3 Drug-Metabolizing Enzymes and P-Glycoprotein

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1. INTRODUCTION

A drug interaction occurs when a drug or another substance modifies the pharmacokinetics or pharmacodynamics of a concurrently ingested drug. With respect to a pharmacokinetic drug interaction, the underlying mechanism may be the result of an alteration in drug absorption, distribution, biotransformation, or excretion. The most common pharmacokinetic drug interactions are those involving biotransformation, particularly the ones resulting from induction or inhibition of cytochrome P450 (CYP) enzymes (1). It is now recognized that drug-transport proteins, such as P-glycoprotein (P-gp), play a critical role in drug disposition (2) and are therefore targets for drug interaction (3). Various types of drug interactions exist, including drug–drug interaction, nutrient–drug interaction, food–drug interaction, and herb–drug interaction (4). In some cases, the consequences of a drug interaction are not clinically significant, but in other instances, it may lead to therapeutic failure (5), severe adverse events (6), or even fatality (7). In fact, adverse effects due to drug interactions are one of the leading causes of deaths in hospitalized patients (8). Drug interactions also have a high economic cost to the pharmaceutical industry because drugs have been withdrawn from the market as a result of adverse consequences. In some cases, the effect of a drug interaction may be beneficial because it reduces the need of a drug (9).

The purpose of this chapter is to provide an overview of the human CYPs, uridine diphosphate glucuronosyltransferase (UGT), glutathione S-transferase (GST), and P-gp. The focus is on the function, induction, inhibition, tissue distribution, and pharmacogenetics of these proteins in humans.

2. CYTOCHROME P450

CYP enzymes are a superfamily of hemoproteins involved in the biotransformation of numerous drugs and other chemicals. Each CYP enzyme is denoted by an Arabic numeral designating the family (e.g., CYP1 family), a letter indicating the subfamily (e.g., CYP1A...
subfamily), and an Arabic numeral representing the individual gene (e.g., CYP1A2 gene) (10). CYP enzymes in the same family have greater than 40% amino acid identity and those in the same subfamily have greater than 55% identity (10). Currently, there are 57 functional human CYP genes (11). CYP enzymes that play a significant role in human drug metabolism are primarily in the CYP1, CYP2, and CYP3 families. This overview focuses on CYP3A, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP2E1, which are the major human CYP drug-metabolizing enzymes.

2.1. CYP3A

At least two CYP3A proteins are expressed in adult human liver. They are CYP3A4 and CYP3A5 (12). CYP3A4 protein has been detected in all human liver samples and it represents, on average, approx 30% of the total CYP content in adult human liver (13). In contrast, the CYP3A5 protein is detectable in only 20% of adult human liver samples (14). Both CYP3A4 and CYP3A5 have been detected along the gastrointestinal (GI) tract (15–18). In the case of the CYP3A5 protein, it is also present in the kidney (19,20), lung (21,22), and pancreas (17). More than 30 single nucleotide polymorphisms (SNPs) have been identified just in the CYP3A4 gene. Among the CYP3A4 allelic variants, CYP3A4*1B (A392→G) is the most common (23). Its expression varies in different ethnic groups, ranging from 0% in Chinese and Japanese to 45% in African Americans (24–26). However, this polymorphism does not appear to have any functional consequences with respect to drug clearance (24,27,28). To date, 12 allelic variants of CYP3A5 have been identified. The most common is CYP3A5*3B (A6986→G), which is present in 95% of Caucasians and 27% of African Americans (29). The homozygote CYP3A5*3B genotype is associated with very low or undetectable CYP3A5 protein expression (29). The functional consequences of this genetic variant remain to be determined.

Numerous drugs with diverse chemical structures and pharmacological functions are substrates for the CYP3A4 and CYP3A5 enzymes (Table 1), which are usually referred to as CYP3A because most of the probes are unable to distinguish the function of CYP3A4 from that of CYP3A5. Both the expression and catalytic activity of these enzymes are subject to modulation (Table 1). CYP3A is inducible not only by drugs, such as rifampin (30), phenobarbital (31), phenytoin (32), carbamazepine (32), and efavirenz (33), but also by a herb, St. John’s wort (34–37). It is now known that the mechanism of CYP3A induction involves transcriptional activation of the gene mediated by receptors, including the pregnane X receptor (38), which is also known as the steroid and xenobiotic receptor (39) and the pregnane-activated receptor (40), the constitutive androstane receptor (41), and the glucocorticoid receptor (42). For example, it has been reported that St. John’s wort activates the pregnane X receptor and this was mediated by hyperforin, but not by hypericin (43). In contrast to enzyme induction in which protein expression is enhanced, CYP3A protein levels can be reduced, as demonstrated by studies with grapefruit juice and Seville orange juice. In biopsy samples taken from human subjects, the ingestion of grapefruit juice (44) or Seville orange juice (45) was associated with a decrease in enterocyte CYP3A protein expression. These effects were attributed to 6',7'-dihydroxybergamottin (45), which are present in grapefruit juice and Seville orange juice. However, grapefruit juice, but not Seville orange juice, enhances the bioavailability of cyclosporine (45). Additionally, the activity of CYP3A enzymes can be altered by the co-administration of