Biotransformation

EO

Lecture objectives

- Understand human disposition of xenobiotics
- Biological processes that convert xenobiotics to disposable metabolites

(Xeno– foreign)

Drug Pharmacokinetics

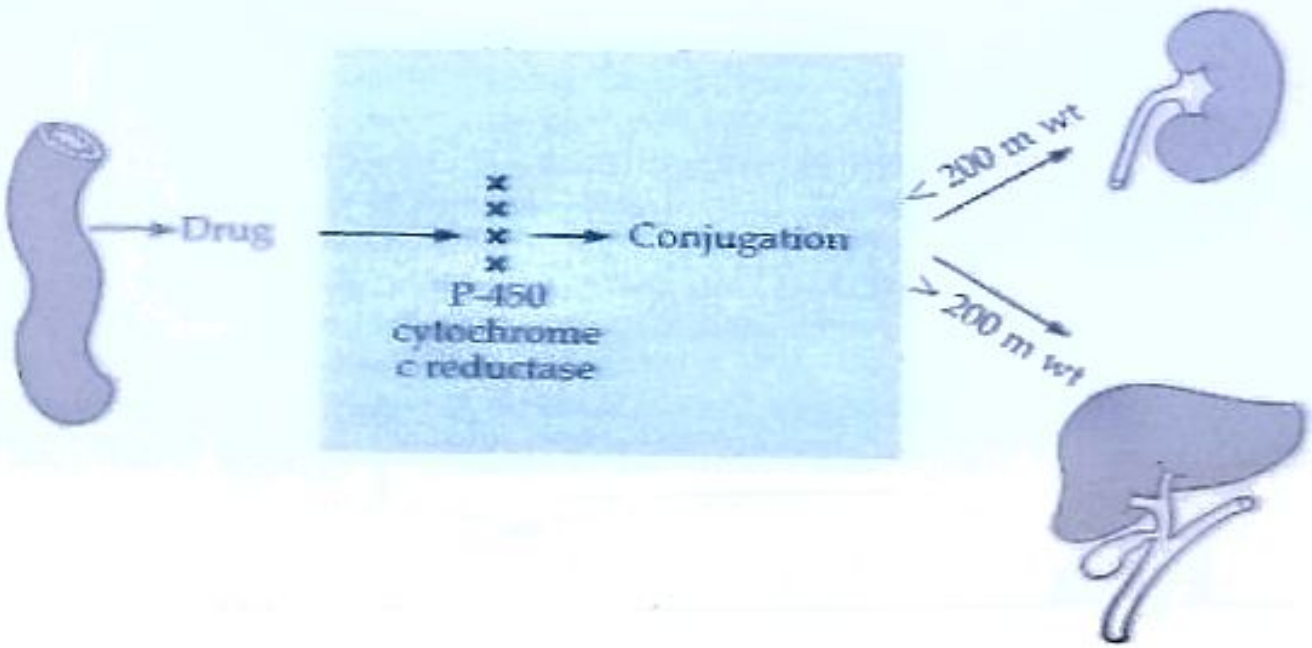


Fig. 18.1. Hepatic drug metabolism (Sherlock, 1979).

- Renal route - excretion to terminate drug activity
- Must be : - small molecules
  - polar compounds
  - fully ionised at physiological PH

Why biotransformation ?

- Pharmacologically active organic molecules tend to be -lipophilic
  - unionised or partially ionised at physiologic PH .
  - PPB strongly (not readily filtered)
  - reabsorbed by the lipophilic renal tubule (hydrophobic drugs)
- Prolonged duration of action -consequence

Metabolism

- Lipophilic compounds transformed to more polar to enhance disposition of drugs
- Inactivates lipid soluble drugs to more water soluble compounds
  - e.g. Phenobarbitone and thiopental
- Lipophilic - reservoir or repository
- Metabolites less active or inactive
- Some may ↑activity or toxicity

Site of biotransformation

- Between absorption and renal elimination
- Intestinal lumen and wall
- Liver is the principle organ of metabolism
- GIT,lung,skin, and kidney

Biotransformation processes

- PO→Portal system → liver (first pass effect)
- First pass -Hepatic
  -GIT(intestinal metabolism)
    - e.g. Clonazepam
      Chlorpromazine
    - lower GIT intestinal microbes
    - Upper GIT-gastric acid
    - Enzymes in the intestinal wall

Mechanisms of biotranformation

- Spontaneous non-catalysed chemical reactions
- Enzyme processes- cellular enzymes in the ER, mitochondria, cytosol, lysosomes ,nuclear envelope and plasma membrane

Types of metabolic processes

- Phase 1 - parent made more polar
  - introduce or unmasking -OH ,-NH_2, -SH
- Metabolites inactive or modified activity
- Excretion of polar compound expedited

- Phase 11 - conjugation to make compound more polar
  - glucuronidation, sulfation , acetylation ,addition of amino acid group

Phase 1 Metabolism

- Involve enzymes in the lipophilic membranes of the ER of the liver and other tissue
- Found in vesicles- microsomes
- Smooth microsomes contain enzymes involved in oxidative drug metabolism i.e. Mixed Functional Oxidaese or Monooxygenases- use NADPH and Oxygen
- Oxidation - reduction reaction use :-

  -flavoprotein - NADPH- Cytochrome c reductase (electron acceptor $NADP^+$)

  -haemoprotein- NADPH -Cytochrome P_{450} reductase (terminal oxidase)

Enzyme induction

- CYP enzyme induction occurs on repeated administration of some substrates
- i.e. by enhancing the rate of enzyme synthesis or reducing the rate of enzyme degradation
- Result in the increased metabolism of inducer and co-administered drugs and reduction in their pharmacologic effect
- Reactive metabolites from increased metabolism can increase toxicity

Q1

1. List some of the drugs that induce the cytochrome p450 microsomal enzymes
2. Which are some of the phase 1 reaction classes ?

Enzyme inhibition

- Inhibition of CYP activity
- May act by binding on the heme iron of CYP450 and reduce substrate metabolism

Q2

- List some of the CYP450 enzyme inhibitors

Phase 11 reactions

- Parent drug or their phase 1 metabolite conjugates with endogenous substance to yield a conjugate that are polar
- Phase 11 metabolites are inactive and readily excreted

Q3

Which are the phase 11 metabolic processes?

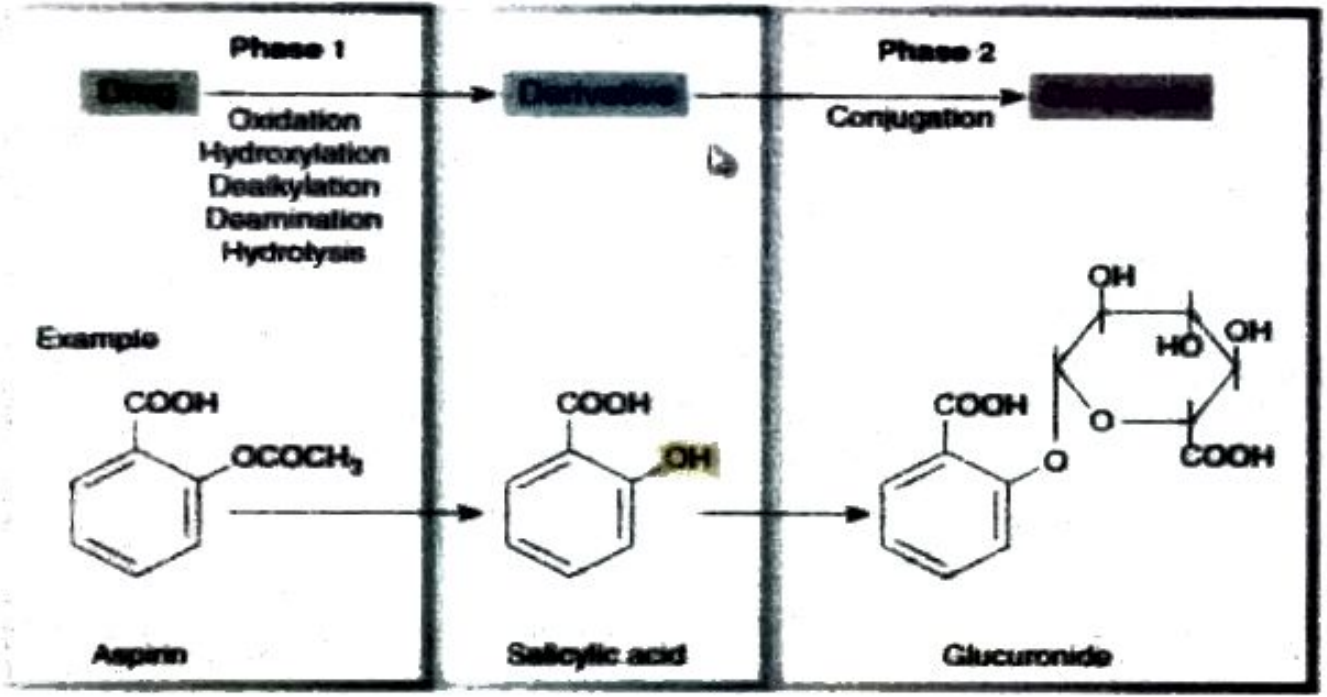


Fig. 9.1 The two phases of drug metabolism.

- **Read**
  - **Rang and Dale**
  - **Katzung**
  - **Lippincort**

Biotransformation of drugs
Phase 1 reactions

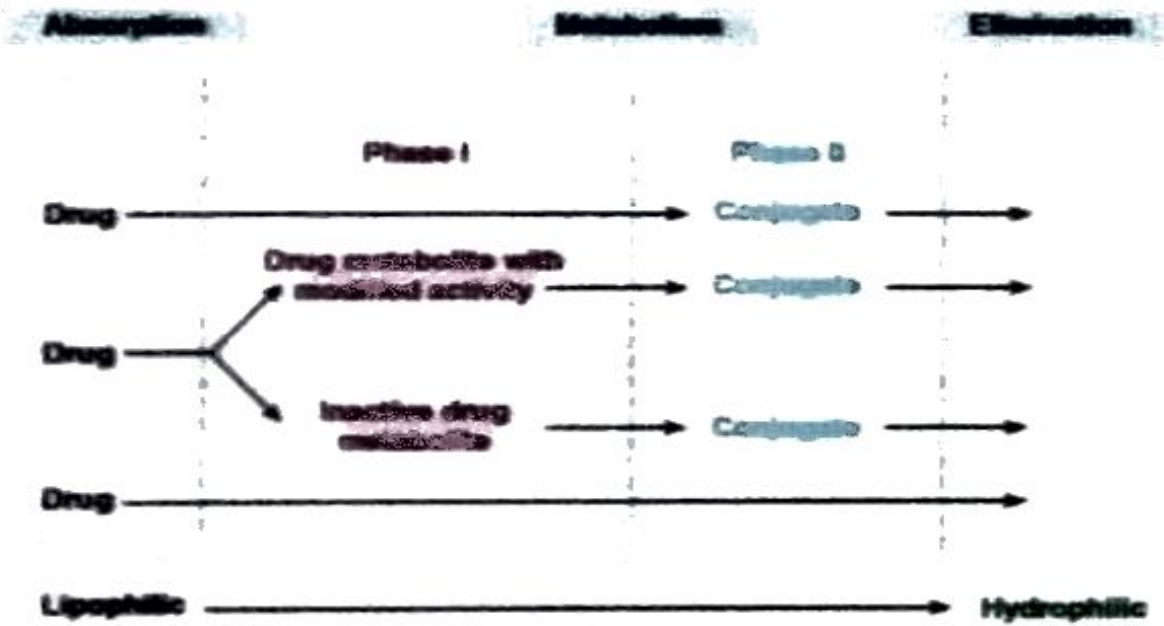
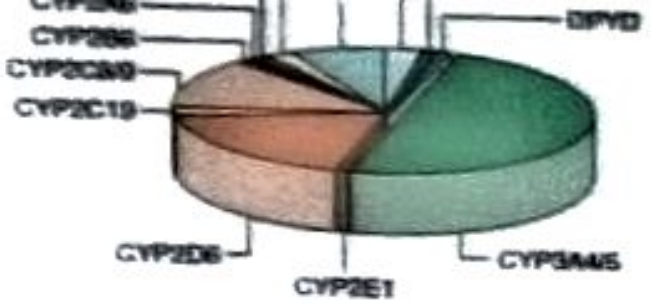


FIGURE 4–1 Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I reactions.



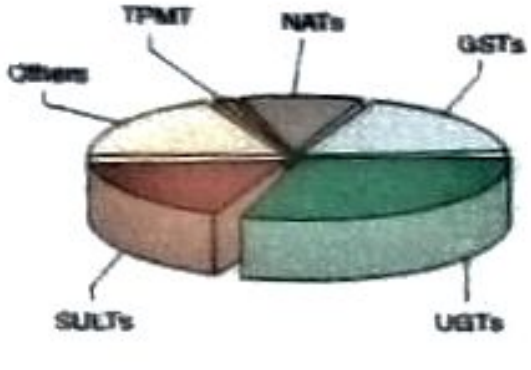


FIGURE 4–4 Relative contributions of various cytochrome P450 isoforms (**A**) and different phase II pathways (**B**) to metabolism of drugs in clinical use. Many drugs are metabolized by two or more of these pathways. Note that two pathways, CYP3A4/5 and UGT, are involved in the metabolism of more than 75% of drugs in use. DPYD, dihydropyrimidine dehydrogenase; GST, glutathione-*S*-transferase; NAT, *N*-acetyltransferase; SULT, sulfotransferase; TPMT, thiopurine methyltransferase; UGT, UDP-glucuronosyltransferase. (Reproduced, with permission, from Rowland M, Lam G, Parker RJ: Goodman & Gilman's the

Example of drug biotransformation

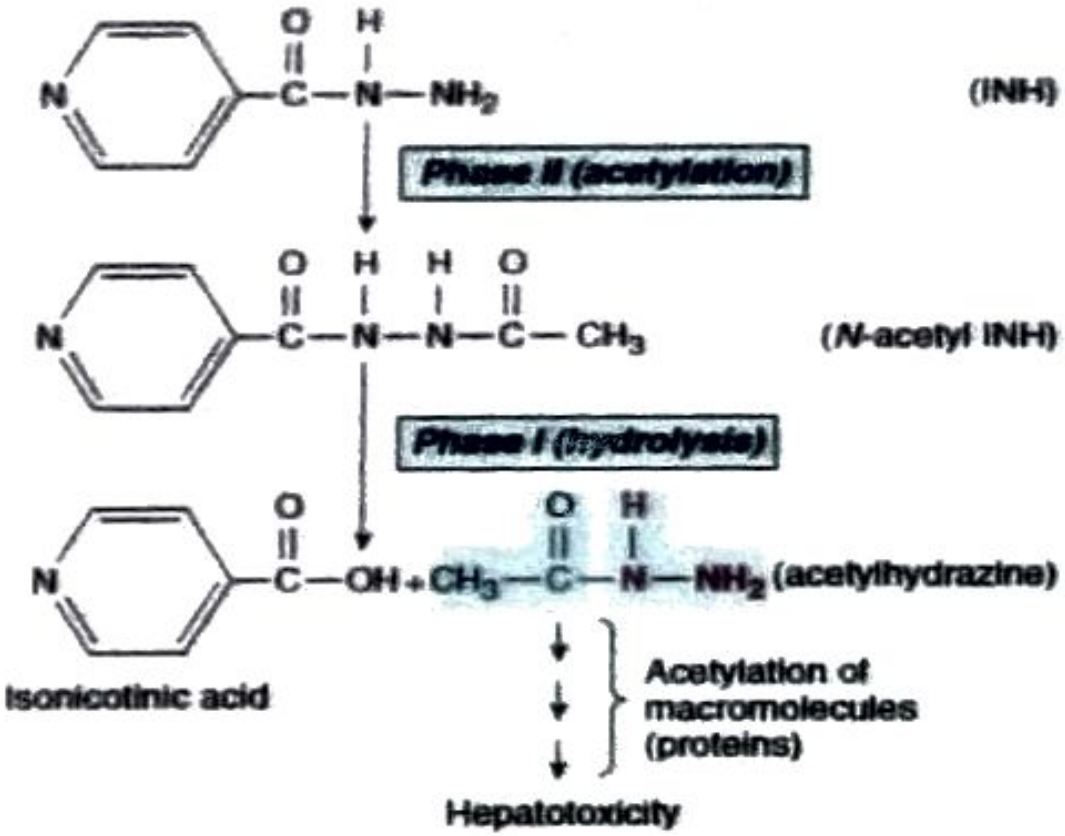


FIGURE 4–2 Phase II activation of isoniazid (INH) to a hepatotoxic metabolite.

Phase II metabolism may precede phase I

Clinical relevance of drug metabolism

- Determines dose and dosing frequency
- Influenced by genetic and non-genetic factors

Genetic variation

- **Enzyme polymorphisms**
- Review the variation in metabolism of the following :-
  - succinylcholine
  - isoniazid
  - warfarin

Non-genetic variables

- Age
- Sex
- Liver size and function
- Circadian rhythm
- Body temperature
- Nutritional and environmental factors
- Concomitant drug interaction