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2.3.15 Hepatic metabolism of drugs

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General concepts

Drug metabolism is the process by which drug molecules are chemically altered, usually to more polar metabolites that exhibit increased water solubility to allow elimination in urine or bile and/or increased access to excretory transporters. The liver is quantitatively and qualitatively the most important site of drug metabolism, although extrahepatic metabolism of drugs is also well recognised, both in the gastrointestinal mucosa and by circulating enzymes such as esterases. Drug metabolism is likely to be a byproduct of metabolic pathways that metabolize endogenously synthesized compounds (endobiotics) such as steroids, sterols, bile acids and eicosanoids. This is supported by the observation that hepatic enzymes involved in drug metabolism often have these endobiotic compounds as substrates, and that some hepatocellular transporters that handle bile acids also transport drugs [1,2].

One of the most surprising features of hepatic drug-metabolizing pathways is their ability to cope with a seemingly

endless array of drug substrates. Thus, many of the newer fully synthetic drugs that have no close structural counterparts in nature are successfully metabolized by the liver and irreversibly removed or ‘cleared’ from the body. This broad substrate recognition is achieved by the presence of multiple drug-metabolizing enzymes in the hepatocyte, and many can metabolize multiple substrates. For example, the calcium channel blocker nifedipine is almost entirely metabolized by the cytochrome P450 (P450) CYP3A4, an enzyme with very broad substrate recognition that is responsible for the metabolism of some 50% of all therapeutic drugs. In contrast, the benzodiazepine diazepam is metabolized by P450s belonging to the CYP2C, 2D and 3A subfamilies to several primary metabolites, some retaining pharmacological activity. Thus, individual drugs may be metabolized in very different ways, and variation in the expression of individual enzymes and transporters for genetic or other reasons may have complex effects, which may sometimes be difficult to model and predict in advance.

Central role of the liver in drug metabolism

In terms of both gross anatomy and microstructure, the liver is ideally designed as a drug clearance organ (Fig. 1). Most foreign chemical compounds (xenobiotics), including therapeutic drugs, enter the body by absorption from the gastrointestinal tract. As covered in Chapter 2.1.1 of this book, venous drainage from most of the gastrointestinal tract is via the portal vein to the liver. Along with drug-metabolizing enzymes and drug transporters expressed in the intestinal mucosa, the liver provides an effective barrier that prevents xenobiotics from entering the systemic circulation. The fraction of an absorbed drug metabolized on this initial postabsorptive pass through the liver is termed ‘first-pass clearance’ and, factored together with the fraction of the drug absorbed from the gastrointestinal tract, determines the ‘bioavailability’ or the fraction of an orally administered drug that reaches the systemic circulation as intact drug [3]. For some drugs, the extent of first-pass clearance can be so great that oral administration is largely ineffective; for example, glyceryl trinitrate and lidocaine (lignocaine).

Within the hepatic lobular architecture, drug metabolism is not evenly distributed. Some important drug-metabolizing P450s such as CYP3A4 are predominantly expressed in pericentral (zone 3) hepatocytes [4]. One reason for this functional specialization may be that metabolism can give rise to highly toxic electrophilic intermediates, which may lead to cell death. With metabolic segregation, only pericentral necrosis occurs, rather than massive necrosis if highly reactive molecules cannot be successfully detoxified.

Drug-metabolizing enzymes

Phase I metabolism refers to a basic structural alteration of a drug molecule, whereas in phase II metabolism, a water-soluble

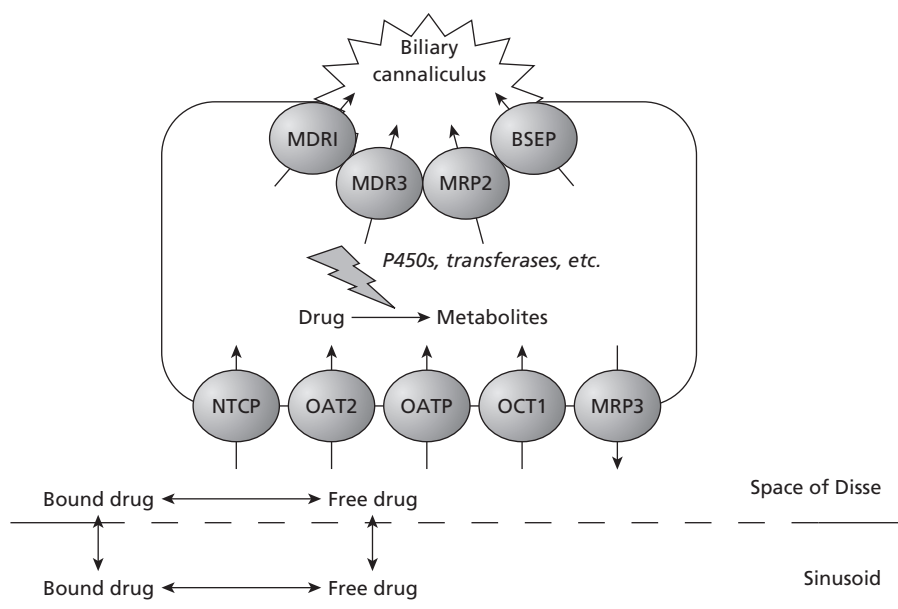


Fig. 1 Organization of drug metabolism at the level of the hepatocyte. Portal blood enters hepatic sinusoids where free drug molecules are transported into hepatocytes. Within hepatocytes, enzyme-mediated metabolism occurs prior to excretion of drug and drug metabolites by transport into bile or back into the circulation. BSEP, bile salt export pump; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OCT, organic cation transporter; NTCP, Na⁺-taurocholate cotransporting polypeptide.

Table 1 Major human drug-metabolizing cytochrome P450s and receptors responsible for inductive regulation.

Cytochrome P450 family	Member	Regulating receptor
CYP1	CYP1A1	AhR
	CYP1A2	AhR
CYP2	CYP2A6	CAR
	CYP2A13	
	CYP2B6	CAR, PXR
	CYP2C8	PXR
	CYP2C9	CAR, PXR
	CYP2C18	
	CYP2C19	PXR, CAR
	CYP2D6	
	CYP2E1	
	CYP2F1	
CYP3	CYP3A4	PXR, CAR
	CYP3A5	PXR, CAR
	CYP3A7 ^a	PXR

AhR, aryl hydrocarbon receptor; CAR, constitutive androstane receptor; PXR, pregnane X receptor.

^aExpressed in fetal liver and uterine endometrium.

moiety is attached or 'conjugated' to the drug. P450 enzymes are the predominant catalysts of phase I metabolism in the liver. P450s comprise a gene superfamily with 57 members in the human genome. A subset of approximately 15 P450 enzymes belonging to the CYP1, 2 and 3 gene families mediates 70–80% of all phase I-dependent metabolism of therapeutic drugs (Table 1) and participates in the metabolism of countless other xenobiotic chemicals. P450s from other families subserve a vari-

ety of specialized functions, particularly cholesterol and steroid synthesis and fatty acid metabolism [1,5].

P450 enzymes function as mono-oxygenases that insert one atom of oxygen into the substrate molecule. They have been alternatively referred to as 'mixed function oxidases' on account of their wide substrate specificities. Within hepatocytes, drug-metabolizing P450s are located in the smooth endoplasmic reticulum, in contrast to some synthetic P450s that are localized to the mitochondrial inner membrane. Drug-metabolizing P450 enzymes accomplish a wide variety of metabolic reactions including aliphatic and aromatic hydroxylation, *O*-, *S*- and *N*-dealkylation, oxidative and reductive dehalogenation, *N*-oxidation and *N*-hydroxylation, demethylation and deamination [6]. For example, CYP2D6 catalyses the *O*-demethylation of codeine to form morphine (Fig. 2), where the metabolite possesses greater pharmacological activity than the parent drug. Phase I-generated metabolites may be sufficiently water soluble for immediate elimination or may form substrates for phase II enzymes.

Phase II metabolism involves the conjugation of a hydrophilic chemical moiety to a drug molecule. Enzymes that accomplish this task are collectively known as 'transferases', as they catalyse the transfer of a moiety from a donor molecule to the drug recipient. For example, the UDP-glucuronosyltransferases (UGT) catalyse the transfer of the sugar α -glucuronic acid from the donor molecule uridine- α -glucuronide to a substrate molecule, as exemplified by morphine (Fig. 2). Most transferases also belong to gene families with individual members catalysing the conjugation of a distinct but often overlapping range of substrates. A list of enzymes commonly involved in phase II human drug metabolism is presented in Table 2. An important function of phase II enzymes is the detoxification of reactive molecules that may be generated by phase I drug metabolism [7].

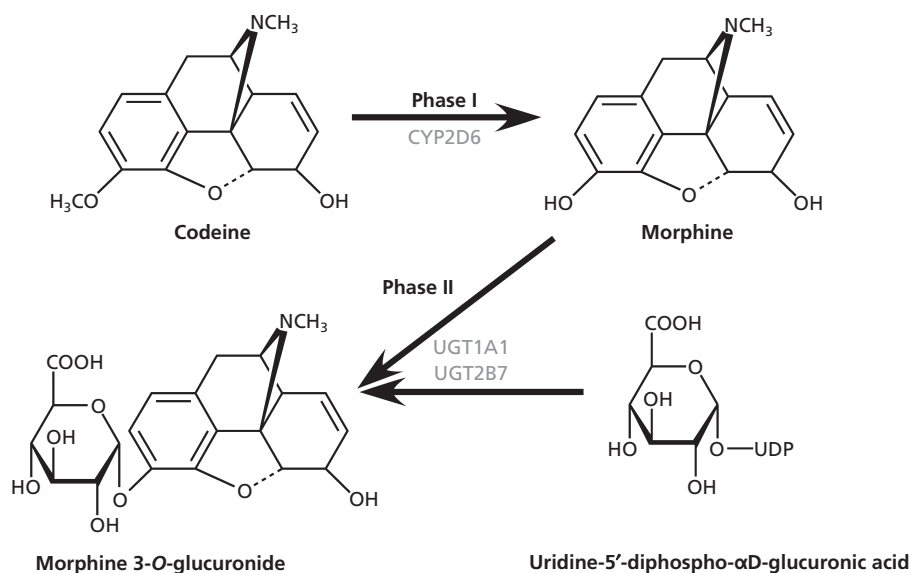


Fig. 2 Phases of hepatic drug metabolism as exemplified by codeine. Codeine is converted to morphine by CYP2D6-mediated *O*-demethylation, a phase I reaction. Morphine is subsequently conjugated by phase II enzymes UDP-glucuronosyltransferases (UGT) to form both 3-*O*- and 6-*O*-glucuronide metabolites, the pharmacologically inactive 3-*O* metabolite being shown in this figure.

Table 2 Some major human phase II drug-metabolizing enzymes and receptors implicated in regulation.

Superfamily	Function	Substrate examples	Gene families ^a	Receptors implicated in regulation ^b
Glutathione <i>S</i> -transferases (GST)	Catalyse nucleophilic attack by GSH on non-polar compounds	Adriamycin, BCNU, busulfan, carmustine, chlorambucil, cyclophosphamide, DDT, inorganic arsenic, pesticides	GSTA ^c GSTM GSTP GSTS GSTT1 GSTZ GSTO	GSTA2 CAR, PXR AhR
Sulphotransferases (SULT)	Sulphation	Steroid hormones, bile acids, isoflavones, paracetamol, minoxidil	SULT1 ^d SULT2 SULT4	SULT1A1 SULT2A1 CAR VDR
<i>N</i> -acetyltransferases (NAT)	<i>N</i> -acetylation, <i>O</i> -acetylation	Arylamines <i>N</i> -hydroxylated heterocyclic amines	NAT1 NAT2	
UDP-glucuronosyltransferases (UGT)	Glucuronidation	Bilirubin, paracetamol, morphine, zidovudine, NSAIDs	UGT1A UGT2B	UGT1A1 UGT1A6 UGT2B4 UGT2B7 PXR, CAR, HNF1α AhR, SHP FXR, ?PPAR HNF1α

BCNU, carmustine; GSH, reduced glutathione; NSAID, non-steroidal anti-inflammatory drug.

^aOnly significant human families are listed.

^bOnly nuclear receptors implicated in the regulation of human enzymes are listed.

^cCytosolic GSTs are shown; mitochondrial and microsomal GSTs are not shown.

^dOnly cytosolic SULTs are included in the nomenclature.

Drug transporters

Cloning and characterization of plasma membrane-bound hepatocyte transporters has revealed that many drugs enter and exit hepatocytes by energy-dependent transporters rather than by simple diffusion (Fig. 1, Table 3) [8]. The predominant trans-

porters involved in drug uptake are members of the solute carrier (SLC) transporter superfamily, which are located on the sinusoidal (basolateral) plasma membrane. In contrast, transporters responsible for the excretion of drugs and drug metabolites from hepatocytes belong to the ATP-binding cassette (ABC) transporter superfamily and are located on

Table 3 Major hepatic drug transporters: nomenclature, function and nuclear receptor regulation.

Trivial symbol (gene symbol)	Name	Nuclear receptor	Function and substrates
Basolateral membrane of hepatocyte			
OATP1B1 (SLCO1B1) ^a	Organic anion-transporting proteins	FXR, HNF1 α , ?PXR	Hepatic uptake of organic anions and cations e.g. enalapril, digoxin, HMG-CoA reductase inhibitors, BA, bilirubin
OATP1B3 (SLCO1B3) ^b			
OCT1 (SLC22A1)	Organic cation transporter		Hepatic uptake of hydrophilic organic cations e.g. cimetidine, choline, dopamine, acyclovir, zidovudine
OAT2 (SLC22A7)	Organic anion transporter		Hepatic uptake of organic anions and drugs e.g. salicylate, methotrexate, non-steroidal anti-inflammatory drugs
NTCP (SLC10A1)	Na ⁺ -taurocholate cotransporting polypeptide	SHP/FXR	Na ⁺ -dependent uptake of conjugated BA from portal blood
MRP1 (ABCC1)	Multidrug resistance-associated proteins	PXR	Drug export from hepatocytes, e.g. VP16, colchicine, etoposide
MRP3 (ABCC3)		PXR, FTF ?CAR	Organic solute transporter: extrudes BA conjugates, methotrexate, etoposide
MRP4 (ABCC4)			Mediates glutathione efflux from hepatocytes into blood by cotransport with BA; also exports purine and nucleoside analogues
Canalicular membrane of hepatocyte			
MDR1 (ABCB1)	Multidrug resistance-1	PXR	Excretion of organic cations, xenobiotics and cytotoxins to bile e.g. colchicine, doxorubicin, adriamycin, vinblastine, paclitaxel, vincristine
MDR3 (ABCB4)	Multidrug resistance-3	FXR, PPAR α	Phospholipid export pump: translocates phosphatidylcholine from inner to outer leaflet of membrane bilayer
MRP2 (ABCC2)	Multidrug resistance-associated protein-2	PXR, CAR ?FXR	Mediates multispecific organic anion transport into bile, e.g. bilirubin diglucuronide, sulphates, glutathione conjugates, vinblastine, sulphapyrazone
BSEP (ABCB11)	Canalicular bile salt export pump	FXR	ATP-dependent transport of monovalent bile salts and ?paclitaxel into bile
FIC1 (ATP8B1)	Familial intrahepatic cholestasis-1		Potential aminophospholipid-translocating ATPase
AE2 (SLC4A2)	Chloride–bicarbonate anion exchanger isoform-2		Facilitates bicarbonate secretion into bile, stimulates BA-independent bile flow
ABCG5/ABCG8	'Half ABC transporters'	FXR, PXR LXR	Transport sterols into bile. May partially mediate biliary cholesterol secretion
BCRP (ABCG2)	'Half ABC transporters'		Mediates cellular extrusion of sulphated conjugates, ?estramustine

BA, bile acids; CAR, constitutive androstane receptor; FTF, fetal transcription factor (also called liver receptor homologue 1, LRH1); FXR, farnesoid X receptor; LXR, liver X receptor; MDR1 protein is also known as P-glycoprotein; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; SHP, short heterodimer partner; HNF, hepatocyte nuclear factor.

^aOATP1B1 is also known as OATP-C, OATP2, LST-1.

^bOATP1B3 is also known as OATP8, LST-2.

the biliary canalicular (apical) plasma membrane, where they mediate the excretion of drugs into bile, or on the sinusoidal membrane, where they mediate efflux back into the circulation. Hepatocyte transporters and their functions are covered in more detail in Chapter 2.2.4.

Interindividual differences in drug metabolism

Clinicians are well aware that individual dose requirements of drugs for patients can vary widely, even in the absence of obvious confounding factors such as drug–drug interactions [9]. For many drugs, a significant component of this interindividual difference can be attributed to variability in drug

metabolism [10]. Importantly, metabolism cannot be reliably predicted by simple anthropomorphic characteristics such as body mass, body surface area, gender, age or race. While some variability can now be attributed to allelic variation within drug-metabolizing genes (Table 4), hepatic and intestinal expression of the most important and abundant human P450 enzyme CYP3A4 exhibits a unimodal distribution that cannot be explained by genetic polymorphism [5]. As CYP3A4 is intimately involved in the metabolism of many endogenously synthesized compounds, such as bile acids and eicosinoids in addition to therapeutic drugs, it now seems likely that variation in CYP3A4 may be the result of homeostatic regulatory mechanisms. In this respect, nuclear receptors that have endogenous ligands, such as the farnesoid X receptor (FXR) and the

Table 4 Genetic polymorphisms of some major human drug-metabolizing enzymes and transporters.

Gene	Major allelic variants	Prevalence of PM phenotype (%)		Examples of drugs affected by PM status
		Caucasian	Asian	
CYP1A2	CYP1A2*1K	–	–	Phenytoin, caffeine
CYP2A6	CYP2A6*4, CYP2A6*9	~ 0	2–4	Nicotine
CYP2B6	CYP2B6*6	–	–	Cyclophosphamide
CYP2C9	CYP2C9*2, CYP2C9*3	1–2	0.04	Phenytoin, glipizide, tolbutamide, warfarin, irbesartan
CYP2C19	CYP2C19*2, CYP2C19*3	2–5	10–25 ^a	Diazepam, omeprazole, lansoprazole, imipramine, fluoxetine, sertraline, nelfinavir
CYP2D6	CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17, CYP2D6*41, CYP2D6*2xn ^b	5–10	1–2	Codeine, metoprolol, tricyclic antidepressants, venlafaxine, ondansetron, tropisetron, perhexiline
DPD	DPYD*2A	3	?	5-Fluorouracil
NAT	NAT2*5B, NAT2*6A ^c	50	< 40	Isoniazid, procainamide, hydralazine, sulphonamides
TPMT	TPMT*2, TPMT*3A, TPMT*3C	0.3	< 0.3	Azathioprine, 6-mercaptopurine
UGT1A1	UGT1A1*28, UGT1A1*6, UGT1A1*27	0.5–10	~ 3	Irinotecan, lamotrigine
MDR1	C3435T, G2677T	–	–	Digoxin, ciclosporin, tacrolimus, protease inhibitors
OATP1B1	OATP-C*5, OATP-C*1b	< 2%	–	Pravastatin

DPD, dihydropyrimidine dehydrogenase; PM, poor metabolizer; TPMT, thiopurine S-methyltransferase.

^aThe CYP2C19 PM phenotype is more common throughout Polynesia and Micronesia, with an incidence between 38% and 79%.

^bCYP2D6 gene duplication results in increased CYP2D6 activity, the ultrarapid metabolizer (UM) phenotype. At least 75 CYP2D6 alleles have been identified.

^cPhenotypes include slow, intermediate or fast acetylators. NAT1*, wide heterogeneity; NAT2*, at least 13 point mutations described [36].

pregnane X receptor (PXR), as well as other transcription factors important in the expression of liver-predominant genes such as hepatocyte nuclear factor 4 α (HNF4 α) and CCAAT/enhancer-binding protein β (C/EBP β), have all been shown to be important regulators of CYP3A4 gene transcription [11–14].

Regulation of drug-metabolizing pathways

In an evolutionary sense, the ability to respond to a potentially toxic chemical challenge through the upregulation of endobiotic and xenobiotic metabolizing and transporting genes would be expected to confer a survival advantage. It is therefore not surprising that many drug disposition pathways are inherently variable and are capable of responding to a wide range of chemical stimuli. Recent work has shown that several drug-metabolizing and -transporting genes are subject to adaptive regulation, predominantly by nuclear receptors [15]. Members of the nuclear receptor superfamily function as ligand-activated transcription factors and have critical roles in diverse cellular processes. A subset of nuclear receptors that heterodimerize with the receptor for 9-*cis* retinoic acid- α (RXR) recognises a range of small lipophilic molecules that includes xenobiotic compounds, including a range of therapeutic drugs. The two receptors identified to date that have this role are PXR and the constitutive androstane receptor (CAR) [16]. PXR and CAR are capable of transcriptional induction of an array of drug-metabolizing and -transporting genes that cover all phases of hepatic drug disposition (Tables

1–3). In addition, nuclear receptors that appear to have exclusively endobiotic ligands such as the farnesoid X receptor (FXR) and the vitamin D receptor (VDR) have also been implicated in the regulation of drug-metabolizing pathways. Interestingly, PXR, FXR and VDR are all capable of binding and responding to bile acids, reinforcing the concept that drug metabolism is interrelated with cholesterol and bile acid homeostasis [17]. CAR appears to subservise additional roles in bilirubin and energy homeostasis [18], although its precise roles as an endogenous regulator remain enigmatic.

Role of genetic variation (pharmacogenetics)

The term ‘pharmacogenetics’ can be defined as the study of genetically determined variation in drug response. Pharmacogenomics is the use of genetic information to individualize drug therapy, a science that is still in its infancy. We now recognize that many genes involved in drug metabolism and transport are subject to genetic polymorphism, which may result in changes in drug disposition and, hence, both drug efficacy and drug toxicity [9,10]. All phases of drug disposition are now recognized to be affected by genetic variability, and some clinically relevant examples are listed in Table 4.

To date, genetic variation in cytochrome P450-mediated metabolism has been most intensively studied, and polymorphic forms of P450s are responsible for the development of a significant number of adverse drug reactions (ADRs) [19].

High-throughput analysis of P450 polymorphisms is already commercially available, but its impact on drug prescribing is not yet clear. All genes encoding P450 enzymes in families 1–3 are polymorphic to some degree. However, the functional importance of the variant alleles differs, and the frequencies of their distribution in different ethnic groups also vary. In general, four phenotypes can be identified: poor metabolizers (PMs), who lack the functional enzyme; intermediary metabolizers (IMs), who are heterozygous for one deficient allele or carry two alleles that cause reduced activity; extensive metabolizers (EMs), who have two normal alleles; and ultrarapid metabolizers (UMs), who have multiple gene copies, a trait that is dominantly inherited. The consequences of PM status have been well characterized for some genotypes (e.g. CYP2D6), and this results in slow drug metabolism, high drug concentrations at ordinary dosage, a higher risk of ADRs and, in some cases, no response to some prodrugs (e.g. codeine). In contrast, UM status results in non-response to drugs that are substrates for the enzyme, particularly well demonstrated with tricyclic antidepressants. For nortriptyline, the optimum dose varies from as low as 20 mg/day in PMs to 500 mg/day in UMs [19]. While genotyping CYP2D6 mutations could prove clinically useful, over 70 allelic variants of this gene have been described, which makes this approach technically difficult and expensive.

An alternative approach to assessing variation in hepatic metabolism is to phenotype through the use of pharmacokinetic studies in which the patient is given a marker drug for a particular metabolic pathway and serum or urinary drug levels are used to estimate the rate of clearance. While technically feasible, this approach has not been widely adopted largely because of the inconvenience and cost involved, with clinicians usually opting for a pragmatic approach, adjusting drug dose based on signs of efficacy or toxicity. At present, the only pharmacogenetic test in routine clinical use is the genotyping or phenotyping of thiopurine S-methyltransferase (TPMT), an enzyme that is crucial for the detoxification of the immunosuppressant 6-mercaptopurine, particularly in bone marrow where alternative metabolism through xanthine oxidase is not present [20].

More recently, it has been appreciated that genetic polymorphism has important effects on phase II enzymes as well as drug transporters such as MDR1 and OATP2. There is still controversy as to whether, and to what extent, the pharmacokinetics and pharmacodynamics of drugs are modified by the various genotypes of *MDR1*. In contrast to the P450 polymorphisms, no loss-of-function mutations have been described for *MDR1* in humans, and the differences between genotypes with respect to protein expression are moderate when compared, for example, with CYP2D6 [21].

Factors determining the rate of hepatic drug clearance

Several factors determine the rate at which the liver clears a drug from the body [22]. The most important of these are: (i) hepatic blood flow, which determines the rate at which drugs

are delivered to the liver; (ii) binding to plasma proteins, as only unbound drug can be taken up by hepatocytes; (iii) affinity for hepatocyte uptake transporters; and (iv) the intrinsic affinity of hepatic enzymes for the drug as a substrate. The relative importance of these factors varies greatly for individual drugs, with hepatic blood flow being the main determinant of the rate of metabolism for very high metabolic clearance drugs and the other factors assuming more importance for drugs with low metabolic clearance. This has significant implications for patients with liver disease (see below).

Metabolic drug–drug interactions

At the level of hepatic drug metabolism, the two mechanisms of drug–drug interactions are induction and inhibition of drug-metabolizing enzymes. Examples of both are listed in Table 5. Inductive drug–drug interactions occur when an inducing drug causes an increase in the metabolism of coadministered drugs with a resultant diminution in their therapeutic effect. The most important enzyme affected by this form of interaction is CYP3A4 because of the potential magnitude of its induction and the vast array of drugs metabolized by this P450 enzyme [23]. Only relatively recently have the mechanisms of CYP3A4 induction by inducing drugs such as rifampicin, phenytoin, carbamazepine and the herbal remedy St John's Wort been elucidated. Most, if not all, CYP3A4-inducing drugs are now recognized to be ligands for PXR, a nuclear receptor that is highly expressed in hepatocytes and intestinal epithelial cells. PXR/RXR heterodimers bind to response elements in the regulatory upstream region of the CYP3A4 gene, resulting in transcriptional activation [12]. Several other drug-metabolizing genes and drug transporters are also induced by ligand-activated PXR, while a lesser number are activated by other receptors, including CAR and the aryl hydrocarbon receptor (AhR) [24,25].

Inhibition of metabolism by coadministered drugs is also a common cause of drug–drug interactions and occurs by two basic mechanisms. The most common mechanism of inhibition is simple competition between drugs for access to the catalytic pocket of the relevant drug-metabolizing enzyme. Some drugs are highly effective competitors for P450 enzymes, including cimetidine, ketoconazole and indinavir. The second way in which drugs inhibit P450s, often referred to as 'mechanism-based P450 inhibition', involves the formation of a catalytically inactive, covalently bound complex between a metabolite of the substrate drug and the P450 enzyme [26]. Macrolide antibiotics such as erythromycin and clarithromycin as well as tamoxifen, fluoxetine and the anti-HIV agents ritonavir and delavirdine are examples of drugs that interact in this way.

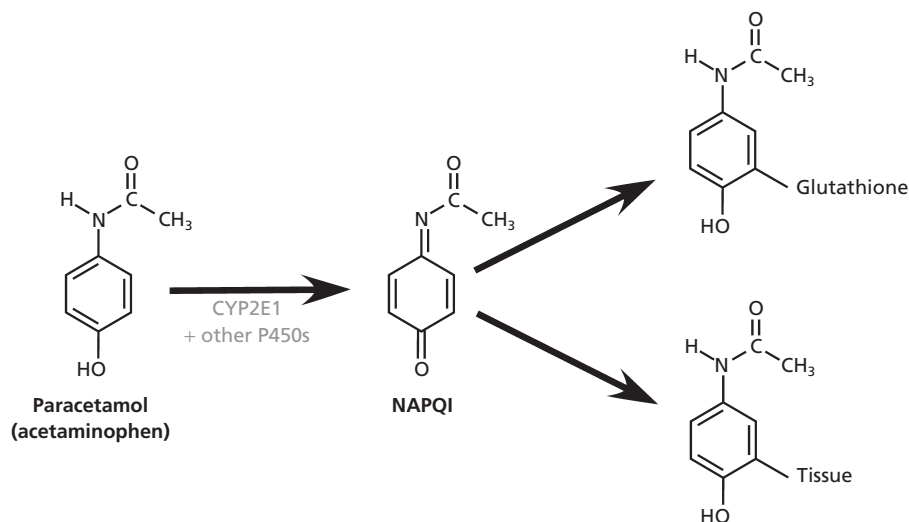
Role of metabolism in drug activation and drug toxicity

Drug metabolism usually results in metabolites with less pharmacological activity and less toxicity, but this is not always the

Table 5 Drug substrates, inhibitors and inducers of some cytochrome P450 enzymes.

P450 enzyme	Common drug substrates	Inhibitors	Inducers
CYP1A2	Clozapine, clomipramine, estrogen, fluvoxamine, haloperidol, tacrine, theophylline	Amiodarone, cimetidine, fluoroquinolones, ticlopidine	Polycyclic aromatic hydrocarbons omeprazole, ritonavir, phenobarbital
CYP2C9	Phenytoin, warfarin, tolbutamide, glipizide	Amiodarone, fluconazole, miconazole, phenylbutazone, sulphinpyrazone	Carbamazepine, phenobarbital, rifampin, St John's Wort
CYP2D6	Alprenolol, bufuralol, carvedilol, metoprolol, propranolol, timolol, amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, flecainide, mexiletine, propafenone, fluoxetine, haloperidol, paroxetine, perphenazine, venlafaxine, codeine, dextromethorphan	Clomipramine, quinidine, fluoxetine, haloperidol, paroxetine	Not inducible
CYP2E1	Paracetamol, benzene, ethanol, isoflurane, theophylline	Disulfiram, diethyl-dithiocarbamate	Ethanol, isoniazid
CYP3A	Diltiazem, felodipine, nifedipine, verapamil, ciclosporin, tacrolimus, alprazolam, midazolam, triazolam, atorvastatin, lovastatin, clarithromycin, erythromycin, indinavir, nelfinavir, ritonavir, saquinavir, losartan, sildenafil	Diltiazem, verapamil, itraconazole, ketoconazole, clarithromycin, erythromycin, troleandomycin, delavirdine, indinavir, ritonavir, saquinavir, grapefruit juice, mifepristone, nefazodone	Rifabutin, rifampin, rifapentine, carbamazepine, phenobarbital, phenytoin, topiramate, efavirenz, nevirapine, St John's Wort

Fig. 3 Metabolic activation of paracetamol (acetaminophen) to a hepatotoxic metabolite. Phase I metabolism, predominantly mediated by CYP2E1, involves *N*-hydroxylation of paracetamol to form the electrophilic intermediate *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI is in turn detoxified by a spontaneous reaction with hepatic glutathione. Non-detoxified NAPQI can bind covalently to macromolecules within hepatocytes causing hepatic necrosis, as occurs in paracetamol overdose.



case. For example, irinotecan, a drug used for the chemotherapy of colorectal cancer, is a prodrug that requires metabolic activation by CYP3A4 to a compound named SN-38, which is the active pharmacological agent. SN-38 is subsequently detoxified by conjugation with α -glucuronic acid catalysed by UGT1A1. Individuals with the common genetic hyperbilirubinaemia Gilbert's syndrome are partially deficient in UGT1A1 and experience excessive toxicity when administered standard doses of irinotecan [27]. Metabolic activation applies not only to therapeutic drugs. Of concern is that some procarcinogens, such as heterocyclic amines, can be activated by P450 enzymes to carcinogenic metabolites [28].

Drug metabolism also contributes to both dose-related and idiosyncratic drug-induced hepatotoxicity. Paracetamol is a classic example of dose-related toxicity. The P450-mediated phase I metabolism of paracetamol (acetaminophen) gives rise to the reactive intermediate *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is detoxified by a spontaneous reaction with hepatic glutathione (Fig. 3), a cysteine-containing triamino acid peptide. In the setting of paracetamol overdose, the rate of formation of NAPQI exhausts hepatic-reduced glutathione stores, and hepatocellular toxicity ensues [7]. While reactive metabolites have been identified for many drugs exhibiting idiosyncratic toxicity, the mechanisms by which tissue damage

occurs and propagates remain poorly understood. It is thought that some idiosyncratic hepatic reactions to drugs are the result of drug metabolites being covalently bound to cellular proteins, either causing altered protein function or engendering an immunological response with subsequent recruitment of inflammatory cells, production of proinflammatory cytokines and Fas- or porin-mediated induction of apoptosis [7] (see also Chapters 3.1 and 14.1). In the past, it has been difficult to estimate the likelihood of a drug causing idiosyncratic hepatotoxicity, but recent advances in proteomics and metabolomics may begin to allow prediction of the proclivity of a drug to cause this form of toxicity, before human studies are undertaken [29].

Drug metabolism in liver disease, portal hypertension and systemic disease states

Liver disease and portal hypertension

In advanced liver disease, drug metabolism mediated by some P450 enzymes or enzyme subfamilies, particularly CYP1A, 2C19 and 3A, appears to be impaired to an extent that cannot be explained by simple hepatocellular loss, and suggests specific downregulation of these genes [30]. This loss of metabolism varies with the cause of liver disease; for example, in patients with a predominant cholestatic aetiology, CYP3A activity is relatively preserved [31], possibly because of positive regulation by retained bile acids acting through PXR and FXR. There is a strong relationship between quantitative measures of hepatic drug metabolism such as the aminopyrine breath test and the Child–Pugh score [30], although such metabolic measurements may not be better predictors of the severity of liver disease than clinical assessment in combination with more readily available and less expensive biochemical tests.

In the presence of portal hypertension, hepatic blood flow may be reduced in combination with increased portal–systemic shunting through collateral blood vessels. This can dramatically increase the bioavailability of high clearance drugs, for example propranolol, a drug that is commonly used in cirrhotic patients to lower portal vascular pressure. Such patients often require a relatively low dose of this drug to achieve a therapeutic effect and avoid side-effects such as excessive bradycardia. At the other end of the spectrum, the rate of metabolism of low clearance drugs is particularly sensitive to any factor that affects the availability of drug-metabolizing enzymes, as occurs with loss of hepatocellular mass in liver disease. A good example is diazepam, which exhibits a 50% reduction in clearance in advanced liver disease [32]. An additional factor that alters drug disposition in advanced liver disease is decreased plasma protein binding due to decreased hepatic protein synthesis. This results in increased action of drugs that usually circulate in a highly bound state. Issues relating to prescribing drugs in patients with liver diseases are covered in Chapter 23.3.

Drug metabolism in inflammatory states

In the early 1980s, it was recognized that theophylline toxicity occurred in children with influenza, despite being on a non-toxic dose of the drug prior to falling ill [33]. It was subsequently shown that several inflammatory states were associated with decreased expression of some hepatic P450 enzymes and that interleukin-1, interleukin-6, interferons and bacterial lipopolysaccharide were capable of mediating this phenomenon, predominantly operating through transcriptional repression [34]. More recently, it has been proposed that some patients with advanced cancer may experience excessive toxicity from chemotherapy because of diminished hepatic metabolism of anticancer drugs, even when the malignant process does not directly involve the liver. In this situation, it appears that the cancer is modulating drug-metabolizing enzymes through either the direct or the indirect release of proinflammatory cytokines [35].

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