CHAPTER 5

THE ROLE OF PHARMACOGENOMICS IN PHARMACOKINETICS

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INTRODUCTION

Recent advances in personalized medicine have demonstrated that genetic variations in genes encoding for drug metabolizing enzymes (DMEs) and drug membrane transporters (DMTs) can have an important impact on drug disposition and efficacy. These variations are integral to the explanation of differences in drug disposition between and within populations. This chapter provides a general review of the role of pharmacogenomics and its established importance in the safe and effective dosing of medications.

BASIC DEFINITIONS

Highlighted fields of study related to drug disposition and therapeutic outcomes include:

- ***Pharmacodynamics:*** What the drug does to the body. It is the science of how the drug and drug-target interact and result in a biological effect.
- ***Pharmacogenetics:*** The study of genetic causes of individual DNA variations in drug response.
- ***Pharmacogenomics:*** A genome-wide analysis (DNA, RNA level) of the genetic determinants of drug efficacy and toxicity.
- ***Pharmacokinetics:*** What the body does to the drug. Pharmacokinetics relates to how drug concentrations of a medication change over a dosing interval. It involves the dynamics of how the drug is absorbed, distributed, metabolized, and eliminated (ADME) by the body.
- ***Pharmacology:*** An investigation of the drug action's impact on biological systems including an understanding of chemical properties, mechanism of action, therapeutic response, and biological transformation.

Overall, the pharmacokinetics, pharmacodynamics, pharmacogenetics, and pharmacogenomics related to a drug interact biologically to influence efficacy and/or toxicity and serve as a framework for improving the understanding of pharmacology and drug development in the creation of more advanced and novel approaches to treat disease and provide precision therapies for individual patients (see **Figure 5-1**).

Pharmacogenomic variation within human populations can impact pharmacokinetics by altering a drug's expected ADME profile. For example, the final bioavailability (F) of a substrate medication is significantly impacted by the interplay of influx transporters such as organic acid transporters (OAT) and organic cation transporters (OCT) and efflux transporters (e.g., P-glycoprotein; P-gp) with DMEs present in the gastrointestinal tract and the liver (e.g., CYP3A4 and CYP2C9). The presence and/or absence of environmental factors (e.g., diet, disease) may also contribute. For example, the overexpression of P-gp and CYP2C9 in a given individual would lead to a lower F because of increased efflux transport back into the lumen of the gut and enhanced first-pass metabolism.

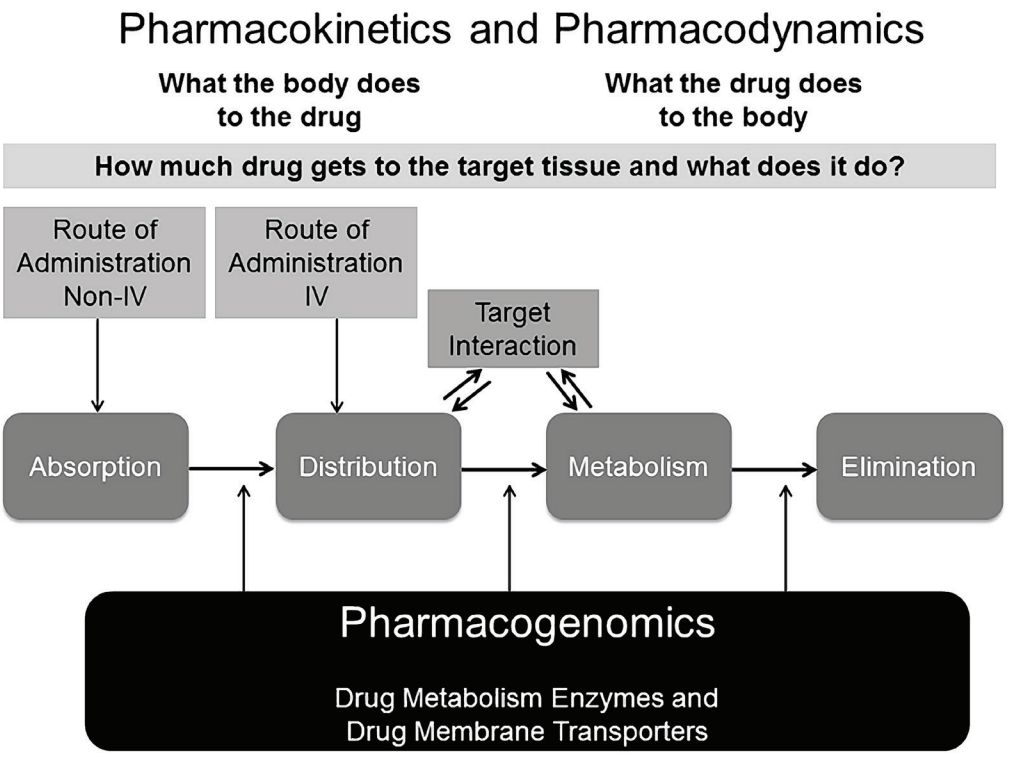

Figure 5-1. Interplay of pharmacokinetics, pharmacodynamics, and pharmacogenomics.

HISTORY OF PHARMACOGENETICS AND PHARMACOGENOMICS

Pharmacogenetics was first described in the scientific literature in the 1930s, when it was theorized that adverse drug reactions that occurred only in some patients taking a drug could be possibly explained through biochemical differences among individuals. Phenylthiocarbamide, which tests for inter-individual differences in tasting capacity, and the clinical observation of primaquine-induced hemolytic anemia that occurred in African American soldiers during World War II are among the first reports delineating the connection between genetic variation and drug disposition.[1,2] Vogel was the first to use the term *pharmacogenetics* in the scientific literature in 1959.[3] Later key discoveries in genetic variation included differing drug profiles with debrisoquine[4] and differences in drug disposition between heterogeneous populations.[5,6] These led to the eventual recognition that variation in drug response was not limited to a single or a few genes, but instead was due to assorted factors including variation in many genes and environmental factors such as age, weight, diet, smoking, concomitant drugs, and occupational exposures. It also led to the evolution of pharmacogenetics into the field of pharmacogenomics, which not only attempts to elucidate the reasons for changes in drug response but also drug-induced changes in gene function (e.g., drug–drug interactions).

The work on, and completion of, the mapping of the human genome in 2003[7-9] has resulted in major advances in recent decades in genotyping and sequencing technologies, bioinformatics, and pharmacogenomic epidemiology that have enabled a more refined understanding of the integral role of pharmacogenomics in drug disposition, development, and discovery.