BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

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Volume I: Principles and Practice

Edited by

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CHAPTER SIX

Drug Metabolism

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1 INTRODUCTION

Xenobiotic metabolism, which includes drug metabolism, has become an important pharmacological science with particular relevance to biology, therapeutics, and toxicology. Drug metabolism also is of great importance in medicinal chemistry, because it influences in qualitative, quantitative, and kinetic terms the deactivation, activation, detoxication, and toxication of the vast majority of drugs. As a result, medicinal chemists engaged in drug discovery (lead finding and optimization) must be able to integrate metabolic considerations into drug design. To do so, however, requires a fair or even good knowledge of xenobiotic metabolism.

This chapter presents knowledge and understanding rather than encyclopedic information. Readers wanting to go further in the study of xenobiotic metabolism should consult available references (1–3).

1.1 Definitions and Concepts

Drugs are but one category of the many xenobiotics (Table 6.1) that enter the body but have no nutritional or physiological value. The study of the disposition (or fate) of xenobiotics in living systems includes the consideration of their absorption into the organism, how and where they are distributed and stored, the chemical and biochemical transformations they may undergo, and how and by what route(s) they are finally excreted and returned to the environment. The word metabolism has acquired two meanings: it is synonymous with (*1*) disposition (i.e., the sum of the processes affecting the fate of a chemical substance in the body) and (*2*) biotransformation as understood in this chapter (5).

In pharmacology, one speaks of pharmacodynamic effects to indicate what a drug does to the body and pharmacokinetic effects to indicate what the body does to a drug; these two aspects of the behavior of xenobiotics are strongly interdependent. Pharmacokinetic effects will obviously have a decisive influence on the intensity and duration of pharmacodynamic effects, while metabolism will generate new chemical entities (metabolites) that may have distinct pharmacodynamic properties of their own. Conversely, by its own pharmacodynamic effects, a compound may affect the state of the organism (e.g., hemodynamic changes and enzyme activities) and hence its capacity to handle xenobiotics. Only a systemic approach can help one appreciate the global nature of this interdependence (6).

1.2 Types of Metabolic Reactions Affecting Xenobiotics

A first discrimination that can be made among metabolic reactions is based on the nature of their catalysts. Reactions of xenobiotic metabolism, like other biochemical reactions, are catalyzed by enzymes. However, while the vast majority of reactions of xenobiotic metabolism are indeed enzymatic ones, some nonenzymatic reactions are also well documented. This is due to the fact that a variety of xenobiotics have been found to be labile enough to react nonenzymatically under biological conditions of pH and temperature (7). But there is more. In a normal enzymatic reaction, metabolic intermediates exist en route to the product(s) and do not leave the catalytic site. However, many exceptions to this rule are known: the metabolic intermediate leaves the active site and reacts with water, an endogenous molecule or macromole-

Table 6.1 Major Categories of Xenobiotics[a]

Drugs
Food constituents devoid of physiological roles
Food additives (preservatives, coloring and flavoring agents, antioxidants, etc.)
Chemicals of leisure, pleasure, and abuse (ethanol, coffee and tobacco constituents, hallucinogens, etc.)
Agrochemicals (fertilizers, insecticides, herbicides, etc.)
Industrial and technical chemicals (solvents, dyes, monomers, polymers, etc.)
Pollutants of natural origin (radon, sulfur dioxide, hydrocarbons, etc.)
Pollutants produced by microbial contamination (e.g., aflatoxins)
Pollutants produced by physical or chemical transformation of natural compounds (polycyclic aromatic hydrocarbons from burning, Maillard reaction products from heating, etc.)

[a]Modified from Ref. 4.

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