METABOLISM

OUTLINE

- Definition
- Sites of metabolism.
- Types of metabolic reactions.
- Modulation of liver microsomal enzymes.
- First pass metabolism.

Drug Metabolism (Biotransformation)

Definition

- Chemical reactions which lead to modification of drugs.

Importance

- Termination of drug action
- Enhance excretion by transforming the drug to a less lipid-soluble, less-readily reabsorbed form.

Sites

1. Liver (the major site)

- Cytoplasm..
- Microsomes.
- Mitochondria

2. Extra hepatic tissues

- Plasma
- Kidney
- Lung

II. EXTRAHEPATIC SITES

- Plasma
  - COMT (Catechol o-methyl transferase).
  - Esterases.
  - Amidases.
- Kidney
- Skin
- Lung

Intestinal Mucosa and Lumen

- **Gut Flora**
- Glucouronidase.
- Azoreductase.

- **Gut Mucosa**
- Monoamine Oxidase.
- Sulphatase.

TYPES OF METABOLIC REACTIONS

- Phase I Reactions (Nonsynthetic).
- Phase II Reactions (synthetic)

Phase I Reactions (Nonsynthetic)•

- Oxidation.
- Reduction.
- Hydrolysis.

I. Oxidation Reactions

- Introduce or unmask functional groups (OH)
- Microsomal (CYT-P450-dependent).
- Non-microsomal (CYT-P450-independent).

Microsomes

- Microsomal enzyme system = mixed function oxidase = mono-oxygenase=CYT -P450.
- Components
  - Cytochrome P-450.
  - NADPH.
  - NADPH-CYT P 450 reductase
  - Molecular oxygen, Mg^{++}.
  - In all cells, mostly in liver and intestinal mucosa

Microsomal Oxidations

Drug + O2 + NADPH + H^+ $\longrightarrow$ changed drug + H2O + $NADP^+$.

Aliphatic hydroxylation.

Aromatic hydroxylation

N-Dealkylation

N-oxidation (Amine Oxidation)

S-oxidation (Sulphoxidation)

Non-microsomal Oxidation

- Oxidation by soluble enzymes in cytosol or mitochondria of cells.

- Dehydrogenases

Ethanol ⟶ acetaldehyde ⟶ acetic acid.

$CH_3CH2OH \rightarrow CH_3CHO \rightarrow CH3COOH$

- Oxidases

II. Reductions

- **Microsomal**

  $NO_2 \rightarrow NH_2$

- **Non microsomal**

  Chloral hydrate → Trichloroethanol (active)

  $CCl_3 - CHO \rightarrow CCl_3 - CH_2OH$

III. Hydrolysis•

- All are NON microsomal
- Important for drugs as esters-C-O- and amides –C-N-

Acetylcholine →choline + acetate.

$$R1\text{-}COOR2 \longrightarrow R1COOH + R2OH.$$

Procainamide (lidocaine, local anaesthetic).

$$R1 - CONH - R2 \longrightarrow R1 - COOH + R2NH2.$$

Characteristics of Phase I products•

1. Inactivation (Abolish the activity).
2. Conversion of active drug to another active one.
3. Conversion of drugs to toxic metabolites.
   - Paracetamol → acetaminophen hepatotoxicity
4. Activation of prodrug
5. Product might undergo phase II.

Phase II Conjugation Reactions (Synthetic Reactions)

Conjugation of drug or metabolite (phase I) with endogenous substance as methyl group, acetyl group, sulphate, amino acid or glucouronic acid.

Types of Phase II Reactions

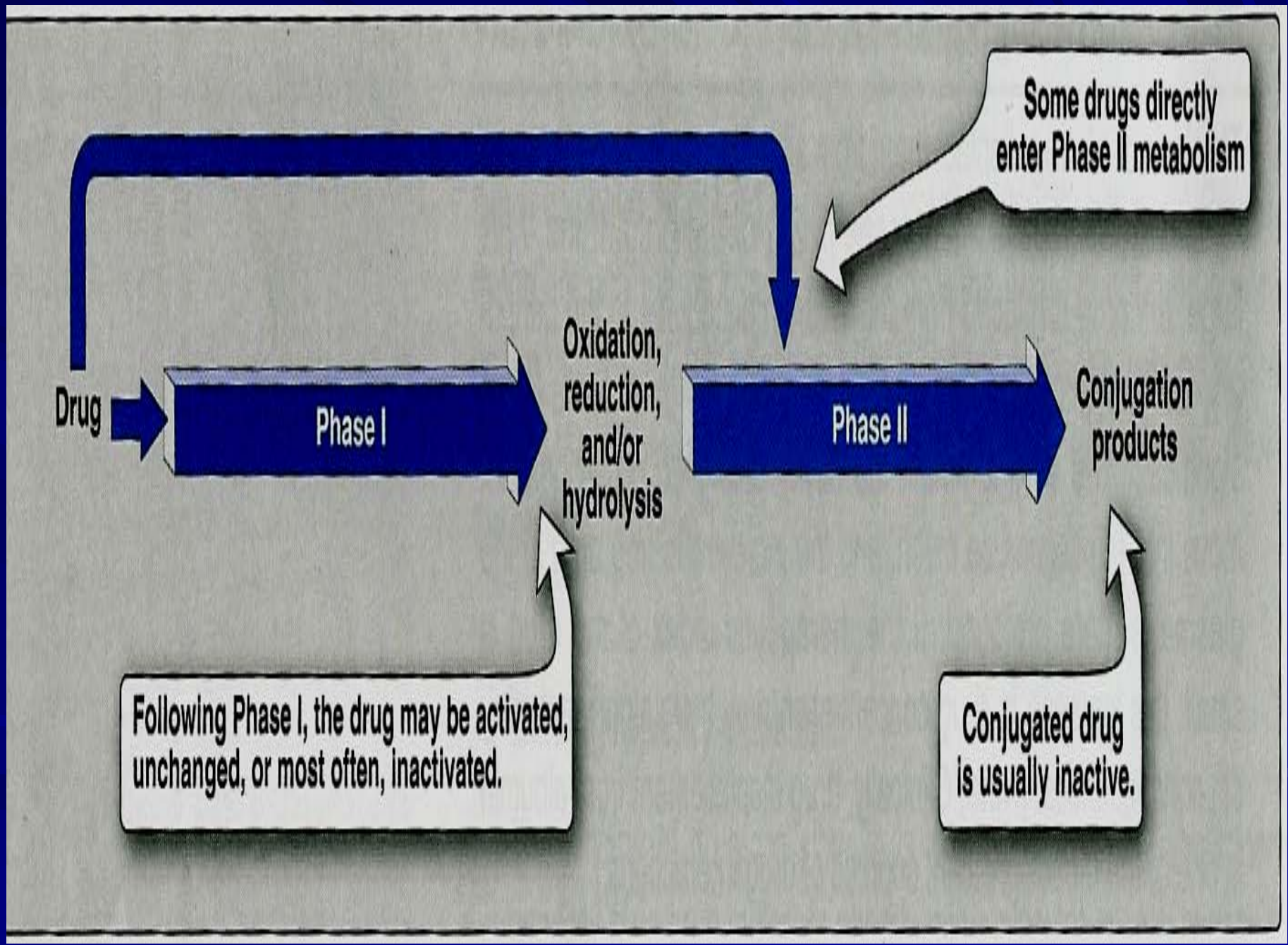
- Glucouronide conjugation.
- Amino acids e.g. glycine.
- Acetylation reactions: CH_3-CO
- Sulphate conjugations. SO4
- Methylation reactions e.g.CH_3

Characters of phase II Reactions

- Non microsomal **EXCEPT** Glucouronidation (Catalyzed by glucouronyl transferase).
- Glucouronidation is
  - The most common reaction
  - The most important reaction.
  - Deficient in neonates chloramphenicol (**Gray baby syndrome**).

Characteristics of Phase II Products

- Product = Conjugate
- Usually Pharmacologically inactive.
- Polar
- more water soluble.
- more readily excreted in urine.


Some drugs directly enter Phase II metabolism
Drug
Phase I
Oxidation, reduction, and/or hydrolysis
Phase II
Conjugation products
Following Phase I, the drug may be activated, unchanged, or most often, inactivated.
Conjugated drug is usually inactive.

(Modulation of liver microsomal enzymes) by co administration of other drugs

- Induction of liver microsomal enzymes
- Inhibition of liver microsomal enzymes

Liver Microsomal Inducers

- Alcohol
- Cigarette smoking
- Barbiturates (Phenobarbitone, hypnotic)
- Phenytoin (antiepileptic)
- Rifampicin (Anti TB)
- Griseofulvin (antifungal).

Enzyme induction may result in:

- Increase metabolism of the inducer.
- Decrease its pharmacological action.

  (TOLERANCE).
- Increase the metabolism of co-administered drugs (drug interactions)

  Phenytoin & Oral contraceptives.
- Increase tissue toxicity by metabolite
- As Therapy

Liver Microsomal Inhibitors

- Cimetidine (anti-peptic ulcer)
- Erythromycin (antibiotic)
- Ketoconazole (antifungal)
- Grape fruits
- Isoniazid
- Disulfuram
- Chloramphenicol
- Primaquine
- Probenicid

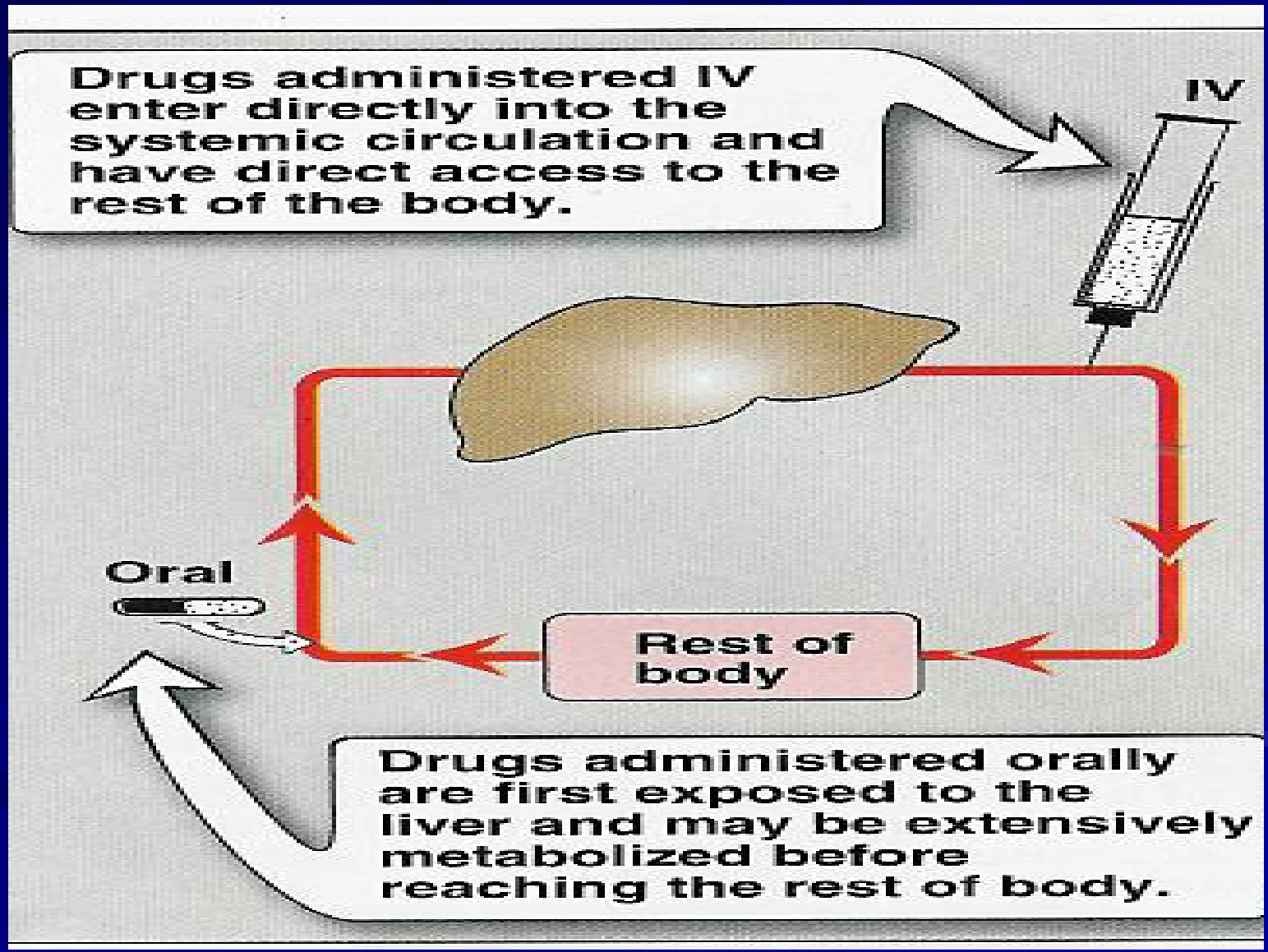
Enzyme inhibition may

- retard the metabolism and excretion of the inhibitor and co-administered drugs.
- prolong the action of the inhibitor & co-administered drugs.

First pass Metabolism

- Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into systemic circulation.
- Drug can be metabolized before reaching the systemic circulation.
- so the amount reaching system circulation is less than the amount absorbed

First pass effect



First pass Metabolism

Where ?

- **Liver**
- **Gut wall**
- **Gut Lumen**

Result ?

Low bioavailability.

Short duration of action (t ½)

How it is given ?