CHAPTER 5

Drug Interactions
and Drug-Metabolising Enzymes

P.F. D’Arcy

A. General Introduction

Induction and inhibition of cytochrome P450 enzymes are mechanisms that underly some of the more serious drug-drug interactions; it is therefore pertinent that the structure, distribution and essential roles of cytochromes P450 are reviewed.

Cytochrome P450 is not a single species of protein; the system is actually a collection of isoenzymes, all of which possess an iron atom in a porphyrin complex. They catalyse different types of oxidation reactions and under certain circumstances may catalyse other types of reaction such as reduction (TIMBRELL 1993).

Since the early experiments of CONNEY et al. (1956; CONNEY 1967) it has often been observed that the rate of oxidative metabolism of various substrates can differ markedly depending on the age, sex, species or the extent of exposure of the animal to different inducing agents. A number of different investigators have directed studies to evaluate the number and types of cytochrome P450s that exist in a single organ. In particular they questioned whether specific types of reactions catalysed by the microsomal electron transport system required specific cytochrome P450, or whether many cytochrome P450s have a rather broad substrate specificity differing only in the rate of catalysis of each reaction.

SCHENKMAN (1993) has well documented the beginning of this interest and study into the cytochrome P450 monooxygenase. It commenced with the compilation of knowledge of the metabolism of xenobiotics by WILLIAMS (1959), who described the many different metabolites produced from xenobiotics in vivo by animals. From the late 1940s into the 1960s knowledge was advanced by BRODIE et al. (1955), who was one of the first to start in vitro biochemical studies on the metabolism of xenobiotics by oxidative enzymes. Work from MILLER’S laboratory augmented these studies (MÜLLER and MILLER 1953) and it soon became clear that liver microsomes were the source of NADPH-dependent, oxidative enzymes capable of metabolising a number of xenobiotics.

Since these early studies in the 1950s more than 800 different xenobiotics, many of which are therapeutic drugs, have been shown to be substrates for liver microsomal oxidative enzymes. The major types of oxidation
reaction catalysed by the cytochrome P450 system can be subdivided into: oxidation or hydroxylation (e.g., many drugs including paroxetine), deamination (e.g., amphetamine), dealkylation (e.g., morphine), sulphoxidation (e.g., chlorpromazine, paroxetine), desulphuration (e.g., thiopentone), dehalogenation (e.g., halogenated anaesthetics) and glucuronidation (e.g., paroxetine).

Certain oxidative reactions of xenobiotics are also catalysed by enzymes other than the cytochrome P450 monooxygenase system, for example the microsomal FAD-containing monooxygenase (Zeigler 1984, 1985; Damani 1988). This is responsible for the N-oxidation of tertiary amines such as dimethylaniline and trimethylamine. The enzyme requires NADPH and oxygen; the substrate specificity also includes secondary amines and sulphides, thioethers and thiocarbamates, and organophosphates (Timbrell 1993). Alcohols may be oxidised by alcohol dehydrogenase; xanthine oxidase catalyses the oxidation of nitrogen heterocyclics such as the purine hypoxanthine. Some amines such as tyramine are substrates for monoamine oxidases; diamines such as putrescine are metabolised by the soluble enzyme diamine oxidase. The peroxidases are also involved in the oxidation of xenobiotics, the most important being prostaglandin synthase, which is known to catalyse the oxidation of p-phenetidine, a metabolite of phenacetin, a process that may be involved in the nephrotoxicity of the drug (Timbrell 1993).

Extensive work by many investigators including Axelrod (1955), Posner et al. (1961), Sladek and Mannering (1966), Alvarex et al. (1967) and Lu and Coon (1968) isolated and purified a number of cytochrome P450 genes from animals and at the current time some 154 cytochrome P450 genes have been characterised from humans, animals, insects and plant species.

During the last 10 years or so, a vast amount of work has been done on the identification and characterisation of human xenobiotic-metabolising cytochrome P450s. Most studies have been done on hepatic and pulmonary enzymes due to the availability of tissues from tissue donor programmes.

Black (1993) has reviewed the cytochrome P450 structure and function and Gonzalez (1993) cytochrome P450 in humans. Mammalian P450 enzymes are tightly bound in both microsomes (endoplasmic reticulum) and mitochondria and have been purified by means of detergent solubilisation. Purified detergent-free preparations exhibit a highly amphiphilic character and exist as micellar aggregates of approximately six protomers (Dean and Gray 1982). The enzymes are discrete gene products of about 57000 molecular weight and contain one equivalent of b-type heme per polypeptide.

The most abundantly expressed cytochrome P450s in human liver are the CYP3A subfamily. A brief description on this subfamily will serve as an example of the whole genus. Other subfamilies in human tissues comprise CYP1A, CYP2B, CYP2C, CYP2D, CYP2E, and CYP2F; the locus, function and activities of these are shown in Table 1.