Microsomal Enzyme Induction & Enzyme Inducers

Drug (Lipophilic) Non polar —Metabolised (Microsomal Enzymes)→ Metabolite (Hydrophilic) Polar —Excreted→ Urine or Faeces

Microsomal Enzymes

eg. Cytochrome P450

More than 100 cytochrome P450 enzymes are known.

CYP3A4/5: Metabolise more than 50% drugs.

Other important enzymes are CYP2D6, CYP2C8/9, CYP2C19 etc.

Enzyme Induction refers to increase in the biosynthesis of microsomal enzymes specifically Cytochrome P450. This causes increased drug Metabolism.

Enzyme Inducers: eg. Rifampicin, Barbiturates, Phenytoin induce CYP3A4/5.

Some Enzyme Inducers:

- → Rifampicin
- → Phenobarbitone
- → Phenytoin
- → Carbamazepine
- → Cigarette Smoking
- → Griseofulvin
- → Glutethimide
- → Ethanol (chronic intake)

Consequences of Enzyme Induction:

I. Loss of Therapeutic Activity:

CYP form	Substrate (Drug)	Enzyme Inducers
CYP3A4	Oral Contraceptives (Estrogen & Progesterone)	Rifampicin Phenobarbitone Phenytoin.

→ Rifampicin, Phenobarbitone, Phenytoin induce CYP3A4, enhancing metabolism of oral contraceptives, thereby reducing their efficacy in preventing pregnancy.

Significance of Enzyme Induction:

II. Increased Drug toxicity

CYP form	Substrate (Drug)	Enzyme Inducer
CYP2E1	Acetaminophen (Paracetamol)	Ethanol (Chronic Intake)

Ethanol (Chronic Intake)
↓ Induce CYP2E1
Enhanced Acetaminophen Metabolism
↓
↑ N-acetyl-p-benzoquinone imine (Toxic Metabolite)
↓
Hepatic Toxicity

→ Chronic Ethanol causes Enzyme induction & increases paracetamol toxicity.

* Clinical Effect –

① Therapeutic Failure – ↓ Duration of action – Failure of oral contraceptive taking – Rifampicin
② Toxicity – Due to ↑ toxic metabolite – Paracetamol + Rifampicin
③ Tolerance to drug – with Carbamazepin (Auto Induction)
④ Result in Disease – Antiepileptic → ↑ Breakdown of vit D = Osteomalacia
⑤ Variable Response – Chronic Smokers and Alcoholics = Response = ∩
*⑥ Therapeutic Application – Neonates have less Microsomal enzyme, so their abi
conjugate with Bilirubin is low = Jaundic, Treated by – Phenobarbitone

Polar (water so
↓
Kidne
↓
Elimination
↓
No-retaint
(Reg. out p

Microsomal Enzyme Induction & Enzyme Inducers

→ Different Cytochrome P450 enzymes are involved in the metabolism of different drugs.

→ Enzyme Inducers increase Metabolism of drug metabolised by induced enzyme.

→ Drugs like Rifampicin, Phenobarbitone, Phenytoin induce CYP3A4/5 & thus affect Metabolism of large number of drugs.

→ Most inducing agents administered in therapeutic doses produce maximum effect within 14 days.

Microsomal Enzyme Inhibition & Enzyme Inhibitors

Drug (Lipophilic) Non Polar —Metabolized (Enzymes)→ Metabolite (Hydrophilic) Polar —Excreted→ Urine or Faeces

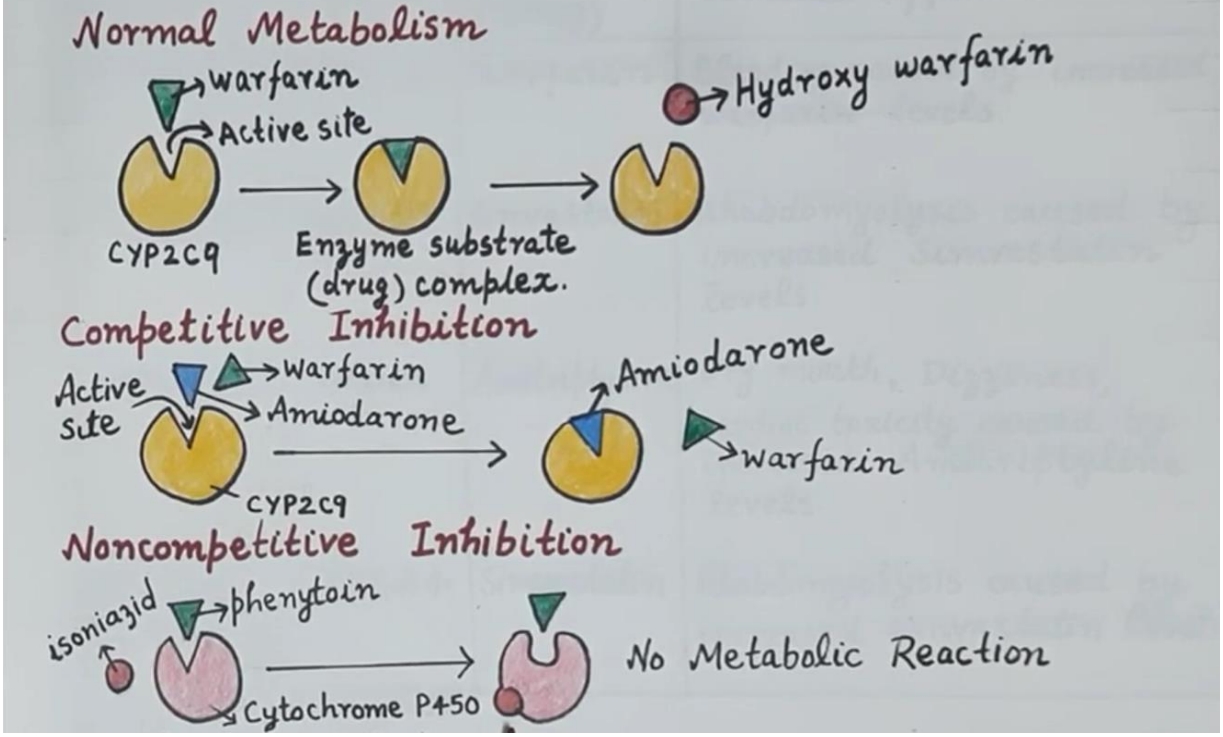
Microsomal Enzymes: eg. Cytochrome P450.
CYP3A4/5 Metabolise more than 50% drugs.

Enzyme Inhibition refers to decrease in enzyme activity. This leads to reduced metabolism of drug. This can further cause serious adverse effects.

Enzyme Inhibitors block the metabolic activity of one or more than one CYP450 enzymes.
CYP3A4/5: Inhibited by Erthromycin, Clarithromycin, Ketoconazole, Itraconazole, Verapamil, Diltiazem etc.

Mechanism of Action of Enzyme Inhibitors

Enzyme inhibitors competitively or noncompetitively inhibit metabolism of substrate (drug).



Consequences of Enzyme Inhibitors:

Enzyme Inhibitor	Enzyme	Substrate (Drug)	Clinical Effects.
Amiodarone	CYP2C9	Warfarin	Bleeding caused by increased warfarin levels.
Erythromycin	CYP3A4	Simvastatin	Rhabdomyolysis caused by increased Simvastatin levels.
Terbinafine	CYP2D6	Amitriptyline	Dry mouth, Dizziness, cardiac toxicity caused by increased Amitriptyline levels.

Microsomal Enzyme Inhibition

Inhibition of cytochrome-P-450 by different drugs is called - Inhibition

points - ① cimetidine, Ketoconazole binds to cytochrome P450 and competitively inhibit metabolism of - Testosterone.

Enzyme Inhibitors — ① Chloramphenicol ② Erythromycin ③ Ketoconazole ④ Cimetidine ⑤ Ciprofloxacin

Suicide Inhibitor - Irreversible binding = Inactivation of enzyme

Exa - ① Selegiline ② Ticlopidine

Types :- ① (A) Microsomal (B) Non-Microsomal
② (A) Competitive (B) Non-Competitive

Competitive — Structurally similar to natural substrate.

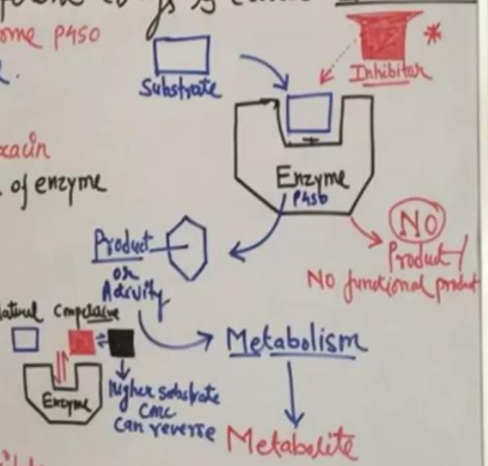
Exa - Xanthine oxidase inhibition by - Allopurinol

Note :- Binding with co-valent bonds = Non Reversible.

Exa - organophosphate inhibiting Acetylcholinesterase

Non-competitive - Generally irreversible because formation of Enzyme-Substrate complex is stopped by changing the shape of Enzyme

Exa :- ① Statins Inhibit - HMG-CoA reductase



Drug	Competi. Enzyme Inhibited
Captopril	ACE
Allopurinol	Xanthine oxidase
Sulfonamide	Folic & Synthetase
Meclobemide	MAO-A
Non-competitive	
Disulfiram	Aldehyde Dehydrogenase
statins	HMG CoA reductase
Digoxin	Na^+-K^+ ATPase