Structure & Distribution

They are heme-containing isoenzymes

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

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).

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

Phase II: CONGUGATION (ADDITION) e.g(Glucuronidation)

Function:

Responsible for most of the OXIDATIVE METABOLISM of:

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

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.

Drug Metabolisim

Elimination

If it is polar (water soluble) ➔ renal elimination

If non polar(lipid soluble) ➔ billiary elimination

metabolism products

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

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 metabolize.

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

-↑ Metabolism of the inducer + ↓ its pharmacological action. (Decrease or absence of the response to the drug)

-↑metabolism of co-administered drugs.

IN RELATION TO Enzyme INHIBITORS:

-they increase the TOXCICITY of the drug

-↓or Retard (slow) metabolism & excretion of inhibitor & co-administered drugs.

-↑ or prolong action of the inhibitor & co-administered drugs.

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 (PXR will not be activated) ➔ REPRESSION of CYT P450 isoenzymes to ➔↓metabolism of Drug B

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

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

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 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 **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