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Review

Stereochemical determinants of the nature and consequences of drug metabolism

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Abstract

Enantiomeric discrimination in drug disposition depends on the mechanism of the process under consideration. Absorption, distribution and excretion are generally passive processes which do not differentiate between enantiomers, but enzymic metabolism and protein binding, to plasma or tissue proteins, can show a high degree of stereoselectivity. In terms of metabolism, chiral discrimination occurs at both substrate and product levels, giving rise to five distinct stereochemical courses for drug metabolism, namely (i) prochiral→chiral, (ii) chiral→chiral, (iii) chiral→diastereoisomer, (iv) chiral→non-chiral and (v) chiral inversion. As a result, the metabolic and pharmacokinetic profiles of enantiomers after administration of racemic drugs can be very variable, so that the exposure to the two enantiomers may be very different. There now an enormous number of examples of each of these possibilities. The net result of the interaction of the stereoselectivities of these various processes can obscure the fact that one (or more) shows a marked stereoselectivity. This is particularly the case for metabolism: while the ratios of the total plasma clearance of the enantiomers of a wide range of drugs never exceed 2, individual metabolic pathways often show much greater stereoselectivity. This is particularly evident for those high-affinity, low-capacity enzyme systems which exhibit genetic polymorphism, namely the human cytochromes P450 2C18 and 2D6. This review provides an introduction to the stereoselectivity of drug metabolism.

Contents

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1. Introduction

One in four of all therapeutic agents is marketed and administered to man as mixtures, not drug combinations in the accepted sense of two or more coformulated therapeutic agents, but combinations of isomeric substances whose biological activity may well reside predominantly in one optical form. The majority of these are racemic mixtures of synthetic chiral drugs; mixtures of diastereoisomers are used less frequently. The use of such agents may be regarded as polypharmacy with the proportions of the various optical forms present being dictated by chemical rather than pharmacological or therapeutic criteria. The use of such mixtures may contribute to the toxicity or adverse effects of the material, particularly when these are associated with the pharmacologically less active or inactive isomers, unrelated to the stereochemistry of the compound(s), not associated with the mechanism of action of the material, or idiosyncratic reactions.

It was a matter of early experience in biochemistry and pharmacology that the receptors and enzymes which are the targets of drug action are able to discriminate between stereoisomers. In contrast, the realization of the importance of chiral discrimination for the pharmacokinetic phase of drug action is more recent. The availability of novel analytical modalities has led to substantial growth in our knowledge of the nature, magnitude and consequences of such discrimination. The pharmacokinetic importance of drug stereochemistry depends on the mechanism of the process under consideration: passive processes such as diffusion across membranes do not involve macromolecular interactions and stereochemistry has little influence, but when the drug interacts with an enzyme or a transporter system, then discrimination may be seen. There are now a range of examples showing differences between stereoisomeric forms of numerous drugs in terms of their absorption, distribution, metabolism and excretion. Although often of biological importance, the magnitude of these differences is generally much less than those exhibited by receptor and enzyme targets.

Much currently available metabolic and pharmacokinetic data on racemic mixtures is derived from the non-selective assay of the total drug present in biological media, i.e. the sum of the individual enantiomers. Such data have at best limited value and can be highly misleading, particularly when attempting to relate plasma concentrations to pharmacological effect or therapeutic benefit. The examination of the pharmacokinetics of individual isomers permits the determination of the "true" pharmacokinetic parameters of the active agent and provides a basis for the determination of enantiomeric potency ratios and, if required, rational therapeutic drug monitoring. Enantiospecific pharmacokinetic studies have explained apparent anomalies in drug concentration–effect relationships with route of administration. Toxicity testing of drugs and other xenobiotics is carried out using animal models and there are a number of examples where the disposition of the enantiomers of racemic drugs differ markedly between species (see below). Examination of the pharmacokinetics of the enantiomers of racemic drugs in various species is therefore necessary for the effective extrapolation of preclinical safety data to the human situation.

The significance of stereochemical considerations in drug metabolism and pharamacokinetics has recently become an issue for both the pharmaceutical industry and the regulatory authorities [1]. Recent developments in methodology for both the analytical and preparative resolution of racemic drug mixtures [2–4] have provided a major stimulus for the present considerable interest in stereochemical considerations in drug disposition.

2. Stereochemistry of drug metabolism

The interaction of the enantiomers of a chiral drug molecule with a chiral macromolecule, such as an enzyme, results in the formation of a pair of diastereoisomeric complexes, which differ energetically. It is therefore not surprising that the products of enzyme-mediated reactions carried out on a pair of enantiomers may vary in

nature and/or extent. Indeed, as to the nature of the enzyme–substrate complex, it is reasonable to assume that enantioselectivity in metabolism is the rule rather than the exception. Similarly, the binding of a prochiral substrate to an enzyme may well orientate two enantiotopic groups differently with respect to the enzyme catalytic site and hence within the enzyme–substrate complex these two groups become diastereotopic. It is therefore relatively easy to appreciate why the formation of a chiral metabolite from a prochiral substrate may exhibit stereoselectivity for one isomeric product. Enzyme-mediated stereoselectivity, in terms of substrate and product, has been extensively reported and is the subject of a number of reviews [5–9].

Metabolic transformations of xenobiotics show two types of stereoselectivity, at substrate and product levels. They may therefore be classified in terms of their stereoselectivity or, if such selectivity is complete, their stereospecificity. This latter term should be used with some caution as the ability to detect "specificity" obviously depends on the analytical methodology employed. The terms substrate and product "stereospecificity" were first applied by Prelog [10] to the enzyme-mediated reduction of ketones, and were later extended to the reactions of drug metabolism by Jenner and Testa [5]. Substrate stereoselectivity refers to the preferential metabolism of one of a pair of stereoisomers over the other, whilst product stereoselectivity refers to the preferential formation of one particular stereoisomer over that of other possible stereoisomers. These two "selectivities" may be closely linked such that substrate–product stereoselectivity may also be observed, i.e., the selective metabolism of one of a pair of enantiomers to produce one of a number of potentially diastereoisomeric products.

Data obtained from in vivo studies must be treated with some care if the enantiomeric composition of a drug or metabolites determined in excreta is to be used as an indication of stereoselectivity in metabolism. In such cases the observed enantiomeric excess may reflect a number of stereoselective processes, e.g., absorption, protein binding, selective tissue uptake, renal and/or bilary excretion, in addition to metabolism. Hence the enantiomeric composition of metabolites may not be a reflection of enzyme activity.

Metabolic transformations may be categorized in terms of their various stereochemical courses. Reaction types in Sections 2.2–2.4 below and the metabolic chiral inversion differ from the type in Section 2.1 in that the stereochemistry of the substrate, together with that of the enzyme binding site and/or catalytic site, influence the nature of the product formed. Hence in the cases of the reactions in Sections 2.2–2.4 and the chiral inversion, use of an individual enantiomer in place of a racemic mixture may have a significant influence on the properties of a drug. Examples of these various possibilities are now discussed under the headings of the various reaction types.

2.1. Prochiral to chiral transformations

A non-chiral compound may become chiral by metabolism of enantiotopic groups, either at a prochiral centre, e.g., oxidation of ethylbenzene to yield 1-phenylethanol and oxidation of 4-tolyl ethyl sulphide to the corresponding sulphoxide, or at a site remote from a prochiral centre, e.g., aromatic oxidation of phenytoin to yield 4-hydroxyphenytoin [5]. The reduction of non-symmetrically substituted ketones gives rise to a new chiral centre in the product secondary alcohols. A considerable number of prochiral ketones have been examined as substrates and their reduction proceeds with high stereoselectivity to give the (*S*)-alcohols in 80% or greater excess [5].

Reactions of this type are potentially the most complex to deal with from a toxicological viewpoint, as the stereochemistry of the product is determined by the binding orientation of the substrate towards the enzyme active site and are not open to control at the level of the stereochemistry of the substrate. The metabolism of prochiral substrates, an example of what has been termed "product enantioselectivity", is of considerable interest. In such cases, the chirality of products is solely a function of the biological

system responsible for the metabolism and obviously cannot be influenced by the drug substrate administered. If the chiral metabolite is biologically active and this activity shows enantioselectivity, a by no means unlikely situation, then inter-species (in animals) and inter-individual (in humans) variation in metabolic enantioselectivity, which is observed with increasing frequency, will have an impact on the drug's action.

2.2. Chiral to chiral transformations

There are numerous examples of chiral compounds whose individual enantiomers are transformed at different rates and/or by different routes to metabolites which retain their original chirality.

The enantiomers of a chiral drug may be transformed by different routes and/or at different rates to yield metabolites without alteration of the stereochemistry of the product relative to the substrate, e.g., the oxidation of warfarin in man is stereoselective for the *S*-enantiomer of the drug to yield (*S*)-7-hydroxywarfarin [7]. The carboxylic acid metabolite of primaquine, a drug used to treat malaria, has been identified as the principal plasma metabolite in man. Primaquine has a chiral centre in its alkyl side-chain and studies have shown that there is a stereoselective formation of the carboxylic acid metabolite from (−)-primaquine [11]. Stereoselectivity in ester hydrolysis has been shown for a variety of ester-containing compounds [12–14]. The stereoselectivity of the hydrolysis of the β-blocker esmolol by blood estereases differs markedly between species [15].

2.3. Chiral to diastereoisomeric metabolites

Chiral drugs may be metabolized to yield diastereoisomers by transformation of prochiral (diastereotopic) groups or by combination with a conjugating agent derived from the chiral pools of the body (see below).

Many chiral drugs undergo metabolic conversion in which a second chiral centre is introduced, thus producing diastereoisomers, e.g., oxidation of perhexiline and pentobarbitone. This is exemplified by the metabolism of hexobarbital by rat liver microsomes [16]. (+)-Hexobarbital was metabolized 1.5 times faster than the (−)-enantiomer, with both enantiomers exhibiting high stereoselectivity for the formation of the hydroxylated metabolites. (+)-Hexobarbital forms β-3′-hydroxyhexobarbital whereas the (−)-enantiomer is preferentially metabolized to α-3′-hydroxyhexobarbital. Investigations of the metabolic stereochemistry of warfarin have shown that the principal routes of metabolism are aromatic hydroxylation of the 7-position of the coumarin ring and ketone reduction in the side-chain [17]. The latter route produces a new chiral centre which results in the production of diastereoisomers. In the cases of warfarin and its analogues, the *R*-enantiomers are converted into the (*S*)-alcohols [18] by two enzymes present in rat liver cytosol.

The conjugation reactions of drug metabolism are energy-requiring biosyntheses, involving the linkage of the drug or a metabolite to an endogenous conjugating agent to give a characteristic product known as a conjugate. The endogenous conjugating agents, or endocons, are generally derived from activated synthetic intermediates with well defined roles in intermediary metabolism. However, in two cases, the required energy is derived by activation of the drug prior to transfer of the conjugating agent. With glutathione conjugation, this is by oxidation or, rarely, reduction, whereas for amino acid conjugation, there is a link with lipid biochemistry through the formation of high-energy acyl CoA intermediates.

The endocons can be divided into two groups, achiral and chiral. The former include methyl and acetyl groups, sulphate and the amino acids glycine and taurine. Chiral endocons, which are quantitatively more significant, are glucuronic acid, glucose, glutathione and glutamine, derived from chiral pools and of fixed configuration. Conjugation of enantiomeric drugs will give epimeric pairs of diastereoisomeric conjugates, in which the configuration of the endocon is fixed. Two possible stereochemical courses can be discerned for conjugation reactions: enantio-

mers can be conjugated at different rates with an achiral endocon, or with a chiral endocon to give pairs of diastereoisomeric conjugates, perhaps at different rates. The first case shows substrate enantioselectivity whereas the second exhibits substrate/product enantioselectivity. The formation of diastereoisomeric conjugates is of considerable significance since they will have different physico-chemical properties: this underlies their facile chromatographic discrimination without the need for chiral phases. Examples include the glucuronides of 2-phenylpropionic acid [19] and oxazepam, the glutamine conjugate of 4-chlorophenoxypropionic acid and the glutathione conjugates of bromoisovalerylurea and bromovaleric acid [20].

A number of examples can be cited to show the importance of conjugation reactions for discrimination between enantiomers in biological systems. The anti-inflammatory drug carprofen shows enantioselective glucuronidation (Fig. 1), which governs its pharmacokinetic properties. The renal clearance of the (S)-D-glucuronide diastereoisomer is twice that of the (*R*)-D-glucuronide epimer. Since there is preferential conjugation of (*S*)-carprofen, the result is

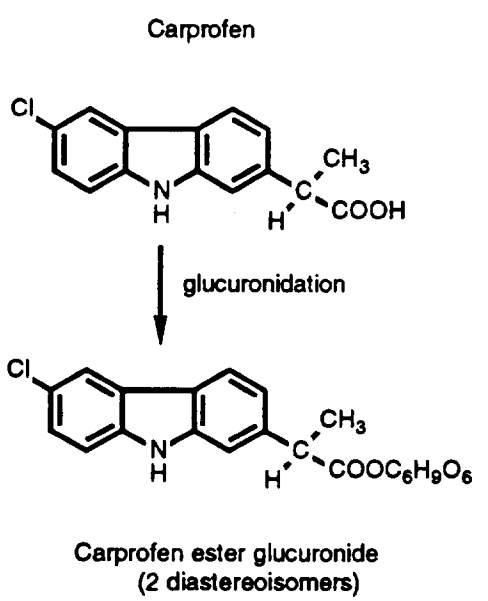

Fig. 1. Conjugation of the anti-inflammatory acid carprofen with glucuronic acid to yield diastereomeric glucuronides.

that the area under the plasma concentration–time curve (AUC) of both (*S*)-carprofen and its glucuronide are lower than those of the *R*-enantiomer [21].

The major biliary metabolites of both (+)- and (−)-menthol are their glucuronides, there being a twofold difference in the rates of their formation by rat liver slices and by rat hepatic microsomes [22]. The plasma elimination half-life of (−)-menthol is 2.4 h compared with 4.0 h for (+)-menthol, with the plasma AUC of (−)-menthol being threefold less than for the (+)-isomer. These pharmacokinetic differences arise from the enormous difference between the isomers in terms of the biliary excretion of their glucuronides: 69% of a dose of the more rapidly cleared (−)-menthol is excreted in the bile in 24 h compared with only 32% for (+)-menthol.

There are numerous other examples of enantioselectivity in the formation of glucuronic acid conjugates with a variety of drug classes, including the 2-arylpropionic acid anti-inflammatory drugs, β-blockers and tricyclic antidepressants.

Many examples can be cited to show the substrate enantioselectivity of glutathione conjugation, notably with epoxides. A well documented example of the importance of the stereochemistry of glutathione conjugation in the metabolism and excretion of a compound is that of bromoisovalerylurea (BIU), which has been systematically studied by Mulders et al. [20]. This now outmoded ureide hypnotic is chiral at the carbon bearing the bromine atom and the major routes of its metabolism are amide hydrolysis to bromoisovaleric acid (BI) and displacement of the bromine atom by glutathione (Fig. 2). The diastereoisomeric isovalerylureide–glutathione (IU–(*S*)-G) conjugates are readily separated by reversed-phase HPLC, allowing the relative rates of the formation and metabolism to be studied. In rat hepatocytes, (*R*)-BIU is converted into both (*R*)-IU–(*S*)-G and (*R*)-BI, but the (*R*)-BI so formed is not conjugated with glutathione (Fig. 3). In contrast, the major pathway of (*S*)-BIU metabolism is hydrolysis, with only small amounts of (*S*)-IU–(*S*)-G formed, but in this case (*S*)-BI is extensively conjugated with glutathione (Fig. 3). The implications of these find-

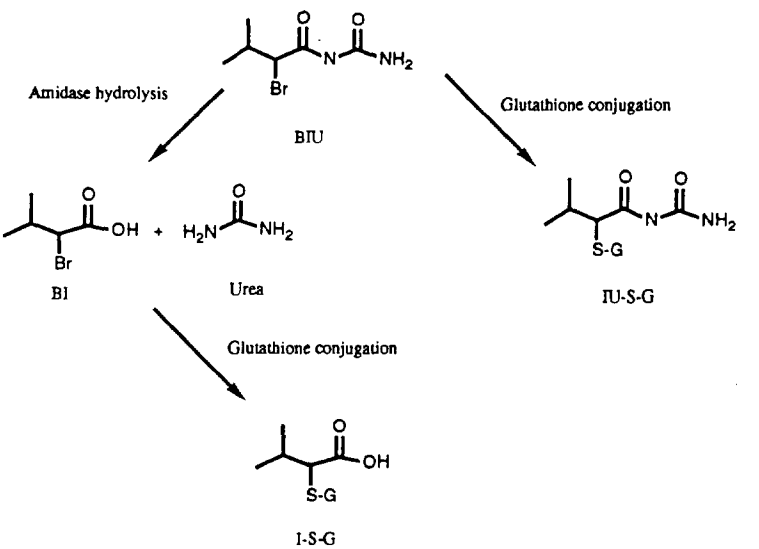

Fig. 2. Metabolic pathways of bromoisoval (2-bromoisovalerylurea).

ings for the eliminations of BIU are harder to discern. Much more (*R*)-IU–(*S*)-G is excreted in rat bile than its *S*-epimer, which agrees with the stereoselectivity of their formation.

Glutathione conjugates undergo extensive further metabolism prior to urinary elimination: in the rat, the major excretion products are mercapturic acids (S-substituted N-acetylcysteine conjugates, produced by hydrolysis and N-acetylation), whose stereochemistry cannot be easily related to that of their parent glutathione conjugates.

2.4. Chiral to non-chiral transformations

Chirality may be lost by oxidative metabolism at a chiral centre, e.g., oxidation of secondary alcohols to yield ketones [5], deamination of amphetamine to yield phenylacetone [5,23] and oxidative aromatization of the dihydropyridine calcium channel blocking drugs such as nilvadipine. Such examples are rare, in part owing to the failure to search for them effectively.

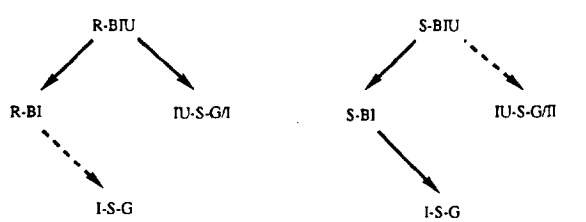

Fig. 3. Stereochemistry of the major metabolic routes of bromoisoval.

2.5. Metabolic chiral inversion

Certain drugs, e.g., oxazepam and thalidomide (Fig. 4), undergo rapid and extensive chemical racemization in vivo so that data concerning the biological properties of a single enantiomer should be viewed with some caution [24–26]. In addition, there are significant cases where metabolic chiral inversion can occur which have great impact on the biological properties of the drugs concerned. Indeed, these reactions are the origin of much of the current interest in stereochemistry in drug development.

Studies on the chiral inversion reaction have mainly involved the 2-arylpropionic acid (the "profens") non-steroidal anti-inflammatory drugs (NSAIDs) [27,28]. These agents possess a chiral centre α- to the carboxyl group and their pharmacological activity resides mainly in the enantiomers of the *S*-absolute configuration, the *R*-enantiomers being only weakly active or inactive in in vitro test systems [29–31]. These

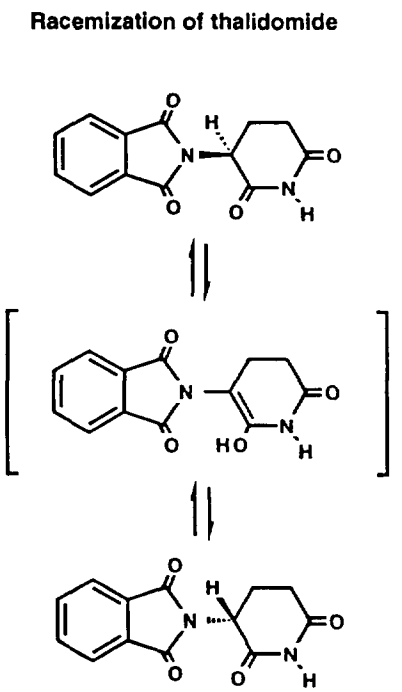

Fig. 4. Chemical racemization of thalidomide in aqueous solution at pH 7.4.

differences in in vitro activity become much less marked in vivo, mainly owing to the metabolic inversion of chirality of the *R*-enantiomers to their active *S*-antipodes [29,30]. The reaction therefore represents a metabolic activation of the *R*-enantiomers, which in some cases may be regarded as pro-drugs for the *S*-isomers.

Since the initial observations with ibuprofen, numerous related 2-arylpropionic acid NSAIDs have been shown to undergo chiral inversion, the extent of which depends on both the structure of the profen and the animal species under investigation.

The mechanism of the inversion reaction is thought to involve the stereospecific formation of a coenzyme A thioester from the *R*-enantiomer of the profen, which undergoes a number of alternative fates:

(i) racemization of the chiral centre in the profen moiety followed by hydrolysis to yield a mixture of enantiomers of the parent molecule;

(ii) hydrolysis with retention of configuration to yield the original (*R*)-2-arylpropionate; or

(iii) acyl transfer of the profen moiety to glycerol resulting in the formation of a hybrid triglyceride.

There are therefore a number of enzymic steps associated with the inversion of these agents, some of which may have toxicological significance.

The involvement of a coenzyme A thioester in the inversion reaction was first shown by Nakamura et al. [32]. Using a rat liver homogenate preparation, they reported that the formation of ibuprofen CoA thioester was dependent on both coenzyme A and ATP. Although synthetic samples of both (−)-(*R*)- and (+)-(*S*)-ibuprofen CoA thioesters were found to undergo racemization and hydrolysis on incubation with rat liver homogenates, only (−)-(*R*)-ibuprofen was converted into a thioester enzymatically. Knadler and Hall [33] examined the enantiomeric composition of the material incorporated into the thioesters and found this to be close to unity irrespective of the form of the compound used, i.e., the *R*-enantiomer or the racemate. Hence the thioesters once formed are racemized readily.

The formation of CoA thioesters of the profens may have considerable toxicological significance. Fears and Richards [34], using racemic mixtures of a number of profens, showed that these compounds were able to inhibit cholesterogenesis and fatty acid synthesis in vitro and that this activity was correlated with their ability to form hybrid triacylglycerols. The formation of such lipid acylglycerols and their incorporation into membranes have the potential to alter membrane structure and may be associated with disordered membrane function [35]. These effects are presumably related to the ability of these compounds to form acyl CoA thioesters with the acyl moiety being transferred to glycerol rather than undergoing hydrolysis to liberate the free profen. If the above is the mechanism, then the stereochemical composition of the profen should influence the incorporation into lipid.

This was first shown to be the case using racemic ibuprofen and its individual enantiomers. Following chronic administration of ibuprofen to rats, samples of fat were collected, the triglycerides were isolated and the stereochem-

istry of the incorporated material was investigated. Incorporation was greatest following administration of the *R*-enantiomer and the levels of both (*R*)- and (*S*)-ibuprofen in lipids were approximately twice those following administration of the racemate. Only trace amounts of drug were found in triglycerides following administration of the *S*-enantiomer [36]. The stereoselective incorporation of (*R*)-fenoprofen into hybrid triacylglycerols has also been reported using hepatocyte and adipocyte preparations [37].

That chiral inversion and lipid incorporation are closely associated is demonstrated by a comparison of the metabolic clearance of the *R*-enantiomers via inversion to the rate of profen incorporation into lipid. Thus fenoprofen undergoes extensive inversion and lipid incorporation, whereas flurbiprofen undergoes no detectable incorporation into lipid and low inversion [38,39].

An example of metabolic inversion which appears to be unrelated to the inversion of the 2-arylpropionic acid derivatives is provided by mandelic acid. This compound has been known to undergo chiral inversion in bacteria, from the *S*-enantiomer to its *R*-antipode, for a number of years [40], but only recently has this reaction been observed in rodents. Following administration of (*S*)-mandelic acid to rats, about 16% of the dose was eliminated in urine in 24 h apparently unchanged. However, an examination of the stereochemical composition of the material the *R*:*S* enantiomeric ratio was found to be 4:1 [41]. The remainder of the dose was recovered as phenylglyoxylic acid. In bacteria, the isomerization of mandelic acid is mediated by mandelate racemase [42], but the mechanism in the rat is unknown.

3. Pharmacogenetics and the stereochemistry of metabolism

"Pfeiffer's rule", which generalizes that the more potent a drug is, the more likely it is to show stereoselectivity of action as a consequence of the greater steric demand for tight receptor binding, may have parallels in drug metabolism. However, the drug-metabolizing enzymes have always been regarded as showing little substrate selectivity, making such generalizations difficult. In the past 10 years, it has become clear that the relative lack of substrate specificity of the major drug-metabolizing enzymes is illusory and that it is the net result of the activities of families of isozymes which often have marked, but overlapping, catalytic specificities. It may therefore be the case that an enzyme with marked specificity may well show stereoselectivity, and this is case with two cytochrome P450 isozymes, CYP2D6, which catalyses the 4-hydroxylation of debrisoquine, and CYP2C18, which performs the aromatic hydroxylation of mephenytoin.

The metabolism of mephenytoin in man is highly stereoselective. (*S*)-Mephenytoin is rapidly metabolized by aromatic hydroxylation to 4-hydroxymephenytoin, a phenolic product which is eliminated rapidly in urine as a glucuronide. However, the inability of the liver to hydroxylate (*R*)-mephenytoin in position 4 of the aromatic ring leads to the alternative metabolic pathway of oxidative demethylation to form 5-phenyl-5-ethylhydantoin (PEH) [43]. The elimination kinetics of the two enantiomers are markedly different, with the *S*-isomer having a half-life of around 4 h and about 47% of a dose of mephenytoin eliminated in the urine as its 4-hydroxy metabolite in 24 h. By contrast, the elimination half-life of PEH is 5–6 days, such that it accumulates upon repeated administration, reaching a steady state over 2–3 weeks. CYP 2C18 exhibits a genetic polymorphism, with a deficiency in this activity being inherited as an autosomal recessive trait. This polymorphism also affects the metabolism of diazepam and mephobarbital [44]. The incidence of the poor metabolizer phenotype varies from 4–5% in Caucasians from Switzerland, Canada and the USA to 13% in Canadian Orientals and 29% in Japanese resident in Canada [44].

The best known of the human genetic polymorphisms of drug oxidation is that affecting the metabolism of debrisoquine and arises from the virtual absence of CYP2D6 from the poor metabolizer phenotype. Drugs such as debrisoquine which are subject to this polymor-

phism are substrates almost exclusively metabolized by this isozyme. Debrisoquine itself is achiral but a number of other compounds whose metabolism is influenced by the polymorphism contain chiral centres and in a number of these cases CYP2D6, a high-affinity, low-capacity isozyme, is able to discriminate between the enantiomers [45,46].

A very significant example of the stereoselectivity of the CYP2D isozymes is given by their differential inhibition by the Cinchona alkaloids, quinine and quinidine, which differ in their configuration at C-8 and C-9 (quinine is 8*S*, 9*R* and quinidine is 8*R*, 9*S*). Quinidine inhibits the human isozyme CYP2D6, converting the predominant extensive metabolizer (EM) phenotype for debrisoquine and sparteine into "phenocopies" of the poor metabolizer (PM) phenotype, which are markedly deficient in CYP2D6 activity [47]. In contrast, quinine has no effect on the metabolism of typical CYP2D6 substrates in humans [47]. The rat orthologue of CYP2D6 is CYP2D1, which shows comparable substrate selectivity. The female dark agouti (DA) rat seemingly lacks CYP2D1 and provides a limited animal model of the human debrisoquine PM phenotype. However, in the rat, the stereoselectivity of CYP2D inhibition by the Cinchona alkaloids is reversed, with quinine inhibiting CYP2D1 whereas quinidine has no effect.

4. Conclusions

More and more new drugs are designed to interact with targets that can be described in atomic detail and chiral discrimination by these targets has to be taken into account ab initio in the design process. In such cases, enantiomeric discrimination by pharmacokinetic and metabolic processes is of academic interest only, since only the active stereoisomers will be advanced into development and use. However, interest in this area has led to the re-examination of a large number of chiral drugs already under development or in use as racemic mixtures to see if they might be improved if used in stereochemically pure form. It should be noted that recent great advances in chemical- and biotechnology-based synthesis mean that for the first time a very wide range of stereochemically pure drugs can be made available on a commercial scale. The use of stereochemically pure drugs would be expected to be advantageous by (i) reducing the total dose given, (ii) simplifying dose–response relationships, (iii) removing a source of inter-subject variability and (iv) minimizing toxicity due to the inactive isomer. The steeper the dose–response curve, the greater the benefit to be expected. It is important to appreciate that although the differences between the total clearances of stereoisomers of chiral drugs may be small, these are the composite of the many processes of absorption, distribution, metabolism and excretion.

This brief review has highlighted the exquisite stereoselectivities which can occur in the metabolism of drugs and other xenobiotics whose considerable magnitude often belies relatively small differences in total clearance. The decision as to the relative value of racemate or pure enantiomer is multifactorial and is driven by the magnitude and significance of the pharmacodynamic and pharmacokinetic differences and their clinical significance as well as marketing advantages. It is evident that metabolic studies are central to decision making in this area and there is every justification for the most detailed consideration of the stereochemistry of drug metabolism at every stage through drug development and safety evaluation.

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