Stereoselectivity of drug action

David J. Triggle

Chirality is a fundamental property of biological systems and reflects the underlying asymmetry of matter. Drug–receptor interactions have long been known to be stereoselective, and it is increasingly recognized that both pharmacodynamic and pharmacokinetic events contribute to the overall clinically observed stereoselectivity. The importance of this phenomenon has now been explicitly recognized by drug regulatory agencies who are issuing guidelines for drug development. This review outlines some of the scientific issues surrounding drug stereoselectivity, with particular emphasis being paid to drug interactions at ion channels where, because of state-dependent interactions, stereoselectivity is a moving target.

Drug regulatory agencies are increasingly concerned with the issue, long recognized scientifically, that the stereoisomers of drugs differ, almost without exception, in their biological activities. Accordingly, a racemic drug may contain two distinct biological entities that should be analyzed and regulated separately for their pharmacodynamic, pharmacokinetic and toxicological properties. Palytoxin, derived from Hawaiian coral and synthesized by Yoshito Kishi at Harvard University in 1989, has 64 centers of asymmetry that define more than 10^{21} isomers[1]. Fortunately, neither the issues nor the molecules facing the FDA and other regulatory agencies are typically at this level of complexity, and most synthetic drugs contain but a single center of asymmetry. Nonetheless, even this elementary level of stereochemical complexity presents plenty of scientific, developmental and regulatory challenges.

This brief review will focus on those stereoisomeric molecules that have one or more asymmetric centers and whose enantiomers are mirror images. Geometric and diastereomers will not be discussed since they are chemically and pharmacologically distinct, and generally exist and are considered (appropriately) as separate species.

Life as a simple twist of fate

Both life and chirality probably owe their coexistence to a simple twist of fate. Life is neither fair nor even-handed, probably never has been and perhaps never will be. Homochirality, reflecting the fact that biomolecules are built from asymmetric building blocks, is generally recognized as a fundamental property of life. There is, as yet, however, no general agreement on the origins of homochirality[2,3]. The physical mechanisms that have been proposed derive from the discovery of parity violation in the weak interactions between elementary particles. This would lead to minute enantiomeric enrichment of L-amino acids and D-sugars which, if followed by autocatalytic enrichment processes, would result in the homochiral world of today. Alternatively, homochirality might have evolved through chemical processes, including, for example, selective adsorption of single enantiomers onto chiral surfaces. Thus, the spontaneous separation of chiral domains in two-dimensional phospholipid bilayers could have been an initial nucleating step[4]. The former mechanism implies a universal conservation of chirality where all possible worlds exhibit identical homochirality, but the latter implies a chance process and the possible existence of alternatively asymmetric worlds where, even now, other drug regulatory agencies are deliberating similar issues, but from a different point of view.

Drug actions are stereoselective

Regardless of origin, chirality is an integral part of all biological processes that derive their inherent asymmetry from

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the chirality of the fundamental building blocks of receptors – the L-amino acids. It would thus be expected that a receptor protein derived from the enantiomeric D-amino acids would have the same fundamental properties, but exhibit opposing chirality of interaction. This is exactly what happens: for example, HIV-1 protease in its D- and L-forms exhibits opposing chiral substrate selectivity[5] (Figure 1). Nature has, on occasion, taken advantage of its own homochirality through the use of post-translational reactions to convert L-amino acid residues to the corresponding D-enantiomers. The resultant peptides and proteins exhibit enhanced stability towards enzymatic degradation. Thus, antibiotic families such as the gramicidins and lantibiotics contain D-residues[6,7], and the naturally occurring dermorphin peptide from the South American tree frog, *Phyllomedusa sauvagei*, contains D-alanine, as do several other peptides from this species[8,9]. More recently, the Ca^{2+} channel toxins from the funnel-web spider, *Agelenopsis aperta*, have been shown to contain a D-serine residue that is important both for their biological activity and for channel selectivity[10,11] (Figure 2).

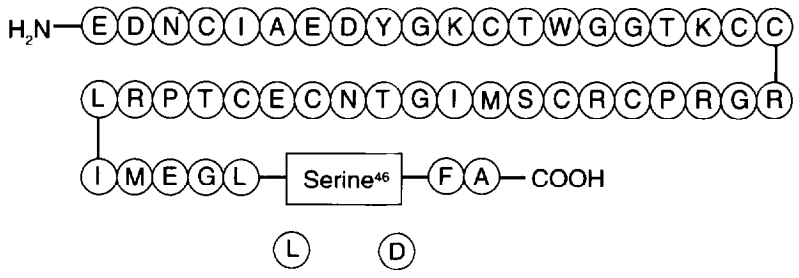

Figure 2. *Sequence of ω-agatoxin-TK, which possesses a D-serine at position 46 (Refs 10,11).*

Nature has also taken advantage of chiral receptor phenomena in that most fundamental of processes – sexual recognition. In scarab beetles, a single sex pheromone is produced (1-decenyloxacyclopentan-2-one), which possesses one chiral center. In *Anomala osakana*, the male attractant is the (+)-(*S,Z*)-5- species, the effects of which are completely antagonized by the *R*-enantiomer. In contrast, the two enantiomers have reverse roles in *Popillia japonica*[12]. This remarkable pattern of enantiomeric discrimination provides for exquisite interspecies discrimination.

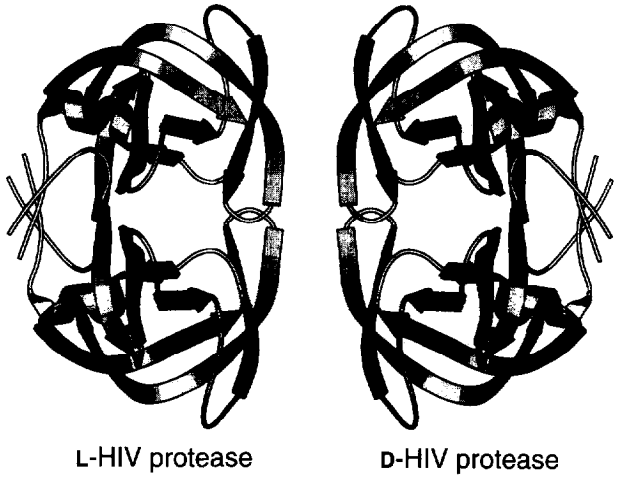

Figure 1. *Three-dimensional structure of the L-HIV and D-HIV proteases. Reproduced from Ref. 5 with permission.*

Stereoselective actions are so common that they are frequently considered to be a defining component of the specificity of drug action. This stereoselectivity of drug action represents a challenge, long recognized scientifically, but now increasingly faced at the clinical, development and regulatory levels. In particular, drug regulatory agencies are issuing guidelines for drug evaluation, development and registration that explicitly recognize racemic drugs as being composed of distinct chemical entities[13–15].

Enantiomers may differ both quantitatively and qualitatively in their biological activities. At one extreme, one enantiomer may be devoid of any biological activity; at the other extreme, both enantiomers may have qualitatively different biological activities. These stereoselective differences may arise not only from drug interactions at pharmacological receptors, but also from pharmacokinetic events, including protein binding and drug metabolism and transport[16–23].

The issues of stereoselectivity of drug actions go beyond simple academic and scientific considerations. Clinical significance stems from considerations of the efficacy of a single enantiomer versus a racemate, from considerations of stereoselective metabolism and disposition, and from the impact of route of administration and patient variability. Regulatory issues derive from considerations that racemic drugs may represent separate agents in fixed combination; development issues derive from considerations of the costs, including those of chemical synthesis, of pursuing a single enantiomer or a racemic mixture.

Table 1. Sales of enantiopure drugs

Category	Sales ($ billion)
Cardiovascular	11.3
Antibiotics	10.8
Hormones	4.5
Central nervous system	2.0
Anti-inflammatory	1.5
Anticancer	1.0
Other	4.5

Source: Ref. 21.

Difficulties and delays of chemical synthesis at the process level may be particularly acute in those molecules in which several chiral centers exist. Thus, the protease inhibitor Crixivan (Merck) has five chiral centers, and at a dose rate of 2.4 grams per patient per day it will be a considerable success in process chemistry for Merck to be able to supply 250,000 patients with this material by early 1997 (Ref. 24).

Particular clinical significance is attached to drugs of which one enantiomer may contribute the side or toxic effects. Thalidomide [2-(2,6-dioxo-piperidine-3-yl)isoindole-1,3-dione], which was withdrawn as a sedative in 1961 because of its human teratogenic effects, contains one chiral center. It has been speculated that only the (–)-*S*-enantiomer is teratogenic and that the (+)-*R*-enantiomer lacks these effects[25]. Given the potential utility of thalidomide in such diseases as leprosy this conclusion would be of great significance. Unfortunately, the enantiomers of thalidomide rapidly racemize in solution, making the determination of enantioselective effects almost impossible. However, configuration-stable analogs (α-methyl substitution) of thalidomide show clear-cut congruent *S*-enantioselectivity for sedation, teratogenicity and inhibition of tumor necrosis factor-α release[26]. These observations suggest that separation of the teratogenic effect from the other biological effects of thalidomide is not possible. Just another simple twist of fate!

The dimensions of drug stereoselectivity

Surveys of the chirality of natural/semisynthetic and totally synthetic drugs reveal, not surprisingly, that the majority of the former are available in single stereoisomer form. However, the extent of availability of synthetic single enantiomer chiral drugs is increasing[19]. In 1982, some 15% of synthetic racemic drugs were available as single enantiomers; by 1991, this had increased to approximately 40%. It is likely that this increased availability of single enantiomer drugs will continue, fuelled both by decisions to pursue single enantiomers rather than racemates and by decisions to switch existing racemic drugs to single enantiomeric forms[20–22] (Box 1). These numbers of drugs also translate to large numbers in terms of sales[20–22] (Table 1).

In principle, stereoisomers may differ in biological activities in several ways[20–23]:

(1) Both (all) isomers are equally active and there is no observed stereoselectivity of interaction. This situation is not commonly found: even general anesthetics show stereoselectivity, albeit of modest magnitude.
(2) The isomers differ quantitatively in their biological activities: in the extreme situation, one isomer is totally devoid of the measured biological activity.
(3) The isomers differ qualitatively in their activities and exhibit distinct biological activities at the same or different receptors.
(4) The behavior of the isomers is different in the racemate than predicted by the properties of either enantiomer alone.

Box 1. Existing racemic drugs that may soon be produced as a single enantiomer

Cardiovascular system (approximately 30)
Acebutolol
Disopyramide
Dobutamine
Nicardipine
Verapamil

Central nervous system (approximately 12)
Fluoxetine
Lorazepam
Meclizine

Respiratory system (approximately 3)
Albuterol
Terbutaline

Anti-inflammatory (approximately 16)
Cicloprofen
Ibuprofen
Ketoprofen

Antihistamines
Terfenadine

Source: Ref. 20.

Examples of all of these differences, derived from pharmacokinetic and pharmacodynamic considerations, are known[27,28] (Figure 3). Not infrequently, the same racemic molecule belongs to more than one class, depending upon what biological actions are considered. Thus, β-blockers exhibit stereoselective actions at β-adrenoceptors, whereby (–)-(*S*)-propranolol is some 40 times more potent than the enantiomer (category 2)[29,30]. However, for local anesthetic and antiarrhythmic activities, the enantiomers are essentially equipotent (category 1). Similarly, the enantiomers of 2-propyl-4-pentenoic acid and pentynoic acid show no stereoselectivity of anticonvulsant activity, but do show stereoselectivity in their teratogenic properties[31]. In contrast, barbiturates exhibit category 3 behavior, with one enantiomer being convulsant and the other anticonvulsant[32]. The enantiomers of picenadol, a narcotic antagonist, are agonist and antagonist, but the racemate is a partial agonist (category 4)[33]. An additional example is labetalol, in which the *R,R*-enantiomer is more hepatotoxic than the racemate[34].

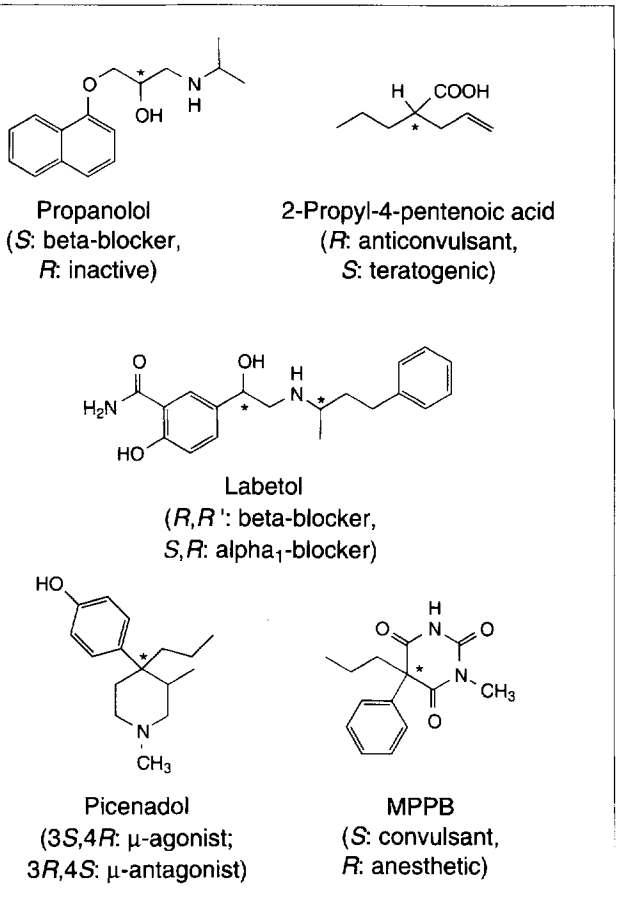

Figure 3. *The stereoselectivity of drug action, illustrating both quantitative and qualitative differences in enantiomeric discrimination. The asymmetric centers are marked with an asterisk; MPPB, methylphenylpropylbarbituric acid.*

With the advent of chiral assays for both drugs and their metabolites, it is increasingly easy, and necessary, to measure the stereoselectivity of pharmacokinetic processes (absorption, protein binding, metabolism, transport and excretion) and to determine their contribution to the observed overall stereoselectivity of drug action[35,36]. Enantiospecificity in pharmacokinetics is generally quite low (factors of 2–4), and the contribution of such factors to eudismic ratios (activities of the more active enantiomer, the eutomer, to the less active enantiomer, the distomer) is usually quite small; however, the clinical implications with respect to dosages and routes of administration may be very important. This contribution of pharmacokinetic events to the overall stereoselectivity profile of a drug is usefully illustrated with disopyramide. Marketed as the racemate, disopyramide is a class I antiarrhythmic that exhibits concentration-dependent binding to plasma proteins, principally α_1-glycoprotein, in the therapeutic concentration range[37,38]. The enantiomers are believed to exhibit qualitatively different pharmacological effects, the (+)-*S*-enantiomer being significantly more potent than the (–)-*R*-enantiomer as an antiarrhythmic and, with less difference, as an anticholinergic agent at muscarinic receptors[39,40]. Administered separately, the enantiomers showed no difference in clearance, renal clearance or volume of distribution in human subjects; however, when the pseudoracemate disopyramide was given, the (+)-*S*-enantiomer had a lower plasma clearance and renal clearance, a longer half-life and a smaller apparent volume of distribution than the (–)-*R*-enantiomer[41]. This difference reveals an important pharmacokinetic interaction between the enantiomers of disopyramide, which is explained by their stereoselective binding to plasma proteins and the resultant enantiomer competition.

Neither the clinical nor the developmental perspective of chiral drugs can be adequately addressed by any simple choice of selection of the single enantiomer. Examples are available where this choice would be indifferent, would be a good strategy or would be a poor strategy[42]. Similarly, the observed clinical stereoselectivity of action of a drug may well be determined by the contributions of both pharmacodynamic and pharmacokinetic processes, including receptor binding, absorption, protein binding, metabolism and clearance. These issues may be conveniently discussed from the perspective of drugs that act at ion channels.

Chirality of drug actions at ion channels

General observations

Voltage-gated ion channels represent a major class of pharmacological receptors and include Na^+, K^+ and Ca^{2+} channels at which major groups of drugs interact, including local anesthetic, antiarrhythmic, antihypertensive and antianginal agents[43–45]. Additionally, a significant number of animals, both vertebrate and invertebrate, have designed offensive and defensive chemical strategies centered around toxins that interact with these channels[46–48]. The interpretation of structure–function relationships for drugs active at these receptors poses particular challenges since drug access and affinity may change according to physiological, pharmacological and pathological conditions[49–51].

Drug actions at ion channels also provide examples of stereoselective toxicity as well as nonstereoselective interactions at receptor targets. Terodiline (*N*-t-butyl-1-methyl-3,3-diphenylpropylamine) possesses both muscarinic receptor and Ca^{2+} channel antagonist properties and was used successfully in Europe as a treatment for urinary incontinence. It was withdrawn in 1991 because of its association with cardiac arrhythmias, most commonly torsades de pointes ventricular tachycardia[52]. The associated prolongation of the Q–T interval indicates that the arrhythmias are associated with delayed ventricular repolarization. The (+)-*R*-enantiomer is antimuscarinic and the (–)-*S*-enantiomer possesses the Ca^{2+} channel antagonism, but the major effect on the bladder appears to be associated with the (+)-*R*-enantiomer. However, it is also the (+)-*R*-enantiomer that is clinically responsible for Q–T prolongation in concentration-dependent fashion[53,54]. This eliminates the possibility of using a single enantiomer of terodiline for the treatment of urinary incontinence without the risk of cardiac arrhythmias. Terfenadine (Seldane) is a nonsedating antihistamine that at high doses or in the presence of ketoconazole, which slows terfenadine metabolism, may lead to Q–T prolongation and torsades de pointes arrhythmias[55]. This is due to the action of terfenadine at a rapidly activating delayed rectifier K^+ current[56]. Whether this is a stereoselective effect remains to be established, but the drug is in the process of being withdrawn.

Verapamil exhibits stereoselectivity in its interactions with voltage-gated Ca^{2+} channels, with the *S*-enantiomer being the more potent, although it is only sold and used clinically as the racemate[51,57]. However, verapamil interacts with the P170 glycoprotein in nonstereoselective manner both *in vitro* and *in vivo* to reverse multiple drug resistance[57,58]. The use of racemic verapamil to reverse multiple drug resistance in cancer patients undergoing chemotherapy has not been encouraging, principally because of the limiting cardiovascular effects of verapamil exhibited by the *S*-component of the racemate[59]. However, since both enantiomers of verapamil are equipotent at the multiple drug resistance glycoprotein the use of the *R*-enantiomer only might be expected to be more beneficial and avoid or reduce the cardiotoxic effects associated with the *S*-enantiomer. Some clinical evidence indicates that this may be so[57,60], and suggests the importance of searching for analogs of verapamil where the stereoselectivity of cardiovascular activity is higher than that of verapamil and where the enantioselective discrimination between the two targets will be correspondingly higher. The feasibility of this approach is strengthened by observations that analogs of verapamil also show nonstereoselectivity in their inhibition of P-glycoprotein function and that this lack of stereoselectivity extends also to the 1,4-dihydropyridines[61] (Table 2).

Specific pharmacodynamic considerations

Ion channels exist in discrete states or families of states between which the equilibrium is defined by the membrane or chemical potential[43,49,50] (Figure 4). These states represent different conformations of the channel proteins, and significant changes may occur between the open and closed channel states. Accordingly, selective interaction of a drug may occur with one or other channel state, and:

Table 2. Activities of calcium antagonists for inhibition of cellular vinblastine accumulation (EC_{50}, μM)

Drug	Mouse leukemia cells	Monkey kidney cells
Phenylalkylamines		
(–)-Verapamil	2.9	2.4
(+)-Verapamil	2.6	1.6
(+)-Devapamil	1.0	1.3
(–)-Devapamil	2.1	3.7
(–)-Emopamil	3.0	3.7
(+)-Emopamil	2.4	3.8
1,4-Dihydropyridines		
(+)-Niguldipine	1.2	1.1
(–)-Niguldipine	1.3	1.1
(+)-Isradipine	9.2	6.9
(–)-Isradipiine	4.7	4.0
(–)-Nitrendipine	9.4	8.6
(+)-Nitrendipine	10.3	9.7
(–)-Felodipine	8.6	19.2
(+)-Felodipine	6.3	19.6

Source: Ref. 62.

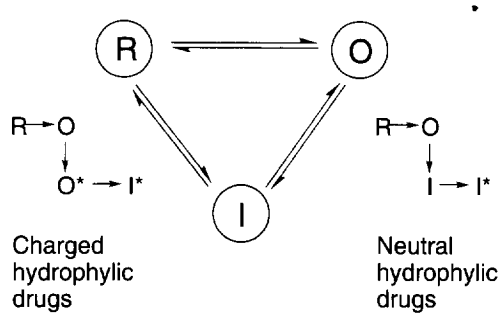

Figure 4. *The state-dependence of drug action at ion channels. An ion channel is illustrated as existing in three families of states: resting (R), open (O) and inactivated (I). The transitions between these states are determined by changes in electrical and/or chemical potential. Each state of the channel presents a different affinity and/or access pathway for drugs. Hence, the observed activity of a drug that has a preferential binding or interaction mode with a channel state will be determined by the equilibrium between the channel states.*

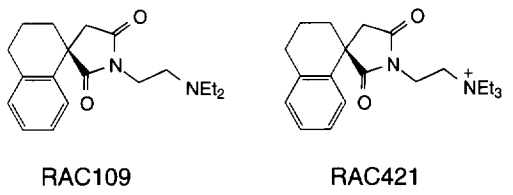

Figure 5. *The structural formulae of optically active local anesthetics RAC109 and RAC421.*

Table 3. Stereoselectivity of local anesthetic action (EC_{50}, mM) at Na^+ channels of squid axon

	Resting	Conditioned block at: 0 mV	+80 mV
(–)-RAC109	1.40	0.14	0.034
(+)-RAC109	1.45	0.79	0.49
(–)-RAC421	1.99	0.10	0.042
(+)-RAC421	2.35	0.98	0.42

Source: Ref. 67.

- Different states may have different affinities/access for drugs;
- Drugs may exhibit quantitative and qualitative differences in structure–function relationships, including stereoselectivity, between channel states.

Examples of such state-dependent interactions are well documented for drugs acting at Na^+ and Ca^{2+} channels and contribute to the selectivity of the antiarrhythmic action of lidocaine and related agents at Na^+ channels[49–51], and of the different cardiovascular profiles of verapamil and nifedipine at Ca^{2+} channels[50,51,62,63]. Lidocaine exhibits K_D values of 4×10^{-4} and 10^{-5} M for the resting and inactivated states of the Na^+ channel[64]; the 1,4-dihydropyridine, nitrendipine, exhibits an almost 1000-fold difference in affinity between the resting and inactivated states of the cardiac Ca^{2+} channel[65], and verapamil shows increasing potency at cardiac Ca^{2+} channels with increasing frequency of stimulus[57,66]. These state-dependent interactions underlie the class I antiarrhythmic properties of lidocaine, the selective vasodilating capacity of nitrendipine and the class IV antiarrhythmic properties of verapamil.

The stereoselectivity of drug action at ion channels may also be determined by these state-dependent interactions. At Na^+ channels, the local anesthetic RAC109 and its quaternary ammonium derivative RAC421 (Figure 5) exhibit increasing stereoselectivity of action with decreasing membrane potential consistent with differences in the local anesthetic binding site geometry in different channel conformations[67,68] (Table 3). A similar enhancement of stereoselectivity has been found under conditions of phasic stimulation for other local anesthetics[69]. Of particular interest are observations that this stereoselectivity of channel blockade may be inverted according to stimulus mode: current depolarization or batrachotoxin activation[69]. On the assumption of a single local anesthetic binding site at the Na^+ channel, the conformation of this site or access of the molecule must differ according to stimulus mode. Analysis of the molecular determinants of local anesthetic binding reveals the binding site to be localized to transmembrane segment S6 of domain IV of the Na^+ channel α-subunit[68]. Mutational analysis reveals the significance of specific amino acids to local anesthetic binding at distinct channel states[68,70,71]. Residue 1764, a Phe residue towards the center of the segment, is critical to selective binding to the open and inactivated states since its replacement by Ala decreases the affinity of the local anesthetic etidocaine by approximately 100-fold and virtually abolishes use- and frequency-dependence[68]. There appear, in fact, to be common molecular determinants in this region for local anesthetics, antiarrhythmics and anticonvulsants[71]. Residues Phe1764 and Tyr1771 are critical to the control of the state-dependent interactions of the local anesthetic and

antiarrhythmic lidocaine, the class Ia and Ic antiarrhythmic interactions of quinidine and flecainide and the anticonvulsant phenytoin, which appear to interact in an overlapping, but nonidentical manner with a common receptor site. Additionally, the IV S6 region of the L-type cardiac Ca^{2+} channel also contains the binding site for verapamil and the phenylalkylamine class of calcium antagonist, which display similarly prominent use- and voltage-dependence[72,73].

At the L-type voltage-gated Ca^{2+} channels, which dominate the functional pharmacology of the cardiovascular system, the 1,4-dihydropyridines, including the first-generation achiral nifedipine, are important therapeutic agents and molecular tools[74,75] (Figure 6). Both antagonist and activator properties of 1,4-dihydropyridines exhibit stereoselective action. Of particular interest are activator species, including BayK8644, that exhibit stereoselectivity where the *S*- and *R*-enantiomers exhibit activator and antagonist properties, respectively[74–76]. These opposing actions are believed to be exerted through interaction at a single 1,4-dihydropyridine binding site[77]. Also very interesting are observations that a single 1,4-dihydropyridine enantiomer may 'switch' pharmacological activity from activator to antagonist according to membrane potential, with antagonist properties appearing with decreasing membrane potential[78] (Figure 7). This special property of the 1,4-dihydropyridine activators may relate to their weak voltage-dependent interactions whereby

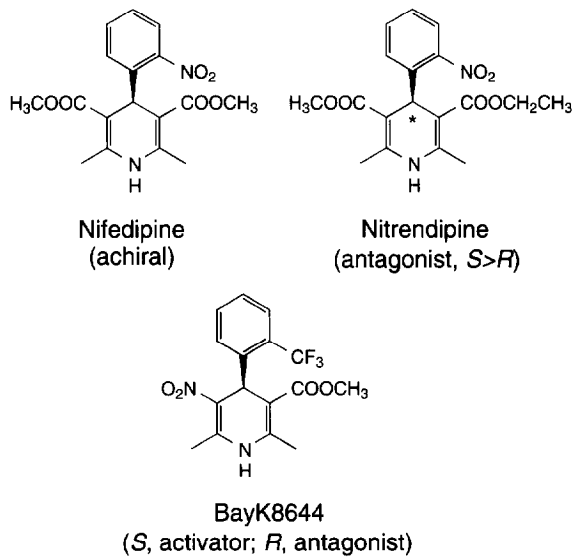

Figure 6. *1,4-Dihydropyridines bearing asymmetric centers.*

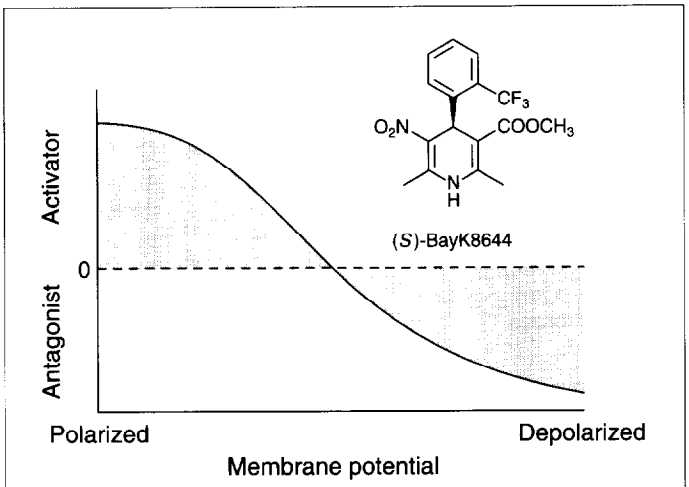

Figure 7. *The dependence of 1,4-dihydropyridine activator/antagonist properties on membrane potential.*

they can interact with and stabilize the Ca^{2+} channel irrespective of state[76]. Thus, 1,4-dihydropyridines are molecular chameleons at the Ca^{2+} channel, changing their pharmacological properties according to the background state of the channel (Figure 8).

Verapamil as a case study

Verapamil is marketed as the racemate and is used for its antianginal, antihypertensive and antiarrhythmic actions as an L-type Ca^{2+} channel antagonist[57,62,79]. The (–)-*S*-enantiomer is more potent than the (+)-*R*-enantiomer in both cardiac and vascular preparations, although the stereoselectivity is higher in cardiac than in vascular preparations[51,57,80,81] (Table 4). Thus, (*S*)-verapamil has both vasodilating and cardiac depressant properties, whereas (*R*)-verapamil is predominantly a vasodilating drug. The stereoselectivity of verapamil derives from both pharmacokinetic and pharmacodynamic factors. The therapeutic profile of verapamil is thus dependent upon the interplay of these factors[57,62,82].

The stereoselective pharmacodynamic effects of verapamil, *S>R*, are complicated by pharmacokinetic factors. There exists a dose–response relationship between plasma concentrations of verapamil and prolongation of the P–R interval of cardiac conduction [as a measure of atrioventricular (AV) node conduction change][83]. However, verapamil is less potent following oral administration than following single intravenous administration[83–85]. This discrepancy, which is of obvious importance in the use of racemic verapamil in the control of supraventricular tachycardias, derives

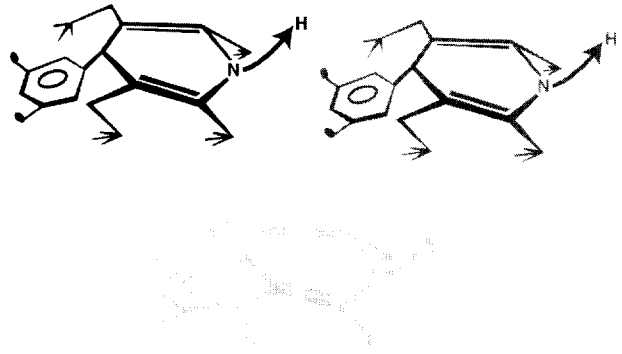

Figure 8. *1,4-Dihydropyridines as molecular chameleons.*

from stereoselective first-pass metabolism[86–88]. The plasma clearance of (–)-(*S*)-verapamil in humans (1400 ml/min) is approximately twice that of (+)-(*R*)-verapamil, and the bioavailability of the pharmacodynamically more active *S*-enantiomer is correspondingly lower. The enantiomers of verapamil interact stereoselectively with serum proteins, purified albumin and α_1-glycoprotein[89,90]. The stereoselectivity is modest, with an *R/S* ratio of between 1.5 and 2.0. The free fraction of the more active *S*-enantiomer is always higher over the entire concentration range and, unlike the situation with disopyramide, no evidence for enantiomer–enantiomer interaction in protein binding was observed. Some evidence exists that the dissolution of verapamil from modified-release formulations of verapamil may also be stereoselective[91].

The stereoselective first-pass metabolism of verapamil is also clinically significant in drug interactions and is well illustrated by verapamil–cimetidine interactions. Cimetidine inhibits the metabolism of a number of high clearance drugs and is known to increase the bioavailability of verapamil[92]. Cimetidine interferes with both hepatic and renal clearance of verapamil in a stereoselective manner: the ratio of plasma *S/R* levels increased in humans from 0.20 to 0.25 after cimetidine administration. The increase in the concentration of (–)-(*S*)-verapamil following cimetidine was accompanied by an increase in AV blockade or in the duration of the negative dromotropic effect of verapamil on AV conduction[93].

Although verapamil exhibits a common stereoselective pharmacodynamic interaction at the Ca^{2+} channels of both cardiac and vascular tissues (*S>R*), the ratio differs significantly, being higher for cardiac than for vascular tissue (Table 4). This difference in ratio probably arises from at least two factors: state-dependent interactions arising from differences in channel state in the two tissues and differences in L-channel subtype behavior between cardiac and vascular tissues. It is known that a number of L-type channel subtypes do exist and that differences in pharmacological characteristics are apparent. These differences may well extend to differences in stereoselectivity of drug interaction[94]. There is some potential clinical relevance to these differences in stereoselectivity. The experimental cardioprotective properties of verapamil accord with the cardiac and vascular stereoselectivity indices during the ischemic and reperfusion phases, respectively, in the Langendorff-perfused heart[81] (Table 5). These data suggest a possible differential strategy of calcium antagonist application in cardioprotection: during the reperfusion phase, vascular-selective compounds or enantiomers are appropriate, whereas during the ischemic phase negatively inotropic drugs or enantiomers are appropriate.

Regulatory issues

Until very recently, the issue of chirality in drugs occupied almost exclusively a scientific arena. Within the past decade, this issue has moved to center stage in the development and regulatory arena[95] for several reasons.

Developments in chemistry, notably in chiral synthesis, have made it much easier to obtain the required stereoisomers. Thus, production and marketing of chiral compounds is no longer a major problem. In the next decade,

Table 4. Cardiovascular activities of verapamil and gallopamil in Langendorff-perfused rat heart[a]

	Coronary flow			MSLVP	
	pEC_{50}	Ratio *R/S*	Ratio flow/MSLVP[b]	pEC_{50}	Ratio *R/S*
(+)-(*R*)-Verapamil	7.31		43.6	5.67	
(–)-(*S*)-Verapamil	7.20		3.4	7.17	
		2.45			31.6
(+)-(*R*)-Gallopamil	7.12		15.8	5.92	
(–)-(*S*)-Gallopamil	7.64		0.93	7.67	
		3.30			56.2

[a]Source: Ref. 80.
[b]MSLVP, maximum systolic left ventricular pressure.

Table 5. Cardiovascular stereoselectivity of gallopamil enantiomers in normoxic and ischemic Langendorff-perfused heart[a,b]

	LVP	Ratio *R/S*	Flow	Ratio *R/S*	t_{EDPm}	Ratio *R/S*	EDPm	Ratio *R/S*	t_{R90}	Ratio *R/S*
(–)-(*S*)-Gallopamil	7.4		7.8		7.8		7.6		8.9	
(+)-(*R*)-Gallopamil	5.6		6.7		6.1		6.0		8.0	
		63		12.6		50		40		8

[a]Source: Ref. 81.
[b]LVP, left ventricular pressure; t_{EDPm}, time to maximum end-diastolic pressure after the onset of ischemia; EDPm, maximum end-diastolic pressure reached during the ischemic period; t_{R90}, time from the start of reperfusion to 90% recovery from the maximum postischemic end-diastolic pressure.

some 50–80 racemate drugs will lose their patent protection, and there will be a significant impetus to extend their protected lifetime by marketing single-enantiomer versions. Between these two boundaries of increasing ease of synthesis and sheer commercial exploitation, there exist a number of scientific and clinical reasons why single-enantiomer drugs may well be the preferred marketed entity. These include:

- the absence of undesired or toxic effects in one enantiomer,
- the elimination or reduction of pharmacokinetic complexities that may arise from differential metabolism, protein binding, transport or excretion of enantiomers, and
- the simplification of drug monitoring.

It has also been suggested that the use of single enantiomers will eliminate the 'isomeric ballast' that pollutes our internal environment[96]. However, this simplistic argument ignores our average daily consumption of some 1500 mg of natural pesticides – materials that plants produce to protect themselves[97].

From the current regulatory perspective, there are no absolute prohibitions to the development of racemic agents. This is appropriate, because currently successful drugs include both single enantiomers, such as diltiazem, and racemates, such as fluoxetine. However, it is increasingly clear that the development of single enantiomers will be the preferred route.

The existing guidelines indicate that, regardless of whether a racemate or a single enantiomer is the ultimate clinical candidate, the chemical, analytical, pharmacological, pharmacokinetic and toxicological properties of both racemates and the enantiomers should be documented. Increasingly, drug design, development and introduction will choose between the right and the left.

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