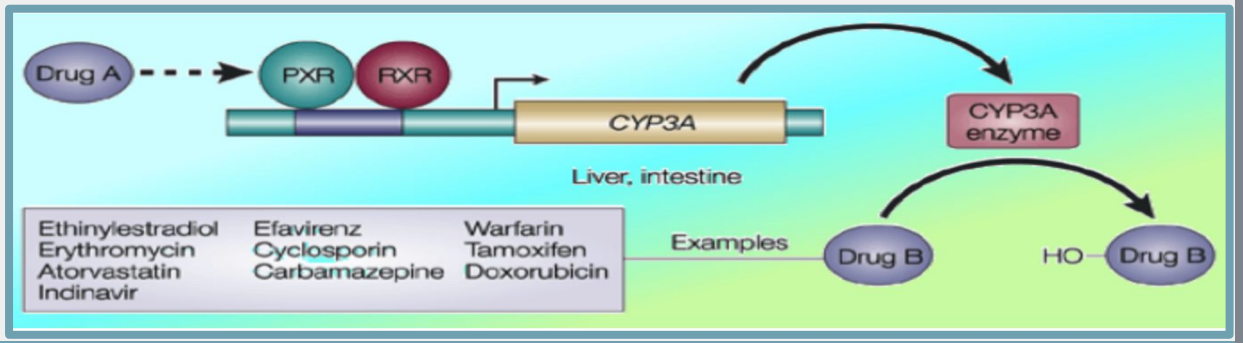
This play a major role in Drug-Drug Interaction.

molecular basis of Drug-drug interaction

The orphan nuclear receptor **PXR** is a **TRANSCRIPTION FACTOR** that regulates the **expression** of the ***CYP P450*** *genes*. **(look at the pic while you are reading)**

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



Example of Drug-Drug interaction

If a patient use 60 mg *Terfenadine* (Antihistamine) which will metabolized by CYP3A4 and only **6 ng/ml** remains in the blood and if the patient takes Erythromycin (Antibiotics) in addition to Terfenadine , this will increase the amount of Terfenadine in the blood 10 times (**60 ng/ml**) because Antibiotics Block CYP3A4 so it will increase the amount of Terfenadine which will remains in the blood in overdose.

Outcome Of Drug-drug Interactions Mediated By CYT P450

In relation with enzyme inducer

this means **both** the drug that causes **enzyme induction** + the **co-administered drug** = increase in their metabolism

1- Increase in **metabolism of the enzyme inducer** → **its pharmacological action. (*Tolerance or complete nullification)***
2-increase metabolism of co-administered drugs.

Decrease in efficacy

In relation with enzyme inhibitor

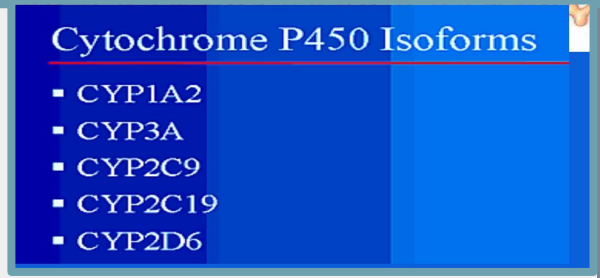
this means **both** the drug that causes **enzyme inhibition** + the **co-administered drug** = decrease in their metabolism

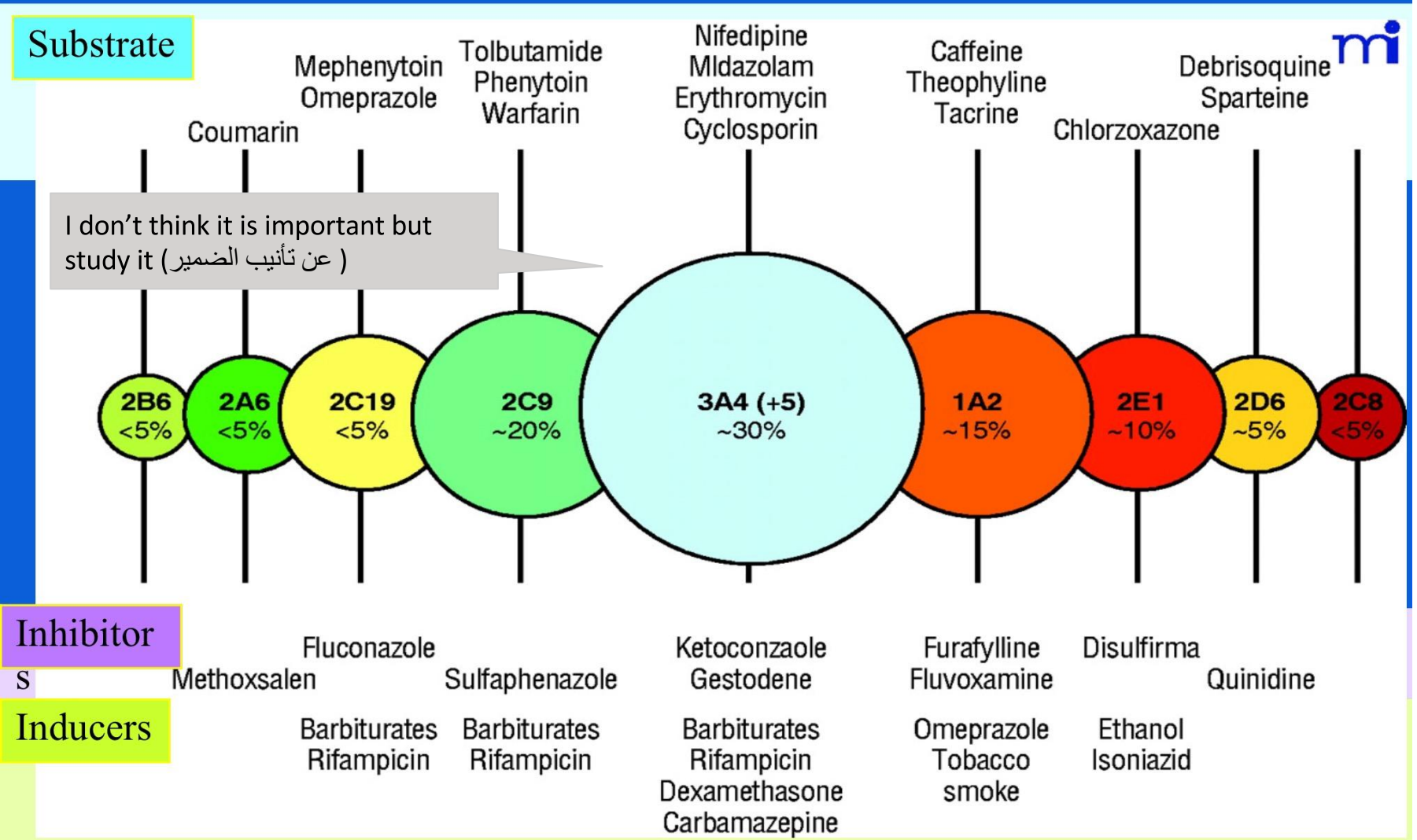
1-Decrease in retard metabolism, excretion of inhibitor & co-administered drugs.
2- Increase in prolong action of the inhibitor & co-administered drugs.

Increase in toxicity

Classification of CYT P450

★ **CYT P450 has been classified into :**
1-Families designated by **Numbers**
2-Sub-families designated by **Letters**




Substrate
Coumarin
Mephenytoin
Omeprazole
Tolbutamide
Phenytoin
Warfarin
Nifedipine
Mldazolam
Erythromycin
Cyclosporin
Caffeine
Theophyline
Tacrine
Chlorzoxazone
Debrisoquine
Sparteine
I don't think it is important but study it (عن تأنيب الضمير)
2B6 <5%
2A6 <5%
2C19 <5%
2C9 ~20%
3A4 (+5) ~30%
1A2 ~15%
2E1 ~10%
2D6 ~5%
2C8 <5%
Inhibitor
s
Methoxsalen
Fluconazole
Sulfaphenazole
Ketoconzaole
Gestodene
Furafylline
Fluvoxamine
Disulfirma
Quinidine
Inducers
Barbiturates
Rifampicin
Barbiturates
Rifampicin
Barbiturates
Rifampicin
Dexamethasone
Carbamazepine
Omeprazole
Tobacco
smoke
Ethanol
Isoniazid

very important

CYT P450 3A4 (most common 30%~)

Substrate	Inhibitors= toxicity	Inducers= no response
Immunosuppressants: Cyclosporine	**Immunosuppressants**: Cyclosporine	
Azole Antifungals: Fluconazole	**Azole Antifungals**: Fluconazole	
Antibiotics: Erythromycin, Clarithromycin	**Antibiotics**: Erythromycin, Clarithromycin	
Ca channel blockers: Amlodepine, Verapamil	• **Protease Inhibitors**: Ritonavir • **Cimetidine** • **Chloramphenicol** • **Nefazadone** • **Grape Fruits**	• **Rifampicin** • **Phenytoin** • **Carbamazepine** • **Barbiturates** • **Dexamethazone** • **Progestins**
Statins: Atorvastatin		
Cancer Chemotherapy: Cyclophosphamide, Tamoxifen		
Non-Sedating Antihistaminics:Astamizole		
Antiarrhythmic: Amidarone		
Benzodiazipines:Midazolam, Clonazepam		

very important

Genetic variation

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

1-CYP2D6

This isoenzyme has the most frequent polymorphisms in all CYT P450.

When polymorphism occurs → **decrease** metabolizing capacity of **CYP2D6**.

those who exhibit this polymorphism become poor metabolizers in:

1. **Metabolism** of some drugs **neuroleptics**, **tricyclic antidepressants**, **antianginals** agent (**perihexiline**), **antiarrhythmics (propafenone & metoprolol)** is suppressed – so **side effects & toxicity develop, such as:**

- ❏ 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

2-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

2-CYP2C19

Polymorphism in CYP2C19 showes **increased & prolonged action** of its substrates as **omeprazole**

This has been an **advantage** as in those variants→ increased cure rates in **peptic ulcer** patient with ***Helicobacter pylori***

case:

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?

A. Metformin + Atrovastatin
B. Atrovastatin + Fluconazol
C. Metformin + Fluconazole
D. Fluconazole + Multivitamins

ANS:B

MCQs

1-Where is Cyt-450 mainly present?

A. Enterocytes
B. Erythrocyte
C. Neuron
D. Hepatocytes

2-Cyt-450 is responsible for oxidative metabolism of which of the following endogenous substances?

A. Testosterone
B. VitC
C. Grape fruit
D. Banana

3-The most common isoform is ?

A. Cyt-P450 3A4
B. CYP2C19
C. CYP2C9
D. CYP3C98

4-Which of the following drugs is metabolized by CYP2C9 ?

A. Penicillin
B. Vancomycin
C. Phenytoin
D. Atrovastatin

5-Drug-Drug interaction that induces Cyt-450 will cause?

A. Toxicity
B. Immunity
C. IF
D. Tolerance

6-Drug-Drug interaction that inhibit Cyt-450 will?

A. Release CD4
B. Increase toxicity
C. Decrease toxicity
D. Increase Efficacy

7-has the most frequent polymorphisms in all CYT P450?

A. CYP2D6
B. CYP2C19
C. CYP2C9
D. CYP3C98

8-Polymorphism in which of the following increase the rate of cure in H.Pylorus peptic ulcer?

A. CYP2D6
B. CYP2C19
C. CYP2C9
D. CYP3C98

9-Do some drugs skip Phase 1 and go to phase 2 immediately ?

A. Yes
B. No
C. No enough information

1-D
2-C
3-A
4-C
5-D
6-B
7-A
8-B
9-A

Good luck!

Done by Pharmacology team 434

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For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com