CYTOCHROME SYSTEM & DRUG METABOLISM

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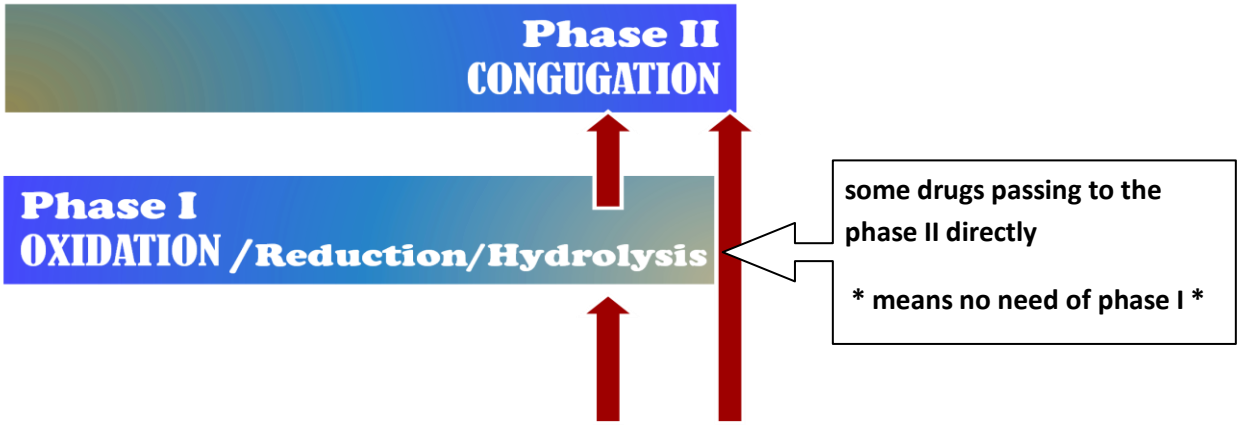
هذي النوتز عبارة عن **المهم والمطلوب في الامتحان**
،، اللي حاب يفهم أكثر يرجع للسلايد ..

!! The metabolism of the drug doesn't mean deactivation of the drug

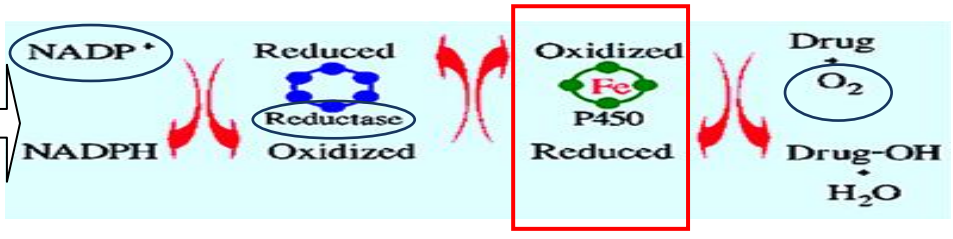
DRUG METABOLISM

- Occurs mainly in the "METABOLIC CLEARING HOUSE = liver "
- When the drug enter the body it is Identified as foreign substances that body must get rid of it by the following steps :
  1- The drug Being mostly lipophylic ➔ The liver subjects them to chemical transformation (METABOLISM) ➔ to become inactive & easily EXCRETED.
  2- Excretion by one of the following :
  -Non-Polar product >>> BILIARY Elimination
  -Polar product >>> RENAL Elimination
- the metabolism (step 1) occurs by passing 2 phases:



- The outcomes of the congugation :
  - Inactive product
  - Active metabolite
  - A product with different effect
  - Toxic metabolite
- CYTOCHROME SYSTEM :
  - Involving in phase I
  - Its enzymes are part of a cascade ➔ shuttles electrons from molecular oxygen to <u>oxidize the drugs</u>
  - Main enzyme of this system is " Cytochrome P450" " CYT 450" which Responsible for most of the <u>OXIDATIVE METABOLISM</u>

Oxidative reactions involve:
-cytochrome P450
- NADPH
-oxygen
Outcome > oxidized drug

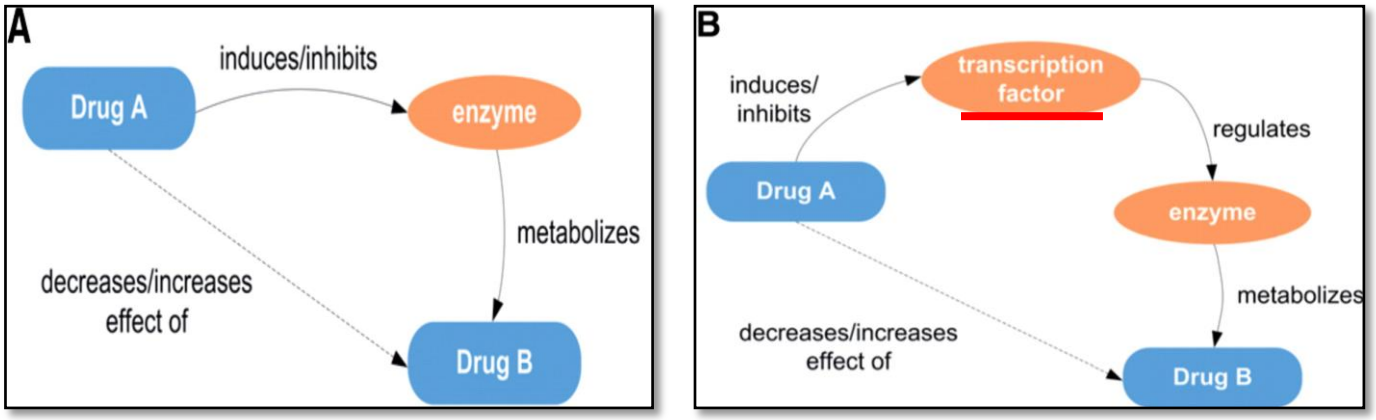


Regulation

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

CYTOCHROME P450 are located mainly in the smooth endoplasmic reticulum (SER) of hepatocytes.

- A: **Directly** (less common)
- 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

PHARMACOKINETIC DRUG-DRUG INTERACTION

- **Molecular Basis Of *Drug–drug Interaction* :**
  - If Drug A is **INDUCER** → it binds & activates PXR* → which translocates in nucleus → dimerize (يشبك) with RXR** → the heterodiamer PXR / RXR will induce EXPRESSION of CYT P450 isoenzymes to >> ↑ metabolism of Drug B

** ***OUTCOME*** of **ENZ INDUCERS** :

↑ metabolism >> ↓ pharmacological action.*(*Tolerance or complete nullification*)*
↑ metabolism of co-administered drugs .

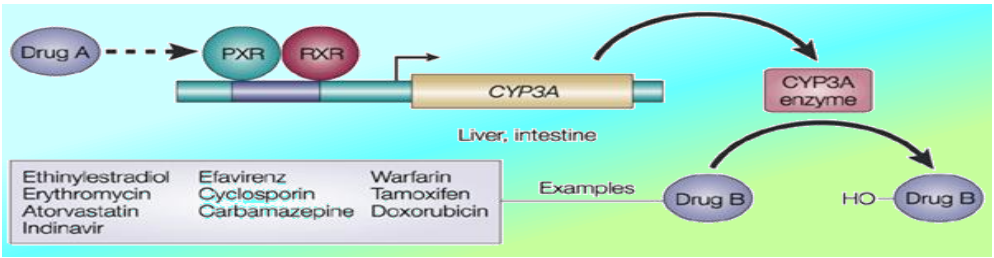
↓ EFFICACY

  - If Drug A is an **INHIBITOR** >> its binding **(to PXR)** will prevent activation → REPRESSION of CYT P450 isoenzymes to >> ↓ metabolism of Drug B

** ***OUTCOME*** Of **ENZ INHIBITORS** :

↓ Retard metabolism + excretion of inhibitor & co-administered drugs.
↑ prolong action of the inhibitor & co-administered drugs.

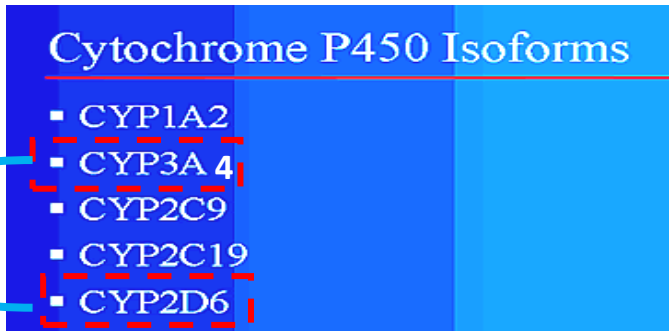
↑TOXCICITY



* PXR (*pregnane X receptor*) is a TRANSCRIPTION FACTOR that regulates the expression of the *CYP P450 genes*.

** *RXR (retinoid X receptor).*

!! imp.



CYT P450 3A4 : is the imp. Isoform of CYTP450 in drug metabolism .

Substrates (Drug B)	Inhibitors (Drug A)	Inducers (Drug A)
Immunosuppressants Cyclosporine →	They are strong inhibitors	
Azole Antifungals Fluconazole →		
Antibiotics Erythromycin, Clarithromycin →		
Ca channel blockers Amlodepine, Verapamil	Protease Inhibitors Ritonavir Cimetidine Chloramphenicol Nefazadone Grape Fruits	Rifampicin Phenytoin Carbamazepine Barbiturates Dexamethazone Progestins
Statins; Atorvastatin Amidarone		
Cancer Chemotherapy: Cyclophosphamide, Tamoxifen		
Non-Sedating Antihistaminics Astamizole		
Benzodiazipines Midazolam, Clonazepam		

to understand Drug A &B
See previous page

1-We have to memorize the drugs in RED and their action (inhib. Or induc.)

2-the MCQ will be as the following 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. "

Q) Which one of the following drug-drug interaction on CYT 3A4 is the likely cause of his current state?

A- Metformin + Atrovastatin

B- Atrovastatin + Fluconazole ←

C- Metformin + Fluconazole

D- Fluconazole+ Multivitamins

طريقة الحل :

١ - تحديد الدرقز الموجودة في السيناريو ..

٢ - حاول تحديد ما إذا كان الـ **drug-drug interaction** اللي صار سبّب Toxicity **(Enz inhibitors)** **OR** ↓ drug efficacy **(Enz inducers)**

هذه الخطوة تساعد في تذكر الأدوية من الجدول واستبعاد الغير مهمة في السيناريو (مثلا **Multivitamins + Metformin**)

٣ - اختيار الإجابة الصحيحة .. بإذن الله :)

Genetic Variation

Genetic polymorphisms (genetic problems**) 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 (CYP2D6 become poor metabolizers) . This will cause the effect on drug by :

1- **Suppression of Metabolism of some drugs >>> so side effects & toxicity develop**
   !! imp.. example of drugs : A) neuroleptics, B) tricyclic antidepressants, C) antianginals agent (perihexiline), D) antiarrhythmics (propafenone & metoprolol)

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

REMEMBER:

therapeutic dose

يعني الطبيب يعطي كل شيء تمام ولا فيه أي مشكلة ظاهرية ، لكن لعدم العلم بوجود هذه المشكلة الجينية يحصل هذا التفاعل الخطير ،،

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