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Metabolism plays a central role in the elimination of drugs and other foreign compounds *(xenobiotics)* from the body. A solid understanding of drug metabolic pathways is an essential tool for pharmacists in their role of selecting and monitoring appropriate drug therapy for their patients. Most organic compounds entering the body are relatively lipid soluble *(lipophilic)*. To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract. Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions. Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine. Xenobiotics then meet their metabolic fate through various enzyme systems that change the parent compound to render it more water soluble *(hydrophilic)*. Once the metabolite is sufficiently water soluble, it may be excreted from the body. The statements above show that a working knowledge of the ADME (absorption, distribution, metabolism, and excretion) principles is vital for successful determination of drug regimens.

If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects. Thus, the formation of water-soluble metabolites not only enhances drug elimination, but also leads to compounds that are generally pharmacologically inactive and relatively nontoxic. Consequently, drug metabolism reactions have traditionally been regarded as *detoxication* (or *detoxification*) processes.[1] Unfortunately, it is incorrect to assume that drug metabolism reactions are always detoxifying. Many drugs are biotransformed to pharmacologically active metabolites. These metabolites may have significant activity that contributes substantially to the pharmacological or toxicological effect(s) ascribed to the parent drug. Occasionally, the parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite).[2, 3] These types of compounds are referred to as *prodrugs*. In addition, it is becoming increasingly clear that not all metabolites are nontoxic. Indeed, many adverse effects (e.g., tissue necrosis, carcinogenicity, teratogenicity) of drugs and environmental contaminants can be attributed directly to the formation of chemically reactive metabolites that are highly detrimental to the body.[4–6] This concept is more important when the patient has a disease state that inhibits or expedites xenobiotic metabolism. Also, more and more drug metabolites are being found in our sewage systems. These compounds may be nontoxic to humans but harmful to other animals or the environment.

GENERAL PATHWAYS OF DRUG METABOLISM

Drug metabolism reactions have been divided into two categories: *phase I (functionalization)* and *phase II (conjugation)* reactions.[1, 7] Phase I, or functionalization reactions, include oxidative, reductive, and hydrolytic biotransformations (Table 4-1).[8] The purpose of these reactions is to introduce a functional polar group(s) (e.g., OH, COOH, NH_2, SH) into the xenobiotic molecule to produce a more water soluble compound. This can be achieved by direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation) or by modifying or ''unmasking'' existing functionalities (e.g., reduction of ketones and aldehydes to alcohols; oxidation of alcohols to acids; hydrolysis of ester and amides

TABLE 4–1 General Summary of Phase I and Phase II Metabolic Pathways

Phase I or Functionalization Reactions
Oxidative reactions
Oxidation of aromatic moieties
Oxidation of olefins
Oxidation at benzylic, allylic carbon atoms, and carbon atoms α to carbonyl and imines
Oxidation at aliphatic and alicyclic carbon atoms
Oxidation involving carbon–heteroatom systems:
Carbon–nitrogen systems (aliphatic and aromatic amines; includes N-dealkylation, oxidative deamination, N-oxide formation, N-hydroxylation)
Carbon–oxygen systems (O-dealkylation)
Carbon–sulfur systems (S-dealkylation, S-oxidation, and desulfuration)
Oxidation of alcohols and aldehydes
Other miscellaneous oxidative reactions
Reductive Reactions
Reduction of aldehydes and ketones
Reduction of nitro and azo compounds
Miscellaneous reductive reactions
Hydrolytic Reactions
Hydrolysis of esters and amides
Hydration of epoxides and arene oxides by epoxide hydrase
Phase II or Conjugation Reactions
Glucuronic acid conjugation
Sulfate conjugation
Conjugation with glycine, glutamine, and other amino acids
Glutathione or mercapturic acid conjugation
Acetylation
Methylation

acid, sulfate, glycine, and other amino acids to the functional "handles" of phase I metabolites or parent compounds that already have suitable existing functional groups to form water-soluble conjugated products. Conjugated metabolites are readily excreted in the urine and are generally devoid of pharmacological activity and toxicity in humans. Other phase II pathways, such as methylation and acetylation, terminate or attenuate biological activity, whereas glutathione (GSH) conjugation protects the body against chemically reactive compounds or metabolites. Thus, phase I and phase II reactions complement one another in detoxifying, and facilitating the elimination of, drugs and xenobiotics.

To illustrate, consider the principal psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC, also known as Δ^1-THC, depending on the numbering system being used). This lipophilic molecule (octanol/water partition coefficient ~6,000)[9] undergoes allylic hydroxylation to give 11-hydroxy-Δ^9-THC in humans.[10, 11] More polar than its parent compound, the 11-hydroxy metabolite is further oxidized to the corresponding carboxylic acid derivative Δ^9-THC-11-oic acid, which is ionized (pK_a COOH ~5) at physiological pH. Subsequent conjugation of this metabolite (either at the COOH or phenolic OH) with glucuronic acid leads to water-soluble products that are readily eliminated in the urine.[12]

In the above series of biotransformations, the parent Δ^9-THC molecule is made increasingly polar, ionizable, and hydrophilic. The attachment of the glucuronyl moiety (with

are presented. Drug metabolism examples in humans are emphasized, although discussion of metabolism in other mammalian systems is necessary. The central role of the cytochrome P-450 monooxygenase system in oxidative drug biotransformation is elaborated. Discussion of other enzyme systems involved in phase I and phase II reactions is presented in their respective sections. In addition to stereochemical factors that may affect drug metabolism, biological factors such as age, sex, heredity, disease state, and species variation are considered. The effects of enzyme induction and inhibition on drug metabolism and a section on pharmacologically active metabolites are included.

SITES OF DRUG BIOTRANSFORMATION

Although biotransformation reactions may occur in many tissues, the liver is, by far, the most important organ in drug metabolism and detoxification of endogenous and exogenous compounds.[13] Another important site, especially for orally administered drugs, is the intestinal mucosa. The latter contains the cytochrome P-450 (CYP) 3A4 isozyme (see discussion on cytochrome nomenclature below) and P-glycoprotein that can capture the drug and secrete it back into the intestinal tract. In contrast, the liver, a well-perfused organ, is particularly rich in almost all of the drug-metabolizing enzymes discussed in this chapter. Orally administered