Drug Metabolism in the Liver

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KEYWORDS

• Drug metabolism • Cytochrome P450 • Conjugation • Drug transporters
• Liver metabolism • Phase I, II, and III metabolism enzyme

KEY POINTS

- Drug metabolism typically results in the formation of a more hydrophilic compound that is readily excreted by the liver, kidney, and/or gut.
- Drug metabolism involves chemical biotransformation of drug molecules by enzymes in the body; in addition, drug transporters facilitate movement of drugs and metabolites in and out of cells/organs.
- In rare cases, a metabolite formed from a drug can cause hepatotoxicity.
- Several disease states and altered physiologic conditions can affect the efficiency of the drug metabolic or transport processes.
- Certain pathophysiologic conditions and use of certain concomitant medications can alter the metabolism or transport of drugs and metabolites and result in altered pharmacokinetic and/or pharmacodynamics of certain drugs.

INTRODUCTION

Drugs are typically small molecules that are generally classified as xenobiotics, which are foreign to the human body. Several endogenous molecules, however, such as steroids and hormones, are also used for the treatment of certain disease conditions and are also referred to as drugs. The term, *metabolism*, refers to the process of transformation of chemicals from one chemical moiety to another by an enzyme. The most well-known drug-metabolizing enzymes are cytochrome P450s (CYP450s), which

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are mainly oxidases, reductases, and hydrolases. The primary purpose of metabolism is to clear endogenous and/or exogenous molecules from the body. Typically, the process of metabolism converts lipophilic chemicals to hydrophilic products to facilitate elimination.[1,2] In certain instances, however, drug-metabolizing enzymes convert substances into their pharmacologically active form. For example, prodrugs (pharmacologically inactive) are synthesized to overcome absorption/bioavailability issues and they are converted to activate drug after being absorbed into the body. To overcome the low bioavailability of ampicillin, pivampicillin is synthesized as a prodrug, which can be hydrolyzed into ampicillin after being absorbed into the blood stream. Another important example of a prodrug is the use of mycophenolate mofetil to increase the oral bioavailability of mycophenolic acid.[3] Mycophenolic acid is used as immunosuppressant in transplant recipient to prevent acute rejection.[4]

The by-products of metabolism are known as metabolites; they can be either pharmacologically active or inactive.[5] CYP450 enzymes that play a major role in drug elimination are mainly present on the smooth endoplasmic reticulum (ER) and mitochondria of the hepatocytes and small intestinal epithelia and to a lesser extent in the proximal tubules of the kidneys.[6] The contribution and importance of conjugating enzymes and drug transporters are increasingly appreciated.[7] These pathways interplay during the absorption, distribution, metabolism, and excretion of drugs, and any alterations may result in changes in the pharmacokinetics and pharmacodynamics of a drug.

This article discusses the major drug-metabolizing/eliminating pathways: phase I, phase II, and phase III (**Table 1**). Additionally, the contribution of the primary organs (liver, gut, and kidneys) involved in drug metabolism is reviewed. In the last part, major factors that could affect these pathways are summarized.

DRUG METABOLISM PATHWAYS

Phase I Pathway

The most common phase I drug-metabolizing enzymes are represented by CYP450 superfamily. CYP450s are the major group of enzymes that chemically modify drugs

Table 1
Summary of main role of liver, gut, and kidneys in the 3 drug metabolism pathways

	Liver	Gut	Kidneys
Pathway I	Hepatic CYP450s are very important in metabolism of xenobiotics and endogenous molecules.	Enterocytes contain enzymes that can metabolize xenobiotics.	Minimal metabolism activity but important in steroid metabolism
Pathway II	Liver expresses UGTs and other conjugation enzymes; UGTs metabolize approximately 40%–70% of the xenobiotics.	Intestinal enterocytes participate in phase II drug metabolism as well.	Kidney also makes significant contribution in phase II drug metabolism, but GST is the main conjugating enzyme in kidney.
Pathway III	Drug transporters uptake compounds into hepatocytes and efflux into bile.	P-gp is well known to decrease the bioavailability of several drugs because of efflux mechanism into the gut.	They are important to actively efflux drugs into the urine.