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SUBSTRATE AND PRODUCT STEREOSELECTIVITY IN MONOOXYGENASE-MEDIATED DRUG ACTIVATION AND INACTIVATION

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Abstract—In this overview, stereoselective aspects of drug metabolism have been examined in a biochemical and pharmacodynamic perspective. From the facts and concepts presented, the conclusion to emerge is that the pharmacokinetic behaviour of mixtures of stereoisomers (e.g. racemates) is not always the simple addition of the behaviour of individual stereoisomers; as a consequence, stereoisomeric mixtures might display pharmacodynamic effects differing somewhat from those caused by the separate eutomers and distomers.

In some circles, the notion of "isomeric ballast" is being mentioned with increasing regularity, leading almost fatally to the conclusion that eutomers should be purified from their distomeric ballast for therapeutic use. A number of examples discussed here show that *in vitro* and also *in vivo*, a racemate often displays a pharmacokinetic and pharmacodynamic behaviour which is not the mere addition of the behaviour of its separate enantiomers. This may seem as an additional argument for the therapeutic use of pure eutomers since a number of interactions are thus avoided. But does this imply that distomers must *always* be considered as detrimental ballast? Enforcing compulsory resolution of stereoisomeric mixtures, in particular racemates, would increase severalfold the cost of many drugs. This is a small price to pay if the benefit is an improved therapeutic index. But, to reword the question, would such a legislation automatically result in therapeutic benefits?

In his message as the retiring president of the ISSX (International Society for the Study of Xenobiotics), Robert L. Smith mentioned the currently important problem posed by chiral drugs, which can be marketed and administered either as a single enantiomer or as the racemate [1]. As a consequence of this issue as well as for other reasons to be discussed below, stereochemical aspects of drug metabolism are the object of a renewed interest and of many research efforts. It is the purpose of this review to examine and illustrate some timely areas of drug research where stereochemical aspects of metabolism have been gainfully taken into consideration. Mechanisms of enantioselective drug metabolism will first be considered and rationalised in terms of the contributions of the binding and catalytic steps. Such a molecular view leads to a better understanding of stereoselectivity in metabolic interactions, in drug activation and inactivation, and in polymorphic drug monooxygenation. As a conclusion to these pharmacokinetic and pharmacodynamic considerations, the problem of the therapeutic use of racemates and pure enantiomers will be examined from the author's viewpoint. The discussion will focus mainly on monooxygenase-mediated reactions, and enantiomers will be given much more attention than diastereoisomers [2, 3]. Thus, many cases of stereoselectivity to be discussed in fact pertain to enantioselectivity.

MECHANISMS OF STEREOSELECTIVE DRUG METABOLISM

The binding of two enantiomers to a chiral macrobiomolecule results in two diastereoisomeric states of different probability. This phenomenon of *enantiomeric recognition* can occur in a number of pharmacological processes, for example binding of inhibitors to enzymes, binding of agonists or antagonists to receptors, and interaction of substrates with xenobiotic-metabolizing enzymes. In the latter case, enantiomeric recognition can occur at the binding step and/or at the catalytic step, resulting in different affinities and/or reactivities of the two enantiomers. In drug metabolism, the recognition of enantiomeric substrates is assessed in terms of *substrate enantioselectivity*, i.e. the differential metabolism of two enantiomers under identical conditions. This concept must be contrasted with *product enantioselectivity*, which implies the differential formation of two enantiomeric metabolites from a single prochiral substrate and results from an enzyme-mediated asymmetric induction [4–9]. Both binding and reactivity factors can be expected *a priori* to contribute to substrate and product enantioselectivity (Fig. 1). It is the aim of this section to examine whether and to what extent these two contributions can be disentangled to reveal some aspects of the mechanisms of enantioselective drug metabolism. Before so doing, however, enzymatic factors *per se* must be acknowledged, i.e. the discrimination of enzymes and isozymes by stereoisomers.

Enzymatic factors in enantioselective metabolism

There is now ample proof that enzyme induction or inhibition influences enantioselectivity in xenobiotic metabolism. For example, the substrate enantioselective *in vitro* glucuronidation of the enantiomers

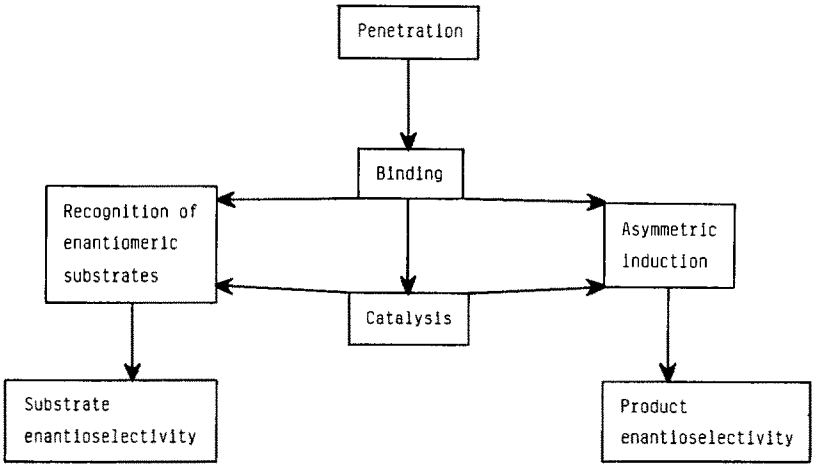

Fig. 1. Possible contribution of the binding and catalytic steps to the phenomena of substrate enantioselectivity (which results from the recognition of enantiomeric substrates) and product enantioselectivity (which results from asymmetric induction).

of oxazepam is markedly influenced by a variety of inducers, the R/S ratio ranging from 0.76 to 1.25 [10]. Similarly, the cytochrome P-450 mediated, product enantioselective epoxidation of styrene (a prochiral compound) to styrene oxide (a chiral metabolite) is altered by pretreatment of the animals with selective inhibitors [11]. Such effects are due to the selective induction or inhibition of specific isozymes, as indicated also by the fact that the epoxidation of styrene was found to occur with a R/S metabolic ratio ranging from 0.9 to 2.0 depending on the purified isocytochrome P-450 being used [12].

Interestingly, examples exist of different enzymes catalysing the same reaction but with different enantioselectivities. This is the case of sulfoxidation as catalysed by cytochromes P-450 and by FAD-monooxygenases. Thus, the formation of the chiral sulfoxide from the prochiral 4-tolyl ethyl sulfide exhibited R/S ratios of 20/1 and 1/4, respectively, when purified FAD-monooxygenases and isocytochromes P-450 were used [13]. Such examples indeed prove that substrate and product stereoselectivities vary with isozymes/enzymes or with isozyme populations, a fact of major significance when pharmacokinetic or pharmacodynamic consequences of stereoselective metabolism are considered (see later). However, this biological factor renders more difficult any mechanistic interpretation of stereoselectivity in xenobiotic metabolism.

Substrate enantioselectivity in binding and catalysis

The contribution of binding to substrate enantioselectivity is due to the chirality of the substrate binding site (usually a hydrophobic pocket in the enzyme protein), although the chirality of the active site should not be ignored, e.g. the chiral orientation of the prosthetic heme in cytochrome P-450 [14]. As regards the catalytic step, its contribution to substrate enantioselectivity depends on the importance of the stereoelectronic (directional) control, which for example is high in NAD(P)/NAD(P)H dehydrogenases/reductases [15].

Despite its limitations, *Michaelis–Menten analysis* offers a potentially interesting but insufficiently explored approach to evaluate the binding and catalytic components of substrate enantioselectivity. An elaborate and illustrative application has been provided by Kurono *et al.* [16] for the hydrolysis of para-nitrophenyl alpha-methoxyphenyl acetate by human and bovine serum albumin. While the K_m values were not significantly different for the D- and L-enantiomer (75 and 59 μM, respectively), the k_2 values (first-order rate constant of product formation from the Michaelis complex) were *ca.* 3 times higher for the D-enantiomer (37×10^{-3} versus 9.6×10^{-3} sec^{-1}), indicating that substrate enantioselectivity in this metabolic reaction is due mainly to the catalytic step. Another example can be found in the rat liver microsomal 4-hydroxylation of the dopaminergic agent 3PPP [3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine]. The affinities (K_m values) of the (−)-(*S*)- and (+)-(*R*)-enantiomer were practically identical (1.4 and 1.0 μM, respectively), while the former was a slightly better substrate than the latter (V_{max} values 2.33 and 1.85 nmol/mg prot/min) [17]. Here again, the substrate enantioselectivity (albeit a modest one) can be ascribed to the catalytic step.

In some favourable cases, *analysis of structure–metabolism relationships* may also help to explain mechanisms of substrate enantioselectivity. This approach is adequately illustrated by the selective hydroxylation of some coumarin anticoagulants. Thus, liver microsomes of rats pretreated with beta-naphthoflavone or 3-methylcholanthrene hydroxylate warfarin and phenprocoumon in the 6- and 8-position with high product regioselectivity, and with high but opposed substrate enantioselectivity, the preferred substrates being (+)-(*R*)-warfarin and (−)-(*S*)-phenprocoumon. This opposed enantioselectivity remained unexplained for years until Heimark and Trager [18] showed that (*R*)-warfarin binds to cytochrome P-450 as the cyclic hemiketal tautomer which renders it topographically equivalent to (*S*)-phenprocoumon despite opposed absolute configurations (Fig. 2). This 3-dimensional congruence

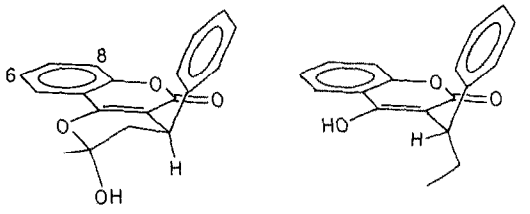

Fig. 2. The topographically equivalent conformations of (*R*)-warfarin (left) and (*S*)-phenprocoumon (right) at the active site of cytochrome P-450 [18].

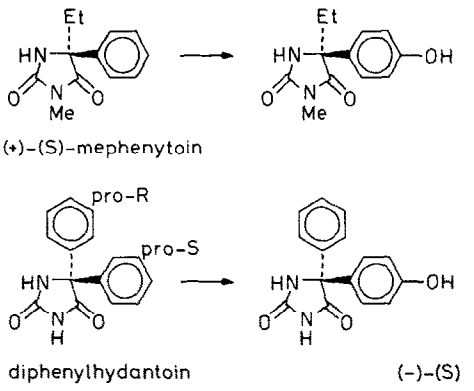

Fig. 3. Substrate and product enantioselectivity in the para-hydroxylation of mephenytoin (a chiral compound) and diphenylhydantoin (a prochiral compound), respectively. Note that the two reactions are mediated by distinct isocytochromes P-450 [23] (see text).

brings evidence for a substrate enantioselectivity controlled by the binding step.

Metabolic inhibitions between enantiomers can also be interpreted in terms of mechanisms of enantioselectivity since it may for example be due to a competition for the binding site. However, these aspects will not be discussed here since stereoselectivity in metabolic interactions is treated separately in a later section.

Mechanisms of product enantioselectivity

Product selectivity implies *different modes of binding* of the substrate molecule to the active site of the enzyme. With each productive binding mode, a different target group comes in the vicinity of the catalytic site, and the ratio of products will depend on the relative probability of the various binding modes (product enantioselectivity) and/or on the relative reactivity of the target groups (product regioselectivity). For example, the oxidation of D-camphor, adamantanone and adamantane by cytochrome P-450$_{cam}$ led in each case to one product only, namely the 5-exo-, 5- and 1-hydroxylated derivative, respectively [19]. These three positions are topographically congruent and indicate a tight enzyme substrate complex. In contrast, the same substrates each yielded two or three metabolites when hydroxylated by cytochrome P-450$_{LM2}$. The ratios of products were approximately proportional to the chemical reactivity of the abstractable hydrogen atoms, indicating moderate steric constraint in the binding site and considerable movement of the bound substrate [19].

A telling example of product enantioselectivity is that of diphenylhydantoin, a prochiral compound having two enantiotopic phenyl rings and displaying highly selective para-hydroxylation of the *pro*-S ring [e.g. 20]. This example can be gainfully compared with that of mephenytoin, a closely related yet chiral compound whose para-hydroxylation is highly selective for the (+)-(*S*)-enantiomer (see later) [e.g. 21]. Interestingly, the predominantly hydroxylated phenyl rings in mephenytoin and diphenylhydantoin are topographically equivalent (see Fig. 3), suggesting that the two compounds might share the same mode of binding to the common isocytochrome P-450 mediating both reactions. However, there is now evidence to prove that the para-hydroxylation of (*S*)-mephenytoin and the *pro*-S para-hydroxylation of diphenylhydantoin are mediated by distinct isozymes. Indeed, diphenylhydantoin is a poor *in vitro* inhibitor of mephenytoin hydroxylation [22]. Even more important is the fact that slow (*S*)-mephenytoin hydroxylators (see later) are deficient not in *pro-S* but in *pro-R* diphenylhydantoin hydroxylation [23], indicating that (*S*)-mephenytoin and *pro-R* diphenylhydantoin hydroxylation are mediated by the same isocytochrome P-450, while *pro-R* and *pro-S* hydroxylation of diphenylhydantoin is mediated by (at least) two distinct isozymes. Thus, product enantioselectivity in this reaction appears to be controlled by the relative affinities of the prochiral substrate to the two isozymes. For each of the two isozymes, a single binding mode is postulated, each bringing another of the two enantiotopic phenyl rings in the proximity of the catalytic site.

The importance of the spatial position of target groups is also documented by some cases of *conformer selectivity* in xenobiotic metabolism. Thus, UDP-glucuronyltransferase has been shown to be specific for equatorial hydroxyl groups in dihydrodiols of polycyclic aromatic hydrocarbons [24].

Mechanistic outlook

To summarise, the above discussion indicates that substrate enantioselectivity (or stereoselectivity) is the result of enantiomer (or stereoisomer) recognition at the binding and/or catalytic step, the relative contribution of the two factors varying from case to case. Product enantioselectivity (or stereoselectivity) on the other hand results from enantiotopic (or diastereotopic) group recognition (proximity of target group and catalytic centre) originating in the binding mode(s) of the substrate. The combined existence of stereoisomer recognition and stereotopic group recognition leads to complex cases of *substrate–product stereoselectivity* [4–6]. These facts, together with structural differences in binding sites, offer a rationale for the variations in substrate and product stereoselectivity seen among isozymes (see above). Figure 4 present a logical scheme summarising such an outlook.

For a number of enzymes, considerable infor-

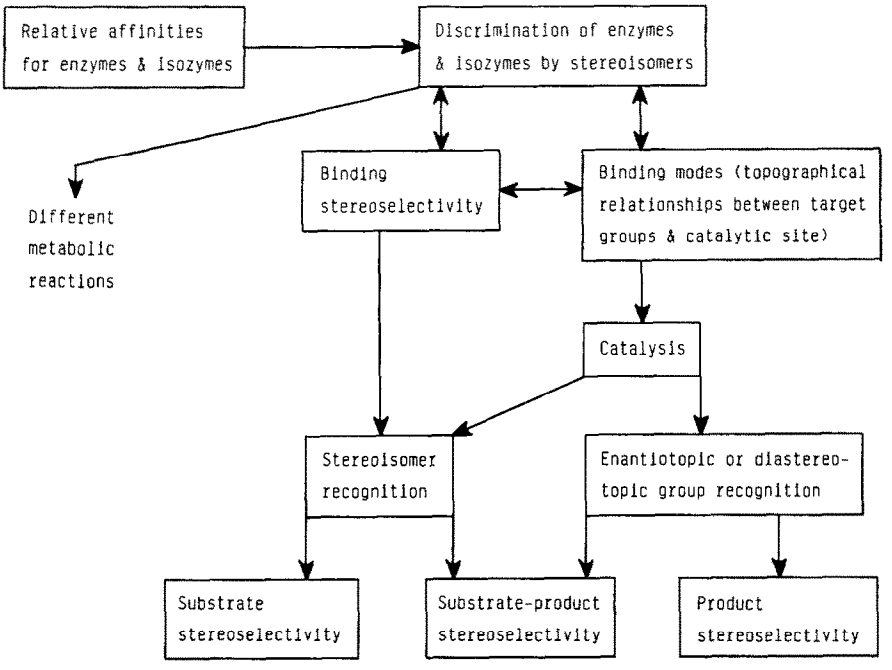

Fig. 4. Enzymatic and mechanistic factors underlying substrate, product, and substrate-product stereoselectivity in drug metabolism.

mation on stereoselectivity and structure–metabolism relationships (SMR) has been summarised in the form of topographical models of binding/catalytic sites. Examples include cytochrome P-450c [25], epoxide hydrolase [26], glutathione transferase [27] and glucuronyltransferase [28]. Such models, despite their limitations and reductionistic character, contribute significantly to a better understanding of SMR and shall lead to the use of computer graphics for improved metabolic predictions.

STEREOSELECTIVITY IN METABOLIC INTERACTIONS

Metabolic interactions between enantiomers, or between enantiomers and another drug, have been briefly reviewed by Trager and Testa [8] and by Walle and Walle [29]. Yet despite their potential (and in some cases well established) significance in clinical and fundamental pharmacology, they are still receiving a relatively modest attention. This section examines such interactions from a mechanistic viewpoint, leading to the conclusion that the phenomenon may be more frequent than currently recognized.

Metabolic interactions between enantiomers

Competitive metabolic interactions between enantiomers are to be expected when both have sufficient affinity for the same enzymes/isozymes (see top of Fig. 4). When this is the case, substrate stereoselectivity occurs, which as schematized in Fig. 4 results from stereoisomer recognition at the binding and/or catalysis step. As far as drug–drug interactions are concerned, a number of possible outcomes can conceivably result from substrate stereoselectivity, two of which are presented in Table 1. Thus, if two enantiomers are substrate of the same isozyme(s), mutual competitive inhibition is to be expected. This situation is aptly illustrated by the rabbit liver microsomal metabolism of para-chloroamphetamine [30]. When incubated alone, the (−)-(*R*)- and (+)-(*S*)-enantiomers were oxidized at rates of 0.329 ± 0.024 and 0.258 ± 0.029 mmol/mg protein/min, respectively, indicating a modest substrate enantioselectivity. However, when the racemate was incubated and the enantiomers monitored separately by an enantiospecific analytic method, the rates of metabolism of the two forms were 0.037 ± 0.008 and 0.145 ± 0.20 mmol/mg protein/min, respectively. In other words, the (*S*)-substrate had a *ca.* ninefold inhibitory effect on the oxidation rate of the (*R*)-substrate, while the latter had a *ca.* twofold inhibitory effect on the oxidation rate of the former. The results of this study can be summarized in terms of (*S*)-para-chloroamphetamine being a slightly poorer substrate, but a distinctly better ligand, of monooxygenases than its (*R*)-enantiomer. The observed substrate enantioselectivity may thus be ascribed predominantly to the catalytic step, with the binding of the higher-affinity ligand being comparatively unproductive.

Table 1. Some possible metabolic interactions between enantiomers displaying affinity for the same enzyme/isozyme

	Substrate	Inhibitor
Enantiomer 1	Yes	Yes
Enantiomer 2	Yes	Yes
Enantiomer 1	Yes	No
Enantiomer 2	No	Yes

Data are missing to conclude whether the above discussed findings are but an isolated case, or whether they exemplify a general phenomenon. However, the earlier quoted example of the 4-hydroxylation of 3PPP is worth mentioning again, since the V_{max} value for the racemate was found to be 1.75 nmol/mg prot/min, i.e. slightly smaller than that of either enantiomer tested separately [17]. This result certainly suggests weak mutual inhibition of the two enantiomers.

The second case in Table 1 is an extreme one, namely one enantiomer being the substrate, and the other the inhibitor. To the best of our knowledge, no such examples have been published which would document this situation for monooxygenase-mediated reactions. In contrast, an example of particular clarity can be found in the reaction of nicotine with azaheterocycle *N*-methyltransferases. Here, full enantioselectivity is seen in that only (+)-(*R*)-nicotine, which is present in tobacco smoke, undergoes *N*-methylation (K_m 14.2 μM with guinea-pig lung aromatic azaheterocycle *N*-methyltransferase) [31]. In contrast, (−)-(*S*)-nicotine is totally unreactive but acts as a strong competitive inhibitor of (*R*)-nicotine *N*-methylation (K_i 62.5 μM). The complete lack of reactivity of (*S*)-nicotine despite its high affinity must therefore be of catalytic origin, arising from an unproductive mode of binding which positions the target pyridyl nitrogen out of reach of *S*-adenosylmethionine.

Metabolic interactions between enantiomers are also documented *in vivo*, as seen with levomethorphan, the analgesic activity of which is significantly enhanced and prolonged by co-administration of its enantiomer, the inactive dextromethorphan, due to metabolic inhibition [32]. The various examples presented here cannot be generalized due to the paucity of relevant data, but they nevertheless suggest that metabolic interactions between enantiomers may occur more frequently than currently assumed, and that the field should be researched more actively.

Metabolic interactions between enantiomers and another drug

A racemic drug is nothing else than a mixture of two xenobiotics each displaying its own pharmacokinetic and pharmacodynamic profile. The administration of a second drug greatly complicates the picture, since we now effectively have three interacting species and there is no reason to suppose that the additional drug will interact with the two enantiomers in an identical fashion [8]. As a consequence, the metabolism of a racemate may be stereoselectively modified, resulting in a variety of possible pharmacodynamic alterations. In humans for example, phenylbutazone was found to significantly retard the clearance of the more active (*S*)-warfarin, while the clearance of the less active (*R*)-warfarin was significantly accelerated [33, 34]. The decreased clearance of (*S*)-warfarin is counterbalanced by the increased clearance of its enantiomer, leaving the total warfarin plasma concentrations practically unaltered but producing an enhanced pharmacological response due to the increased *S*/*R* ratio [8]. Other examples include a stereoselective interaction between (*R*)-warfarin and cimetidine [35].

Such interactions are one element among many in the complex disposition of numerous drugs. Up to now, these phenomena have received far too little attention, but future studies may well show that they have a more general character than suggested by the isolated examples reported here and elsewhere [8, 29].

STEREOSELECTIVITY IN DRUG ACTIVATION AND INACTIVATION AND IN POLYMORPHIC OXIDATION

Pharmacodynamic consequences of stereoselective drug metabolism

The pharmacodynamic (pharmacological and toxicological) consequences of drug metabolism are documented in countless publications. Thus, a drug may be eliminated mainly by biotransformation into inactive metabolites, or it may yield active metabolites responsible for some or all therapeutic effects. Similarly, toxic metabolites may be generated and detoxified by further biotransformation. Stereoselectivity in drug action and in drug metabolism being the rule and not the exception, it is only logical that stereoisomeric factors should contribute an additional dimension in the already complex interplay between pharmacokinetic and pharmacodynamic events. Indeed, beyond rather straightforward consequences such as stereoselective activation or inactivation, metabolic interactions between stereoisomers may also operate with beneficial or detrimental therapeutic consequences.

A particularly complex and as yet partly assessed example is that of propranolol (Fig. 5), whose β-adrenoceptor antagonistic activity resides in the (−)-(*S*)-enantiomer. The drug is transformed into a large number of metabolites some of which are active, e.g. (*S*)-(4-hydroxy)-propranolol and the two enantiomers of the glycol metabolite produced by deamination [36, 37]. As a consequence, the stereoselectivity of the various routes conditions not only the metabolic clearance and hence the duration of action of the active propranolol enantiomer, but also the concentrations of active metabolites. A compilation of substrate enantioselectivities seen in the major routes of propranolol biotransformation is given in Table 2, resulting in humans in higher plasma concentrations of the eutomer over the distomer (i.e.

Table 2. Substrate stereoselectivity in the metabolism of propranolol [compiled from 36, 39–41]

Reaction	Human	Dog
N-Dealkylation	$R > S$	$R > S$
Deamination	$S > R$	$R > S$
4-Hydroxylation	$R > S$	$S > R$
Total oxidation	$R > S$	$(S > R)^*$
Glucuronidation	$S > R$	$S > R$
Plasma levels	$S > R$	$R > S$

* Indirect evidence.

the more potent and less potent isomers, respectively, see [38]), and in the reverse situation in dogs. As far as active metabolites are concerned, less active (*S*)- than inactive (*R*)-(4-hydroxy)-propranolol is produced in humans from (*S*)- and (*R*)-propranolol, respectively [39]. In contrast, both propranolol enantiomers are transformed by deamination into the active glycol metabolite, an interesting case of metabolite activation of (*R*)-propranolol [37]. Dose-dependent kinetics [39] and metabolic interactions between enantiomers [40] further complicate the picture and make it obvious that the metabolism of racemic propranolol is not the simple sum of that of its separate enantiomers.

The significance of stereoselectivity in pharmacogenetics

For some metabolic reactions affecting a number of drugs, human populations exhibit bimodal polymorphism, i.e. some subjects are slow metabolizers while others are extensive metabolizers. A limited number of distinct drug oxidation phenotypes have been discovered in humans, their pharmacodynamic consequences always being of significance when the metabolic clearance of the drug and/or the generation of active metabolites are affected. Stereoselective aspects add to the complexity of some reactions, as illustrated here with two examples.

The β-blocker bufuralol (see Fig. 5) undergoes 4-hydroxylation and 1′-hydroxylation, and the two reactions are under the same genetic control, namely the debrisoquine/sparteine oxidation phenotype [42]. The stereochemical aspects of the reaction of 1′-hydroxylation (carbinol formation) have been particularly investigated showing for example that poor metabolizers excreted less carbinol than extensive metabolizers. The latter individuals excreted larger amounts of carbinol from the inactive (+)-(*R*)- than from the active (−)-(*S*)-bufuralol. In contrast, poor metabolizers excreted about the same amounts of carbinol from both enantiomers, showing that the polymorphic pathway is selective for (*R*)-bufuralol.

In vitro investigations using human liver microsomes have significantly contributed to our understanding of the molecular mechanisms involved [42, 43]. As shown in Table 3, there is only negligible enantioselectivity in the binding of bufuralol, which, however, has a much smaller affinity for PM microsomes and P-450 buf II than for EM microsomes and P-450 buf I, respectively. The reaction is substrate enantioselective for (*R*)-bufuralol in microsomes from EM and with P-450 buf I, but the enantioselectivity is fully lost in microsomes from PM and with P-450 buf II. As stated by Meyer *et al.* [42], these results are consistent with the view that bufuralol 1′-hydroxylation in poor metabolizer microsomes could be due largely to the presence of P-450 buf II, while most if not all of the activity of P-450 buf I is missing due to a structural alteration of the latter.

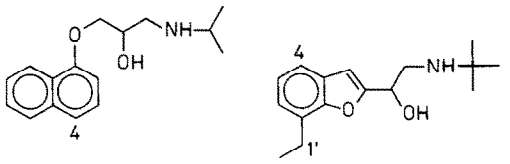

Fig. 5. The chemical structure of the β-blockers propranolol and bufuralol.

The anticonvulsant mephenytoin is another telling example of a drug the metabolism of which is under genetic control in humans. While (*S*)-mephenytoin ($t_{\frac{1}{2}} \sim 1$ hr) is rapidly para-hydroxylated, its (*R*)-enantiomer ($t_{\frac{1}{2}} \sim 70$ hr) is slowly *N*-demethylated to 5-phenyl-5-ethylhydantoin (PEH), an active metabolite which tends to accumulate due to very slow elimination ($t_{\frac{1}{2}} \sim 150$–200 hr) [44]. In approximately 5% of a Caucasian population, a genetic defect exists which is not related to the debrisoquine phenotype [22, 45]. In such slow metabolizers, (*S*)-mephenytoin is not significantly para-hydroxylated, has a $t_{\frac{1}{2}}$ of *ca.* 70 hr similar to that of its enantiomer, and, like the latter, is now available for *N*-demethylation to PEH, which is thus formed in amounts approximately threefold higher than in extensive hydroxylators [44]. *In vitro* studies have shed additional light on the phenomenon. Indeed, liver microsomes from extensive metabolizers para-hydroxylated (*S*)-mephenytoin ten times faster than its (*R*)-enantiomer. In liver microsomes from poor metabolizers, only (*S*)-mephenytoin hydroxylation was affected, its rate being reduced to that of (*R*)-mephenytoin [46].

Should only eutomers be used in therapy?

As a conclusion to this review, a logical scheme is offered which addresses the question "Should chiral drugs be used in therapy as the pure eutomer?" [47–49] and decomposes it into a number of specific questions (Fig. 6). The capital difficulty with such an approach lies in the limitations of bivalued (Aristotelian) logic, which ignores intermediate cases. Many factors, explicit and implicit, should be taken into account before reaching "yes or no" answers. Such factors must be primarily scientific, and they

Table 3. Kinetic parameters of bufuralol 1′-hydroxylation in human liver microsomes from extensive metabolizers (EM) and poor metabolizers (PM), and in reconstituted isocytochromes P-450 buf I and P-450 buf II [42, 43]

	K_m (μM)		V_{max} (nmol/nmol P450/15 min)		Ratio
	(*S*)	(*R*)	(*S*)	(*R*)	(*S*)/(*R*)
EM	35.3	47.3	4.1	8.6	0.48
PM	233.5	182.5	1.5	1.9	0.77
P-450 buf I	50.8	60.3	8.9	53.9	0.16
P-450 buf II	304.0	245.0	36.1	36.4	0.99

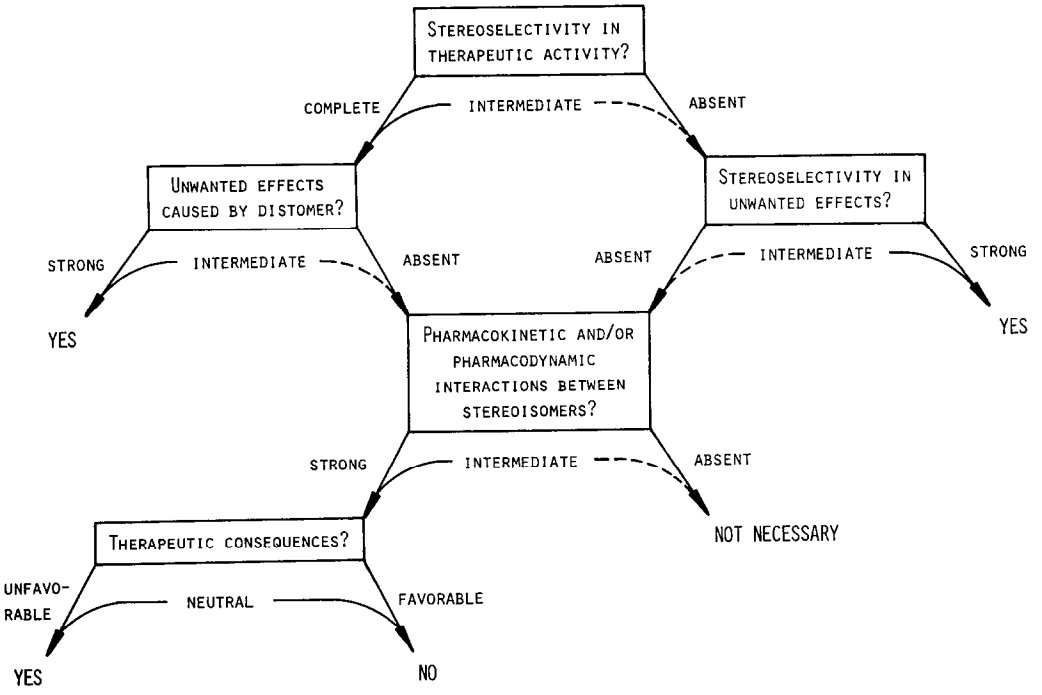

Fig. 6. Proposed logical scheme addressing the question "Should chiral drugs (and more generally drugs existing in stereoisomeric forms) by used in therapy as the pure eutomer?". An earlier version of this scheme has already been published [9].

require a wealth of pharmacokinetic and pharmacodynamic data which is seldomly available.

Note that an earlier version of this scheme has recently been published [9]; fruitful discussions with a number of colleagues have led to the more elaborate version presented in Fig. 6, which hopefully will be useful in avoiding arbitrary decisions.

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