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REVIEW ARTICLE

The physiological and pharmacological roles of cytochrome P450 isoenzymes

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Summary

The cytochrome P450 isoenzymes are a superfamily of haemoprotein enzymes that catalyse the metabolism of a large number of endogenous and exogenous compounds. Recently, the cytochrome isoenzymes have been shown to be important in the synthesis of steroid hormones and bile acids, the arachidonic acid cascade and in central nervous function. These enzymes are a major determinant of the pharmacokinetic behaviour of numerous drugs. Furthermore, alterations in cytochrome P450 activity have been implicated in some diseases.

Keywords *Enzymes*; cytochrome P450.

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The cytochrome P450 isoenzymes are a superfamily of haemoproteins that are the terminal oxidases of the mixed function oxidase system found on the membrane of the endoplasmic reticulum. These isoenzymes are so called because they have a spectrophotometric absorption peak at or near 450 nm when bound and reduced by carbon monoxide [1]. The P450 isoenzymes are thought to have existed for more than 3.5 billion years and are found to exist in bacteria, fungi, plants and animals. It is well established that the cytochrome enzymes, in humans, are involved in the metabolism of exogenous substances (drugs, alcohols, anti-oxidants, organic solvents, anaesthetic agents, dyes, environmental pollutants and chemicals) producing metabolites which may be toxic or carcinogenic [1–4]. They are also important in the oxidative, peroxidative and reductive metabolism of endogenous physiological compounds such as steroids, bile acids, fatty acids, prostaglandins, biogenic amines and retinoids. Recent research has revealed new physiological [5–7] and pathological roles [2] for the cytochrome isoenzymes besides their involvement in metabolism.

Classification

It was not known that different species and tissues had similar isoforms when initial investigations demonstrated multiple forms of cytochrome P450. Researchers initially assigned names to the isoenzymes according to their spectral properties, electrophoretic mobility or their substrates. As a result of rapid advances in knowledge of the amino acid sequences, a general nomenclature based on the presence of common amino acid sequence was proposed by Nebert and colleagues [8]. This system is widely accepted and it groups the isoenzymes and genes into families and subfamilies with the prefix 'CYP' to designate cytochrome P450 isoenzymes in all species (except *Drosophila* and mouse gene where 'Cyp' is used). In this system, cytochrome P450 proteins from all sources having more than 40% identity in amino acids are placed in the same family and this is designated by an Arabic numeral. A subfamily consists of enzymes in which the amino acid sequence is more than 55% identical and this is designated by a capital letter. Finally, an Arabic numeral after the letter denotes the individual enzyme and the gene associated with the enzyme is denoted in italics. For example, the CYP2 family [3, 8] has several subfamilies such as CYP2C, CYP2D and CYP2E. The individual enzyme is denoted by a numeral, as in CYP2D6, and the gene is denoted as *CYP2D6*. The advantage of this nomenclature is that structurally identical or highly similar cytochrome P450s are easily identified regardless of their sources or their catalytic activities.

A list of 481 P450 genes and 22 pseudogenes has been reported [8] (as of October 1995). Of the 74 gene families

Table 1 Activity of selected human cytochrome P450 isoenzymes.

Isoenzyme	Substrate	Inducer	Inhibitor
CYP1A1	Chlorinated benzenes	Polycyclic hydrocarbons	Propofol, NO
CYP1A2	Caffeine, phenacetin	Phenytoin	Quinolone
	TCA, R-warfarin	Phenobarbitone	Antibiotics
	Erythromycin	Omeprazole	Cimetidine
	Haloperidol, antipyrine	Polycyclic hydrocarbons	
	Theophylline, Paracetamol		
	Ropivacaine		
CYP2C8	TCA, Diazepam	Rifampicin	Cimetidine
	Hexabarbitone	Phenobarbitone	
CYP2C9/10	Phenytoin, S-warfarin		Sulfaphenazole
	Diclofenac, Tolbutamide		
CYP2C19	Mephenytoin, Diazepam, TCA	Phenobarbitone	Sulfaphenazole
CYP2D6	Debrisoquine, Sparteine	Pregnancy	Cimetidine
	Codeine, Dextromethorphan		Quinidine
	β-Blockers, SSRIs, TCA		Methadone
CYP2E1	Paracetamol, Isoflurane	Ethanol, Isoniazid,	Disulfiram
	Sevoflurane, Methoxyflurane	benzene	
	Enflurane, Trichlorethylene		
CYP3A4	Nifedipine, TCA,	Rifampicin	Cimetidine
	Dextromethorphan	Glucocorticoid	Troleandomycin
	Alfentanil, Sufentanil	Carbamezepine	Propofol
	Fentanyl, Erythromycin	Phenobarbitone	Grapefruit juice
	Lignocaine, Ropivacaine		Ketoconazole
	Midazolam, Codeine,		
	Granisetron, Diltiazem		
	Hydrocortisone		
CYP3A5	Caffeine, Diltiazem	Dexamethasone	Troleandomycin
CYP3A7	Midazolam		
CYP7	Cholesterol		
CYP11A1	Cholesterol		
CYP17	Pregnolone		
CYP19	Testosterone		
CYP21A2	17-Hydroxyprogesterone		

TCA = tricyclic antidepressants, SSRI = selective serotonin reuptake inhibitors.

described, 14 families have been reported in humans and 20 subfamilies have been mapped in the human genome.

Biochemistry

Each cytochrome P450 isoenzyme consists of a single protein and one haem group as the prosthetic moiety [9]. The cytochrome P450 enzyme systems catalyse the metabolism of endogenous and exogenous compounds [3] (Table 1). The biotransformation of the endogenous and exogenous substrates render these compounds hydrophilic or polar so that they can be excreted. The reactions are grouped into phase 1 and 2 reactions. In phase 1 reactions oxidation or demethylation mediated by cytochrome P450 enzymes occur. The haem prosthetic group binds oxygen after electron transfer reactions from the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and this reaction incorporates one atom of molecular oxygen into the substrate [2, 10]. The typical reaction catalysed by cytochrome P450, a mono-oxygenation, can be summarised as follows:

$$NADPH + H^+ + O_2 + RH \Rightarrow NADP^+ + H_2O + R\text{-}OH$$

where R represents a substrate such as a steroid, fatty acid or compound with an alkene, alkane, aromatic ring or heterocyclic ring substituent that serves as a site for oxygenation. Drug metabolising cytochrome P450s have a distinct but often overlapping substrate specificity. Another characteristic of cytochrome P450s is the large intra- and interspecies variability in catalytic activity and in regulation. More than one cytochrome P450 isoenzyme can be involved in the metabolism of a drug.

The cytochrome P450 system catalyses a wide variety of reactions including epoxidation, N-dealkylation, O-dealkylation, S-oxidation and hydroxylation of aliphatic and aromatic residues. Oxidation can result in both activation and inactivation of a compound. Like all enzymes, cytochrome P450 isoenzymes show saturable Michaelis–Menten kinetics and need co-factors for their activity. They

may be induced or inhibited [2, 10, 11]. The CYP1A enzyme is induced by polycyclic hydrocarbons, CYP2B by phenobarbitone, CYP3A by glucocorticoids, CYP2E by ethanol and CYP4A by clofibrate [1–3, 10, 11].

The cytochrome P450 enzymes may be inhibited by a variety of mechanisms [9, 12, 13] such as simple competition for substrates for cytochrome P450 (quinidine, sulfaphenazole), compounds that bind to the haem (cimetidine), compounds whose oxidation products bind to haem (troleandomycin) and direct irreversible inactivation (disulphiram).

Drugs such as secobarbitone, cyclophosphamide and chloramphenicol are oxidised to metabolites that irreversibly bind to the enzyme. Some drug metabolites have a high affinity for the reduced (ferrous) form of cytochrome P450 so that it is not available for further oxidation. It is thought that erythromycin inhibits CYP3A by this mechanism resulting in the impaired metabolism of alfentanil, theophylline and warfarin [13].

Drug interactions can occur through reversible interactions with cytochrome P450 enzymes. The N-demethylation of midazolam by CYP3A4 is inhibited by this mechanism by the fluoroquinolone antimicrobials (ciprofloxacin). Cimetidine exerts its nonselective inhibitory effects on oxidation by directly interacting with the cytochrome P450 haem iron through one of the nitrogen atoms of its imidazole nucleus [13]. The elimination of drugs affected by cimetidine include warfarin, diazepam, phenytoin and propanolol. Other drugs that contain the imidazole group such as ketoconazole may be potent inhibitors of cytochrome P450 enzymes. Ranitidine, which contains a furan ring rather than an imidazole one, does not inhibit cytochrome P450 enzymes.

Direct stimulation of cytochrome P450 catalytic actions has been demonstrated in human microsomal preparations. Such stimulation has been shown with chemicals in food such as aflatoxin B1, a hepatocarcinogen [4]. Dietary chemicals [14] may affect the concentration of cytochrome P450 enzymes by a variety of mechanisms such as changes in the rate of gene transcription or degradation of mRNA, and altering the translation process. Fasting has been shown to induce the CYP2E1 enzyme. In general, vitamin deficiencies lower cytochrome P450 activity [14].

Distribution

It is well known that the cytochrome P450 system is associated with hepatic metabolism. CYP1, 2 and 3 families account for 70% of the total hepatic P450 content and are responsible for most drug metabolism [12]. Based on their expression in the liver, it appears that CYP3A accounts for about 30% of the total hepatic P450; CYP2, about 20%; CYP1A2, 13%; CYP2E1, 7%; CYP2A6, 4%; and CYP2D6, 2%. Extra hepatic cytochrome P450 has been identified in a wide range of tissues [15] which include the small intestine, pancreas, brain, lung, adrenal gland, kidney, bone marrow, mast cells, skin, ovary and testis.

The cytochrome P450 isoenzymes are present in varying amounts throughout the mucosa of the gut [12, 15]. CYP3A4 is found in the mucosa of the small intestine and CYP1A1 present in the duodenum. Smaller quantities of CYP2C8-10 and CYP2D6 are present in the duodenum and jejunum. Examples of drugs that may be metabolized by cytochrome P450 enzymes in the gut are phenacetin and flurazepam.

Cytochrome P450 isoenzymes have been identified throughout the brain with high concentrations in the brain stem and cerebellum [15]. These are thought to be important in regulating the concentrations of progesterone and corticosterone which play a role in mood changes and sleep–awake cycles during stress, pregnancy and through the menstrual cycle [16].

Cytochrome P450 isoenzymes have been identified in the brush border of the proximal tubular cells and medulla of the kidney [6]. They appear to be involved in the catalytic reactions involving the arachidonic acid in the kidney leading to the formation of eicosanoid products which have vasoactive properties and effects on ion transport, and consequently affect the physiological mechanisms that control fluid volume and composition [6]. Type II pneumocytes in the lung also contain cytochrome P450 isoenzymes but have a limited contribution to metabolism as the total amount of enzyme is relatively small [15]. Adipose tissue contains high concentrations of CYP19 enzymes which are thought to be important for the synthesis of oestrogens in the elderly [15].

Genetics

Genetic polymorphism is a Mendalian trait that exists in the normal population in at least two phenotypes, neither of which has a frequency of less than 1% [17]. Poor or slow metabolisers possess the homozygous autosomal recessive allele (usually mutant alleles), whilst the extensive or rapid metabolisers have the heterozygous or homozygous dominant allele. Several cytochrome P450 isoenzymes are associated with genetic polymorphism [13].

The best known polymorphic isoenzyme is the CYP2D6 or debrisoquine hydroxylase enzyme [3, 12, 17]. The gene, *CYP2D6*, is located on chromosome 22 and mutation of this gene can result in reduced or low affinity forms of the enzyme. About 5–10% of Caucasians and 0.9% of Asians metabolise debrisoquine and other substrates of CYP2D6 at a markedly decreased rate. In addition to the poor and extensive metabolisers, a group called the ultra rapid metabolisers has been identified. This group is

associated with CYP2D6 of extremely high activity and results from gene amplification [17].

The CYP2C19 enzyme is also associated with genetic polymorphism and this was first recognised with the hydroxylation of S-mephenytoin. Slow metabolisers of S-mephenytoin are found in 2–5% of Caucasians, about 20% of the Japanese population, 19% of African Americans and 8% of Africans [18].

The enzyme CYP2E1 [19] also demonstrates genetic polymorphism affecting the 5′-flanking region (the non-coding region of the gene containing DNA that interacts with proteins to facilitate or inhibit transcription) of the human cytochrome gene, *CYP2E1*. It contains several restriction fragment length polymorphisms that may influence transcription or functional activity of the expressed protein, and it may be associated with the development of alcoholic liver disease and liver and lung cancer [19] related to cigarette smoking.

The clinical consequences of genetic polymorphism in drug metabolism depend on whether the activity of the drug lies with the substrate or its metabolite, as well as the extent to which the affected pathway contributes to the overall elimination of the drug [20]. The antihypertensive effects of debrisoquine reside in the drug itself and its elimination is dependent on the pathway. As such, pronounced and prolonged effects with an increased likelihood of adverse effects may occur in individuals who are poor metabolisers with a normal dose. In contrast, the analgesic activity of codeine is due to morphine formed from the demethylation of codeine by CYP2D6 (debrisoquine hydroxylase) and as a result poor metabolisers may obtain less analgesia from the drug [17]. In addition, the degree of drug interactions involving inhibition and induction of metabolising enzymes is influenced by genetic factors and is predictable. Quinidine, which is a potent inhibitor of debrisoquine hydroxylase, can convert a normally effective metaboliser to an apparently poor one and hence increase the potential for adverse effects. Phenotyping patients for a particular pathway before the administration of drugs that have a narrow therapeutic index has been proposed [20]. This is based on the ratio of the drug and its metabolite concentrations in the urine following a single dose of a marker. Sparteine, debrisoquine and dextromethorphan have been used as markers for CYP2D6 polymorphism. Other markers include caffeine for CYP1A2 and lignocaine for CYP3A4. Metabolic phenotyping is not widely used because it may be costly, inconvenient and have low specificity and sensitivity. Genotyping by DNA analysis of peripheral lymphocytes using polymerase chain reaction provides a direct approach towards predicting the metabolic phenotype. Currently, DNA tests can predict the phenotypes of CYP2D6 in 95% of healthy volunteers [17, 20].

Physiological role

Over the last few years it has become apparent that the cytochrome P450 enzymes are involved in the biosynthesis and/or degradation of endogenous compounds such as steroid hormones, cholesterol and fatty acids [21].

Recent evidence suggests that the cytochrome P450 enzymes may have physiological roles in the brain [16] such as signal transduction by arachidonic acid metabolites which are thought to be involved in the release of peptide hormones from the hypothalamus and pituitary; the regulation of cerebral vascular tone by arachidonic acid metabolites; the regulation of progesterone and corticosteroids in the brain which are thought to influence mood and state of arousal by interacting with GABA receptors; and the control of intracellular concentrations of cholesterol which influences the transcription of low-density lipoprotein receptor and enzymes involved in cholesterol synthesis. It has been suggested that the CYP2D6 enzyme regulates the metabolism and processing of neurotransmitters such as dopamine and serotonin and therefore may have a role in determining the mental state and personality of individuals [16].

Adrenal and gonadal steroidogenesis [22, 23] are influenced by the enzymes CYP11A, CYP11B, CYP17, CYP19 and CYP21. The adrenal steroids (cortisol and aldosterone) produced are important for the maintenance of electrolyte and glucose homeostasis while the gonadal steroids (dehydroepiandrosterone and androstenedione) are responsible for reproductive function and sex differentiation. CYP19 plays an important role in oestrogen biosynthesis [3] in the gonads, brain, placenta and adipose tissue.

The cytochrome P450 system plays an important role in arachidonic acid metabolism and intensive research is being undertaken in this area [6, 24]. The metabolites resulting from pathways modulated by cytochrome P450 enzymes (1A1, 1A2, 2B1, 2B2, 2C11) may be important in determining ion permeability of membranes and the enzyme activity and turnover of membranes. In the kidney, metabolites of arachidonic acid produced by renal cytochrome P450 enhance Na^+K^+ATPase and the $Na^+K^+2Cl^-$ co-transporters resulting in diuresis and natriuresis [6]. These metabolites have been shown to have both vasoconstrictive and vasodilatatory activity. As a consequence of these effects, the cytochrome P450 system has an important role in the integration of body fluid volume and composition and hence blood pressure regulation [6]. The renal CYP2C isoform is induced by salt loading and increases arachidonic acid metabolites which inhibit proximal and distal Na^+ reabsorption, suggesting an adaptive role to increased salt intake.

In the liver, the biosynthesis of bile acids [25] and endogenous steroids [11] involves CYP 7, 17, 19, 21 and

27. Bile acid synthesis from cholesterol can occur by two pathways, one initiated by CYP 7 (cholesterol 7 α-hydroxlase) in the liver and the other by CYP 27 (sterol 27-hydroxlase) which is a widely distributed mitochondrial enzyme, notably in vascular endothelial cells [25]. Human CYP2C8 enzyme appears to be responsible for retinol and retinoic acid metabolism [12].

Pharmacological role

The cytochrome P450 system in the liver plays a major role in drug metabolism by converting drugs from a hydrophobic state to a more readily excretable hydrophilic form [2, 3, 12]. The biotransformation reactions are generally grouped into cytochrome P450-dependent phase 1 and phase 2 conjugation reactions. During the last few years it has become apparent that extrahepatic metabolism of drugs [15] can contribute to the overall degradation of the drug in the body. Biotransformation within the gastrointestinal tract is important because it decreases bioavailability after oral administration. Changes in the activity of the cytochrome P450s can result from genetic polymorphism, enzyme inhibition, enzyme induction and physiological factors. These have several clinical implications as they may result in changes in the pharmacokinetics of the drugs leading to altered efficacy of the drugs, increased toxicity due to reduced metabolism or increased production of toxic metabolites, and drug interactions.

The CYP1A family

The CYP1 family [12] is characterised by two genes and is mainly involved in the metabolism of polycyclic aromatic compounds and arylamines. CYP1A1 (aryl hydrocarbon hydroxylase) is found in low concentrations in the liver and extrahepatic tissues such as the lungs. It is induced by polycyclic hydrocarbons [12]. The mechanism of induction in the liver has been studied extensively. Inducing agents diffuse into the liver cells where they bind to the receptors of carrier proteins. The carrier protein complex enters the nucleus where it associates with DNA and stimulates the transcription of mRNA, which leaves the nucleus and promotes the formation of the cytochrome enzyme at the rough endoplasmic reticulum. Nitric oxide (NO) binds to the catalytic haem moiety of cytochrome P450 enzymes. *In vitro* studies [26] using V79 Chinese hamster cells (genetically engineered for stable expression of human CYP1A1 and 1A2 enzymes) have shown that CYP1A1 was more sensitive to the inhibitory effects of NO.

CYP1A2 (arylamine oxidations) is important for demethylating methylxanthines such as caffeine and theophylline, O-demethylation of naproxen, hydroxylation of tacrine, ropivacaine (to 3 OH ropivacaine), R-warfarin and caffeine, dealkylation of phenacetin and demethylation of the tricyclic antidepressants [3, 12]. The enzyme may be induced by cigarette smoking, charbroiled meat, phenytoin, phenobarbitone and omeprazole. Quinolone antibiotics such as erythromycin and ciprofloxacin inhibit CYP1A2 by the binding of the 4-oxo-carboxylic acid portion of quinolone to the enzyme [12, 13]. Fluvoxamine [18], a selective serotonin reuptake inhibitor (SSRI), also inhibits CYP1A2.

CYP2 family

This is a large family [12] and includes 2A, 2B, 2C, 2D and 2E subfamilies. The human 2A subfamily has not been extensively studied. The 2A6 is an important liver enzyme that hydroxylates coumarin compounds [12]. The role of the 2B subfamily in human liver drug metabolism is limited.

The CYP2C subfamily of enzymes demethylates diazepam, tricyclic antidepressants (amitriptyline, imipramine) and oxidises omeprazole. The 2C9 substrates are phenytoin, tolbutamide and diclofenec. 2C10 enzymes are involves in the hydroxylation of tolbutamide and hexobarbitone [12]. These two enzymes are inhibited by sulfaphenazole and sulfinpyrazone. The 2C19 is involved in the metabolism of hexobarbitone, diazepam and S-mephenytoin.

The 2D6 (debrisoquine hydroxlase) enzyme [2, 3, 12] has been investigated intensively and is involved in the metabolism of a large number of drugs such as debrisoquine, tricyclic antidepressants, selective serotonin reuptake inhibitors [18] (except fluvoxamine), analgesics (codeine, dextromethorphan), anti-arrhythmics (sparteine, encainide, flecanide), β-blockers (metoprolol) and ondansetron. The activity of the CYP2D6 enzyme exhibits a bimodal distribution indicating the presence of dominant and recessive alleles in the population [20]. The isoenzyme is not inducible by pharmacological agents. Quinidine and the selective serotonin reuptake inhibitors (SSRIs) bind tightly and inhibit the enzyme [13]. Quinidine effectively changes patients taking drugs which are metabolised by CYP2D6 into poor metabolisers. The SSRIs such as paroxetine and fluoxetine are potent competitive and reversible inhibitors whilst sertraline and fluvoxamine do so to a lesser extent [18].

The CYP2E subfamily contains only one gene and is toxicologically an important enzyme [12, 19, 27]. The CYP2E1 (dimethylnitrosamine N-demethylase) is responsible for the metabolism of many volatile anaesthetic agents [28] (such as sevoflurane, enflurane, isoflurane, methoxyflurane, diethyl ether, trichloroethylene and

chloroform), ethanol and aromatic compounds such as benzene, paracetamol and nitrosodimethylamine. The enzyme can be induced by isoniazid and ethanol and is inhibited by disulfiram. Chronic ethanol consumption increases the rate of metabolism of pentobarbitone, tolbutamide, propanolol and rifampicin as a result of induction of CYP2E1. In contrast, acute ethanol consumption may competitively inhibit 2E1 and decrease the metabolism of benzodiazepines, phenothiazines, barbiturates, morphine and warfarin.

The CYP3 family

The CYP3 family is involved in the metabolism of a large number of endogenous and exogenous compounds and may be induced by steroids, macrolide antibiotics, antifungal drugs and phenobarbitone [12]. The endogenous compounds metabolised by the 3A subfamily include progesterone, oestradiol, cortisol, testosterone and androstenedione. The exogenous compounds that are metabolised by these enzymes include erythromycin, lignocaine, midazolam, alfentanil, cyclosporine and the dihydropyridines (nifedipine) [2, 12]. The major pathways for these substrates include oxidation, dealkylation, nitroreduction and hydroxylation. These enzymes account for about 30% of the hepatic and 70% of the gut wall P450 content [19]. This subfamily in humans is controlled by four genes, *CYP 3A3*, *3A4*, *3A5* and *3A7*. The CYP3A4 is the most common and abundant cytochrome subfamily in the liver. CYP3A4 is the main catalyst for the oxidation of fentanyl to norfentanil in humans [29] and 3A1/2 in rats. Although CYP1A2 catalyses the metabolism of ropivacaine to 3-OH-ropivacaine, the main metabolites *in vivo* (4-OH-ropivacaine, 2-OH-ropivacaine and 2-6-pipecoloxylidide) are catalysed by CYP3A4 [30]. It is also responsible for the hepatic metabolism of lignocaine to monoethylglycinexylide [31]. A significant first-pass oxidation of midazolam is brought about by mucosal CYP3A4 of the small intestine [32]. CYP3A7 is only found in fetal liver. Rifampicin is the most potent inducer of CYP3A enzymes. Other inducers of CYP3A are phenobarbitone and phenytoin. The enzyme is inhibited by ketoconazole, troleandomycin, erythromycin, cimetidine and grapefruit juice. The possibility of genetic polymorphism of CYP3A has not been confirmed.

Specific anaesthetic drugs

The CYP3A4 enzyme is responsible for the metabolism of several classes of drugs used in anaesthesia: opioids [29, 33] (fentanyl, sufentanil, alfentanil, dextromethorphan), benzodiazepines [2] (midazolam, diazepam) and local anaesthetics (lignocaine, ropivacaine) [29, 30]. Thus, interindividual variation in the clearance of these anaesthetic agents may result from differences in CYP3A4 expression and to CYP3A4-related drug interactions. A recent study [34] reported that the elimination half-life of midazolam was prolonged by 50% and its clearance reduced by 30% by the co-administration of fentanyl at induction, probably as a result of competitive inhibition of CYP3A activity.

Propofol has been shown to interfere with the metabolism of alfentanil and sufentanil [35] by inhibiting the CYP2B1 and CYP1A1. It has been demonstrated to exhibit a concentration dependent inhibitory effect on CYP2B1 and 1A1 by binding to the haem moiety of the enzymes [36]. Propofol inhibits CYP2E1 only to a limited extent as the propofol molecule is too large to bind effectively to the active sites of the enzyme. Thus, propofol [36] may potentially alter the metabolism of co-administered drugs such as alfentanil and sufentanil but it does not effectively inhibit the metabolism of volatile agents (enflurane, sevoflurane, methoxyflurane) by CYP2E1.

The volatile fluorinated anaesthetic agents (sevoflurane, isoflurane, enflurane, methoxyflurane) are metabolised by cytochrome P450 enzymes. CYP2E1 is the predominant enzyme responsible for the metabolism of trichloroethylene, halothane, sevoflurane and enflurane in the liver. Approximately 5% of sevoflurane is rapidly metabolised to fluoride and hexafluoroisopropanol (HFIP), which is glucuronidated and excreted in the urine [28, 37]. However, other P450 enzymes, such as CYP1A2, 2C and 2D6, in addition to hepatic CYP2E1 are involved in the metabolism of methoxyflurane. Sevoflurane and methoxyflurane has been shown to undergo defluorination by human kidney microsomes [38] and the amount of fluoride ions produced was dependent on time, anaesthetic concentration and the concentration of NADPH. Renal CYP 2E1, 2A6 and 3A are implicated in the metabolism of methoxyflurane and sevoflurane in the kidney. The rates of defluorination of methoxyflurane in the kidney were 3–10 times faster than that of sevoflurane, generating fluoride ions and increasing intrarenal fluoride concentration and the potential for nephrotoxicity [38]. Renal cytochrome isoenzymes showed minimal metabolism of sevoflurane resulting in lower intrarenal fluoride concentration. Serum fluoride ion concentrations do not predict nephrotoxicity of all fluorinated inhalational agents [38].

Recent studies [39] have shown that CYP2E1 is a major catalyst for the formation of trifluoroacetylated proteins from halothane which have been implicated as target antigens responsible for halothane hepatitis.

The concentrations of cytochrome P450s in the brain are increased in pregnancy and lactation and by ethanol. Pregnancy has been shown to induce CYP2D6 and result in an increase in the activity of the enzyme [40]. Ethanol

increases the concentrations of CYP2C, 2E1 and 4A by three- to five-fold and this suggests that ethanol, the steroid anaesthetics [41] and other exogenous psychoactive drugs may be metabolised in the brain. It also raises the question of the role of brain cytochrome P450s [16, 19] in the development of tolerance and neurotoxicity of exogenous drugs.

The CYP1A2 and 3A4 isoenzymes are important for the metabolism of the amide local anaesthetic agents in the liver [30]. CYP1A2 is responsible for the formation of 3-OH-ropivacaine and CYP3A for the formation of pipecoloxylidide in the metabolism of ropivacaine. Lignocaine is metabolised to monoethylglycinexylide by CYP3A4.

Several oral analgesics are metabolised to active metabolites. CYP2D6 metabolises tramadol [42] to a metabolite [(+)-M1] which binds to the μ-opioid receptor to produce its analgesic effect. It is also important for the analgesic effects of codeine and hydrocodone as they are O-demethylated to morphine [43], and to hydromorphone [44], respectively. However, it is inhibited by methadone [45] and this is important because the use of methadone in the treatment of opioid abuse can lead to unexpected toxicity from drugs that are substrates of the enzyme.

Role in disease states

Altered activity of certain isoenzymes has been implicated [2] in the development of cancer, adrenal hyperplasia and Parkinson's disease. Smokers with increased CYP1A1 (aryl hydrocarbon hydroxylase) activity are more prone to developing lung cancer [46, 47]. Genetic differences in CYP1A1 in individuals with a high risk of developing lung cancer have been identified and individuals who are homozygous for a specific rare allele are at a greater risk of developing the disease [47].

The CYP1B1 isoenzyme is increased in patients with breast cancer [48]. As it is involved in the metabolism of oestrogens in the breast, it is suggested that it may have a role in the aetiology of oestrogen-dependent breast tumours.

The CYP2D6 enzyme [17] has been implicated in mediating carcinogenesis by activating procarcinogens in tobacco smoke leading to lung cancer. CYP 2E1 catalyses the metabolism of aniline, chlorinated hydrocarbons and benzene, leading to the formation of procarcinogens. It is suggested that genetic polymorphism of CYP2E1 may play an important role in the development of hepatic cancer [27].

Reactive metabolites produced by catalytic reactions within neuronal cells may cause neurotoxicity resulting in Parkinson's disease [3]. Epidemiological studies have indicated a trend in which poor metabolisers of debrisoquine [49] tend to develop an early onset of Parkinson's disease. A deficiency of 21 hydroxylase is responsible for 90–95% of cases of congenital adrenal hyperplasia and this results from defective genetic coding of CYP21A2 [50].

Despite the recent advances in the knowledge of human cytochrome P450 enzymes, there is a need for methods to be developed to monitor cytochrome P450 expression reliably in humans. This may make it possible to predict drug interactions and the metabolic clearance of drugs. Patients who are to receive drugs with narrow therapeutic indices can be phenotyped or genotyped to guide dosage and reduce toxicity. Individuals may be screened to determine whether they are predisposed to cancer or toxicity if they have a high expression of a particular form of cytochrome P450 isoenzyme. Therefore, research on human cytochrome P450s can have an impact on both drug therapeutics and prevention of various diseases such as cancer.

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