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## Three-Dimensional Pharmacology, a Subject Ranging from Ignorance to Overstatements

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**Abstract:** Stereoselectivity has been known to play a role in drug action for 100 years or more. Nevertheless, chiral drugs have been developed and used as racemates, neglecting the fact that they comprise mixtures of two or more compounds which may have quite different pharmacological properties. A very limited access to pure enantiomers in the past has been responsible for this unsatisfactory state of affairs. During the last 20 years, significant achievements have made it possible to perform stereoselective synthesis and analysis. Today, novel chiral drugs are as a rule developed as single enantiomers. Yet, studies of old racemic drugs are still designed, performed and published without mention of the fact that two or more compounds are involved. In recent years, a number of old racemic drugs have been re-evaluated and re-introduced into the clinical area as the pure, active enantiomer (the eutomer). While in principle correct, the clinical benefit of this shift from a well established racemate to a pure enantiomer often seems to be limited and sometimes exaggerated. Racemic drugs with a deleterious enantiomer that does not contribute to the therapeutic effect (the distomer), may have been sorted out in the safety evaluation process. However, in the future any pharmacological study of racemic drugs must include the pure enantiomers. This will generate new, valuable information on stereoselectivity in drug action and interaction.

The interaction between a drug and its receptor is a three-dimensional event. If the drug molecule is chiral, thus forming optically active isomers, this interaction is usually stereoselective. The first definitive example of a difference in pharmacological action between optical isomers, or enantiomers, of a chiral molecule was offered by Arthur Cushny almost hundred years ago. He showed that the natural, levorotatory alkaloid hyoscyamine was twice as potent as its racemic form, atropine, in antagonizing cholinergic stimuli. Moreover, Cushny was able to show that endogenous adrenaline, which is also levorotatory, is twice as potent as synthetic adrenaline which is racemic. The dextrorotatory isomer of adrenaline was much less potent. These and other fundamental observations were discussed in a monograph (Cushny 1926). A few years later, Easson & Stedman (1933) postulated a three-point interaction between a drug and its receptor to explain stereoselectivity in drug action.

Despite this early understanding of the problem, chiral drugs were developed and used as racemates throughout the twentieth century, often on the assumption that only one enantiomer (the eutomer) is pharmacologically active in relevant doses and that the counterpart (the distomer) is inactive as well as harmless. A major reason for this policy was

that available synthetic methods yielded racemates and that full scale production of pure enantiomers was, for technical and economic reasons, not judged to be feasible. It is true that with time an increasing number of enantiomer pairs were resolved on a laboratory scale and the individual pharmacological properties of the components explored. For adrenergic drugs, in particular, significant knowledge on the relationship between molecular geometry and drug activity accumulated (Patil *et al.* 1975). It became evident that enantiomers may differ not only in potency, but that they may possess quite different pharmacodynamic and pharmacokinetic properties. For the main part, however, pharmacological and clinical evaluation has been carried out with racemates, neglecting the fact that the results obtained are compound effects of two different chemical entities which may have different biological properties. A rough estimation shows that on an average, less than one of hundred publications on racemic drugs contain information on the separate enantiomers (table 1). Very aptly, Ariëns (1984) described this unsatisfactory state of affairs as *sophisticated nonsense in pharmacokinetics and clinical pharmacology*. During the past two decades, a significant development in stereoselective methods of synthesis and analysis has taken place, followed by a renewed interest in three-dimensional pharmacology. Thus a series of seven articles on the subject was published in *Trends in Pharmacological Sciences*, starting with the origin of chirality in nature (Mason 1986) and

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ending with stereoisomerism and drug action (Lehmann 1986). Stereoselectivity of drug action has been highlighted also in this journal (Ariëns 1989; Smith 1989), and a comprehensive appraisal of enantioselective drug action and disposition covering some 70 drugs used as racemates was presented at about the same time (Jamali *et al.* 1989). An updated and extensive description of the field has been given by Eichelbaum & Gross (1996).

The present state of the art is that new chiral drugs as a rule are developed as pure enantiomers, and that old racemic drugs are being re-evaluated in an effort to find out if there is anything to gain by a switch from a racemate to enantiomer. This development is encouraged also from a regulatory perspective (De Camp 1989). In the rapidly expanding field of three-dimensional pharmacology, two extreme attitudes emerge: ignorance and overstatements. Ignorance, because studies on racemic drugs are still designed, carried out, and published without mention of the chiral state of the drug under study and without discussion of the consequences thereof. Overstatements, because the real benefit of a pure enantiomer compared to the racemate of a well-established drug is sometimes exaggerated due to biased study design and interpretation of data. To that comes that even today leading textbooks of pharmacology usually fail to highlight the problems associated with racemic mixtures. Only when a complex interaction between the enantiomers of a racemate is known, specific details are given, and then often in small print. This review will direct attention to the consequences of a conservative view of chirality in pharmacology. Moreover, the pros and cons for the development of pure enantiomers of established racemates in clinical use will be discussed. The nomenclature for stereoisomers in the literature is not uniform. In this paper optical activity is noted as (–) and (+) for the levo- and

dextro-rotatory enantiomers, respectively. When the absolute configuration is known, the designation (R) and (S) according to Cahn *et al.* (1956) is used.

### Eudismic ratios and enantiomeric purity

From the first observations of differences in pharmacological action between enantiomers, the potency ratio between the more active and the less active enantiomer, the eudismic ratio, and its meaning has attracted much interest. Thus Pfeiffer (1956) postulated that the lower the effective dose of a racemic drug, the greater the difference in the pharmacological effect of the optical isomers. Furthermore, a difference in the eudismic ratio between different tissues was suggested to be used as a criterion for differentiation of receptors (Patil 1969). As a matter of fact, the (–)-enantiomer of the adrenoceptor antagonist, amosulalol was 48 times more potent than the (+)-enantiomer in blocking  $\beta_1$ -adrenoceptors in the rat heart while it was 14 times less potent in blocking  $\alpha_1$ -adrenoceptors in rabbit aorta (Honda *et al.* 1986). Thus the eudismic ratio for amosulalol was not only different for the two receptor types, it was actually reversed. From this follows that the term eudismic ratio can be used only in relation to a particular biological action (Ariëns 1984). However, it is not always recognized that a true eudismic ratio is critically dependent on the enantiomeric purity of the compounds used. Suppose that the distomer of an enantiomer pair is contaminated with 1% of the eutomer. Then a eudismic ratio of about 100 will be obtained, even if the true activity of the distomer is below the limit of detection. If the true eudismic ratio is low, the influence of the contaminant is less critical. When the degree of resolution of an enantiomer pair is known, the true eudismic ratio can be calculated from the experimental result (Barlow *et al.* 1972).

Since the enantiomeric purity of the compounds under study is seldom specified adequately in the literature, published data on eudismic ratios must be regarded as tentative until confirmed by independent laboratories (Waldeck 1993). For example, the first report on the stereoisomers of the long-acting  $\beta_2$ -selective adrenoceptor agonist, formoterol (which contains two asymmetric carbons), indicated that the (R;R)-enantiomer was about four times more potent in relaxing airway smooth muscle than was the (S;S)-enantiomer (Murase *et al.* 1978). With highly purified enantiomers of formoterol, a potency difference approximately thousand times in favour of the (R;R)-enantiomer was observed, and yet it could not be excluded that the activity of the (S;S)-enantiomer was due to residual traces of the eutomer (Trofast *et al.* 1991). This latter study also showed that the diastereomers, (R;S)- and (S;R)-formoterol (not present in the pharmaceutical formulation) are mutually equipotent although less potent than (R;R)-formoterol. Obviously, eudismic ratios for closely related compounds may be quite different. Some compounds have a labile chiral centre and may undergo interconversion (Testa *et al.* 1993). Enantiomers of such compounds may be difficult to obtain

Table 1.

Enantiomers in the literature. Articles on a number of racemic drugs, representative for different therapeutic areas, found in a medical data base. Number of hits without and with the search term "enantiomers" added to the drug name. Source: PubMed (June 2003).

Drug name	Number of hits		
	In total	Enantiomers	Percentage
Amphetamine	17,243	120	0.7
Citalopram*	1,638	39	2.4
Dobutamine	5,157	10	0.2
Halothane	16,500	12	0.1
Ipratropium	1,618	1	0.1
Ketamine*	7,937	70	0.9
Mepivacaine	1,685	14	0.8
Ofloxacin*	4,516	27	0.6
Omeprazole*	5,864	27	0.5
Promethazine	2,473	8	0.3
Propranolol	36,422	221	0.6
Salbutamol*	6,898	62	0.9
Verapamil	19,576	147	0.8
Warfarin	9,505	174	1.8

\*Retrospectively developed as single enantiomers.

and maintain in pure form. Consequently, analysis of their stereoselectivity in action will be complicated as will be discussed below.

### Old chiral drugs in current pharmacological research

Established chiral drugs in clinical use, developed as racemates, are currently subject to research, either to elucidate further their mechanism of action or their usefulness as tools in experimental pharmacology. It is disappointing to find that few of the recent investigations appear to include a study of the enantiomers separately. In this way, important information may be lost. For example, the interaction between the glucocorticoid budesonide and the  $\beta_2$ -adrenoceptor agonist formoterol was studied in cultures of human bronchial smooth muscle cells using highly advanced molecular techniques such as Western blotting, DNA mobility shift assay, and a luciferase reporter gene assay (Roth *et al.* 2002). In support of the beneficial effect of this drug combination in asthma (Pauwels *et al.* 1997) it was found that the combination of these two antiasthma drugs in low concentrations resulted in a synchronised activation of transcription factors and an enhanced antiproliferative effect (Roth *et al.* 2002). In this otherwise very elegant study no reference to the racemic nature of formoterol (two enantiomers) and budesonide (two epimers) was made. In fact, what the authors observed was the interaction between four, not two, different molecules. Control experiments with the individual stereoisomers would have been a very welcome contribution to the ongoing debate on possible counterproductive and proinflammatory effects of (S)-enantiomers of bronchodilating  $\beta_2$ -adrenoceptor agonists (Handley *et al.* 1998a; Waldeck 1999), a subject in which also formoterol has been implicated (Schmidt *et al.* 2000; Handley *et al.* 2002).

Salmeterol, another long-acting  $\beta_2$ -adrenoceptor agonist, is perhaps the last member of this class of drugs which from the beginning was developed as a racemate. For this compound there is very extensive documentation, but only scanty information on the effects of the individual enantiomers is given (Johnson 1995). Also with this drug we see an uncritical use of racemates in advanced molecular biology. In an attempt to prove the exosite binding hypothesis, explaining the long duration of action of salmeterol, site-directed mutation of the  $\beta$ -adrenoceptor in combination with radioligand binding assays was used (Green *et al.* 1996). While the changes in the  $\beta$ -adrenoceptor amino acid sequences were properly described, there was no consideration of the fact that the drug being studied was a racemate. Moreover, the reader is left in the dark whether the ligand,  $^{125}\text{I}$ -labelled cyanopindolol, the reference compounds isoprenaline, adrenaline and noradrenaline and the antagonist propranolol, all chiral drugs included in the study, were racemic or single enantiomers.

The list of publications overlooking stereoselectivity in drug action could be made long, but one more example may suffice. Multidrug resistance protein (MRP) 3 transports

i.a. conjugated xenobiotics from cells into the blood. Very recently, it was reported that in liver tissue taken from patients treated with the proton pump inhibitor, omeprazole, there was a five times higher MRP3 protein expression compared with the rest of the population (Hitzl *et al.* 2003). Furthermore, the authors showed that there was a significant induction of MRP3 mRNA and protein in HepG2 cells incubated with omeprazole for 48 hr. There was no reference to the fact that omeprazole is a racemate and that its metabolism is stereoselective (Åbelö *et al.* 2000; Andersson *et al.* 2001). Since the isomer with the more favourable pharmacokinetic properties, (S)-omeprazole, is now in clinical use (Lindberg *et al.* 2003), it would be pertinent to know if the induction of MRP3 mRNA and protein by omeprazole is also stereoselective.

Almost two decades have elapsed since Ariëns (1986) stated: *Neglect of stereochemistry results in the collection of senseless data and the drawing of misleading conclusions* –, and he added: *If studies on racemic mixtures are presented, at the very least it should be announced that the therapeutic agent etc. discussed is composed of two or more isomers to be regarded as different compounds each of which has its own specific properties*. It is obvious that authors, peer referees and editorial boards of scientific journals alike have not fully adopted this simple message in practice. There may be reasons to carry out certain documentative studies with racemates, but any study of explorative character should include the pure stereoisomers whenever possible. The persistent reluctance to comply with basic principles of pharmacology regarding racemates is difficult to understand. One possible factor may be that pure enantiomers of chiral drugs, marketed as racemates, are only occasionally freely available. Among companies producing well established racemates, there may be a hesitation to find out what is hidden behind the compound effect of the drug in question, particularly if the product is regarded as safe and efficient. However, to supply independent pharmacologists with pure enantiomers for scientific purposes would be a very welcome initiative from the manufacturers of racemic drugs. Few academic laboratories have the resources necessary to conduct such studies without external support.

### Classical delusions

#### *Thalidomide and the problem with interconversion.*

Thalidomide was introduced as a relatively safe sedative agent in the late fifties, but soon thereafter it was withdrawn because it caused serious foetal malformations. Since thalidomide is a racemic mixture of two enantiomers, the question arose whether the catastrophe could have been avoided by using a single enantiomer of the drug, devoid of teratogenic effect. The first study addressing this problem, using oral administration to rabbits and mice, showed that both enantiomers were equally teratogenic and had the same sedative effect (Fabro *et al.* 1967). A subsequent study, with chromatographically purified enantiomers, showed that (S)-(-)-thalidomide, but not (R)-(+)-thalidomide, caused dose-

dependent teratogenicity in both rats and mice when given intraperitoneally (Blaschke *et al.* 1979). This study has given rise to the belief that the tragedy with thalidomide might have been avoided if only the pure (R)-enantiomer had been used (Smith 1989). More recent research has confirmed that in man, the sedative effect is related to the blood concentration of (R)-thalidomide (Eriksson *et al.* 2000). However, the enantiomers of thalidomide undergo rapid interconversion in biological media as shown *in vitro* as well as *in vivo* (Knoche & Blaschke 1994; Eriksson *et al.* 1995). This makes determination of enantioselectivity in action almost impossible. Rapid interconversion, more pronounced after oral than after intraperitoneal administration, may explain the different outcomes of the two teratogenicity studies referred to above. Therefore, the teratogenic effect of thalidomide could not have been avoided by using pure (R)-thalidomide.

While totally excluded as a sedative, thalidomide has attracted interest for its anti-inflammatory properties, first demonstrated in the treatment of erythema nodosum leprosum (Sheskin 1965). It goes without saying that the drug is absolutely contraindicated in women in fertile age. The antiinflammatory properties of thalidomide appear to be associated with its ability to inhibit the release of tumour necrosis factor  $\alpha$  as demonstrated in stimulated human monocytes (Sampaio *et al.* 1991). Later work has indicated that this effect is linked to (S)-thalidomide (Wnendt *et al.* 1996). Since rapid interconversion of thalidomide enantiomers makes an estimation of the degree of stereoselectivity unreliable, these authors supported their conclusion with data obtained on the enantiomers of stable, methylated derivatives of thalidomide. With a pure enantiomer of a stable analogue of thalidomide it might be possible to separate the antiinflammatory effect from the sedative effect, now regarded as a disturbing side effect.

#### *The "classical" $\beta_1$ -adrenoceptor agonist dobutamine.*

Dobutamine is a catecholamine derivative, developed as a cardiotonic agent in the form of a racemate. It was early regarded as a  $\beta_1$ -selective adrenoceptor agonist due to its ability to selectively increase the force of the heart *in vivo* (Tuttle & Mills 1975). However, the  $\beta_1$ -selectivity of dobutamine was soon questioned. Detailed analysis on tissues *in vitro* showed that this compound was active also on  $\beta_2$ - and  $\alpha$ -adrenoceptors, and it was concluded that  $\beta$ -adrenoceptor classification with dobutamine is a theoretically unsound practice (Kenakin 1981). This warning, based on data obtained with racemic dobutamine, was strongly underlined when it was found, *in vitro* as well as *in vivo*, that the (+)-enantiomer is a relatively unselective  $\beta$ -adrenoceptor agonist with an antagonistic effect at  $\alpha_1$ -adrenoceptors. The (-)-enantiomer of dobutamine, on the other hand, was about ten times less active as a  $\beta$ -adrenoceptor agonist but had a strong partial agonistic effect at  $\alpha_1$ -adrenoceptors. This agonistic effect prevailed over the competitive antagonism exerted by the (+)-enantiomer in the racemate (Ruffolo *et al.* 1981; Ruffolo & Yaden 1983; Vidal-Beretervide

1991). To this comes that the (+)-enantiomer of 3-O-methyldobutamine, a significant metabolite of dobutamine, behaves as a potent  $\alpha_1$ -adrenoceptor antagonist (Ruffolo *et al.* 1985). Thus the purported  $\beta_1$ -selectivity of dobutamine stems from a complex interaction between two enantiomers: stimulation of  $\alpha_1$ - and  $\beta_1$ -adrenoceptors in the heart increases the force in a synergistic way while  $\alpha_1$ -adrenoceptor mediated constriction in peripheral vessels is nullified by relaxation via  $\beta_2$ -adrenoceptors (Kenakin 1981; Ruffolo & Messick 1985).

In spite of this well-documented knowledge, racemic dobutamine has remained the standard tool for classifying  $\beta$ -adrenoceptors. A closer look at some of the investigations on dobutamine published during the last year will illustrate the unsatisfactory state of the art. In a study on  $\beta$ -adrenergic effects on insulin signaling in adipocytes from  $\beta_3$ -adrenoceptor "knock-out mice", dobutamine was used as "the classical  $\beta_1$ -adrenoceptor agonist" (Jost *et al.* 2002). Furthermore, dobutamine was employed to investigate the mechanism of adrenergic inhibition of catecholamine secretion from trout cromaffin cells *in vitro* (Montpepit & Perry 2002) and to test "the hypothesis that nitric oxide has a positive inotropic effect on mammalian cardiac muscle contractility and that this effect sums with the positive inotropic effect of  $\beta_1$ -adrenergic agonists when both are present" (Reading & Barclay 2002). None of these authors appear to have considered the chiral nature of dobutamine. Indeed, the effects observed might result from a mixed action of two enantiomers on  $\alpha$ - and  $\beta$ -adrenoceptors. It is the responsibility of referees and editors to prevent misconceptions like the  $\beta_1$ -selectivity of dobutamine from being perpetuated.

#### *Labetalol, a drug that blocks both $\alpha$ - and $\beta$ -adrenoceptors.*

Labetalol was originally introduced as a drug that blocks both  $\alpha$ - and  $\beta$ -adrenoceptors with the understanding that both properties reside in the same molecule (Brittain & Levy 1976; Weiner 1980). This was a remarkable new finding since antagonists selective for  $\alpha$ -adrenoceptors known at that time did not block  $\beta$ -adrenoceptors and vice versa (Weiner 1980). However, labetalol has two chiral centres and consists of an equal mixture of four stereoisomers. When all four isomers were examined, it appeared that the non-selective inhibitory effect at  $\beta$ -adrenoceptors resides in the (R;R)-isomer while the (S;R)-isomer is largely responsible for antagonism at  $\alpha_1$ -adrenoceptors (Brittain *et al.* 1982). The two remaining isomers were weaker as inhibitors. It was concluded that the adrenoceptor blocking profile of labetalol is not attributable to the properties of any individual stereoisomer; instead each of the stereoisomers contributes to the overall effect of labetalol.

The pure (R;R)-enantiomer of labetalol, given the generic name dilevalol, was later found to possess partial agonist activity at  $\beta_2$ -adrenoceptors (Wallin & Frishman 1989). While dilevalol had the advantage of not producing postural hypotension, it never reached the market owing to hepatotoxicity not seen to the same extent with labetalol (Tucker 2000). So it came that labetalol continued to be



marketed as a racaemic mixture of four stereoisomers. As a matter of fact, it comprises a fixed ratio mixture of four drugs with one fourth each. It is unknown whether this given ratio is optimal for a well balanced hypotensive effect.

#### Development of single enantiomers from established racemates

The progress made in chiral synthesis and analysis has lead to a re-evaluation of many old racaemic drugs. From a theoretical point of view it would be favourable to develop single enantiomers of all chiral drugs in clinical use thus avoiding superfluous drug load, potential adverse effects and complex pharmacokinetics (Ariëns 1984). This is, however, a simplistic view because many factors must be taken into consideration. Firstly, chiral compounds may be subject to spontaneous or biological interconversion as exemplified by thalidomide (Eriksson *et al.* 1995). Secondly, both enantiomers may contribute to the therapeutic effect in a concerted way as is the case for dobutamine discussed above (Ruffolo & Messick 1985). In those cases there is no reason for the development of single enantiomers. Finally, the use of the pure, active enantiomer must offer a clinically significant advantage to the established racemate to justify the cost of development and a higher price. Such advantages may be a higher efficacy, elimination of adverse effects, or improved pharmacokinetic properties. With these considerations in mind, the enantiomers of a number of old racaemic drugs have been subject to a closer examination. A few of them have been developed and launched as pure enantiomers (Tucker 2000). On the whole, a conspicuous improvement in efficacy or safety is seldom seen when the pure eutomer is compared to its racemate. Probably, racaemic drugs with a detrimental distomer may have been sorted out in the drug evaluation process before they reached the market. Two examples from different therapeutic areas will be given below to illustrate possible improvements in pharmacodynamic and pharmacokinetic properties achieved with a pure enantiomer.

##### Levalbuterol

Bronchodilating  $\beta$ -adrenoceptor agonists have been developed and used as racemates throughout the 20th century. Whenever tested it has been found, with few exceptions, that the (R)-enantiomer of  $\beta_2$ -agonists is the carrier of the pharmacological activity and that the (S)-enantiomer is virtually inactive in therapeutic concentrations (Waldeck 2002). In recent years, based on some observations in guinea-pigs challenged with histamine (Sanjar & Morley 1988; Mazzoni *et al.* 1994), the suspicion has been raised that the (S)-enantiomer of  $\beta$ -agonists may not be inactive but rather induce airway hyperreactivity, eventually contributing to increased morbidity and mortality in patients with asthma (Handley *et al.* 1998a). This suspicion, backed up by the finding that (S)-salbutamol is metabolized and eliminated more slowly than (R)-salbutamol (Walle *et al.* 1993; Boulton & Fawcett 1996), has led to the development of levalbuterol (Handley *et al.* 1998b), the pure (R)-enantiomer of salbutamol which is now on the market. It has been

claimed that levalbuterol when inhaled is about four, rather than the expected two, times more potent as a bronchodilator compared to the racemate, and that it has an improved safety margin (Nelson *et al.* 1998). This statement could not be confirmed when a full dose-response relationship for inhaled (R)-salbutamol and the racemate was obtained in asthmatic patients (Lötvall *et al.* 2001). In this study (R)-salbutamol was twice as potent as the racemate, for bronchodilation and systemic effects as well, while the (S)-enantiomer was inactive. When all available data are taken together, there is to date little to support a clinically significant advantage of levalbuterol over the well-established racemate (Waldeck 1999; Ahrens & Weinberger 2001).

##### (S)-Ketamine

Ketamine, a phencyclidine derivative in racaemic form, has been used for the induction and maintenance of anaesthesia for more than 30 years. There are numerous publications on the enantiomers of this compound, and it was early recognized that (S)-(+)-ketamine is the more potent of the two as an anaesthetic agent and that it may have less pronounced side effects, such as emergence delirium, compared to (R)-(-)-ketamine (White *et al.* 1982). Moreover, (S)-ketamine was four times more potent than (R)-ketamine as an analgesic agent in human volunteers, a difference which correlated positively with the relative affinity of the enantiomers for phencyclidine binding sites associated with the N-methyl-D-aspartate (NMDA) receptor operated ion channel (Klepstad *et al.* 1990). In support of blockade of NMDA receptors as a mechanism for the anaesthetic effect of ketamine, it was also found that (S)-ketamine was twice as potent as (R)-ketamine in blocking voltage- and use-dependent NMDA receptor currents in cultured rat hippocampal neurones (Zeilhofer *et al.* 1992). However, pure (S)-ketamine did not fully meet the expectations of an improved side-effect profile since it also caused some of the well-known psychotomimetic effects seen with the racemate (Engelhardt 1997; Persson *et al.* 2002). This is not due to an interconversion since no (R)-ketamine was detected in plasma after administration of (S)-ketamine (Ihmsen *et al.* 2001).

Furthermore, (S)-ketamine appears to be eliminated more rapidly as a single enantiomer than as a component of the racemate since (R)-ketamine inhibits the elimination of (S)-ketamine (Ihmsen *et al.* 2001). Thus the recovery time after (S)-ketamine may be shorter than after the racemate, a favourable property of an anaesthetic agent. Ketamine has also a bronchospasmolytic component which may be helpful in patients with hyperreactive airways (White *et al.* 1982). In order to find a mechanistic explanation for the bronchospasmolytic property of ketamine, experiments on isolated airway smooth muscle preparations have been performed. However, these attempts produced conflicting results favouring either the (S)-enantiomer (Hirota *et al.* 1996) or the (R)-enantiomer (Pabelick *et al.* 1997) and a

direct relaxing effect was observed only in concentrations approaching 1 mmol/l. On the whole, most data on the enantiomers of ketamine argue in favour of using pure (S)-ketamine rather than the racemate.

### New chiral drugs in development

With the growing awareness of the significance of chirality in pharmacology and with the achievements made in chiral synthesis and analysis, new drugs are as a rule developed as single isomers. Sometimes problems with racemic mixtures are best avoided by developing achiral compounds. This was apparently the case with AR-C68397AA, a dual  $\beta_2$ -adrenoceptor and dopamine  $D_2$ -receptor agonist (Bonnert *et al.* 1998). Among the emerging new chiral drugs two categories may be discerned, new chemical entities belonging to an established class of drugs and those comprising a quite novel class based on new discoveries in pathophysiology. Since the improvement gained by producing a single enantiomer from an established racemate in most cases is limited, the development of a congener with significantly improved pharmacodynamic or pharmacokinetic properties may sometimes be a better option.

#### *New drugs of an old class.*

TA-2005 is a highly selective, potent and long-acting  $\beta_2$ -adrenoceptor agonist with a fast onset of action (Kikkawa *et al.* 1991; Voss *et al.* 1992). Chemically, TA-2005 is the pure (R;R)-enantiomer of a carbostyryl derivative of formoterol. In early clinical trials on patients with asthma, inhalation of as little as 3  $\mu$ g TA-2005 produced an efficient bronchodilation lasting for more than 24 hr, thus allowing once daily dosing (Voss 1994). Clinical studies now appear to be in progress and it will be interesting to find out whether, in addition to a longer duration of action, TA-2005 may have also an improved safety margin compared to formoterol. Ropivacaine, a long-acting local anaesthetic agent, is another example of a new chemical entity of an old class of drugs. From the beginning it was developed as the pure (S)-enantiomer on the premise that the (R)-enantiomer has a higher cardiotoxicity than the (S)-enantiomer as is the case for the structural analogue, bupivacaine (McClellan & Faulds 2000).

#### *New drugs of a novel class.*

Inhibitors of angiotensin-converting enzyme were developed as novel anti-hypertensive agents following the discovery of bradykinin-potentiating factors in the 1960's. The first of them to reach the market was captopril (Cushman *et al.* 1977), soon followed by a number of congeners such as enalapril and ramipril, all with two or more chiral centres and developed as single enantiomers (Jackson 2001). Another novel class of drugs is the leukotriene receptor antagonists. They emerged from the discovery that the elusive compound, the slow-reacting substance of anaphylaxis (SRS-A), consists of a mixture of leukotrienes (Samuelsson 1997). This discovery initiated a number of projects leading

to selective leukotriene receptor antagonists (Bernstein 1997). Among the first of them appear to be zafirlukast (Krell *et al.* 1990) and montelukast (Jones *et al.* 1995). While zafirlukast is achiral, montelukast has one centre of asymmetry and has been developed as a single enantiomer.

### Concluding remarks

In the past, the vast majority of investigations in pharmacology describe racemic drugs as if they were defined single molecules. This dubious practice, extending even to standard textbooks, reveals a remarkable ignorance since knowledge about stereoselectivity in drug action has been available for more than hundred years. The reason for this apparent inconsistency may be found in the poor availability of pure enantiomers of drugs used as racemates. With the recent development in stereoselective synthesis and analysis, this excuse is no longer acceptable. Whenever the pharmacology of a racemic drug is being explored, the pure enantiomers should be included in the study. This would generate new valuable information since there is a marked paucity of data in this area. New chiral drugs should be developed as single enantiomers. Old racemic drugs must be reevaluated and supplied as pure active enantiomers if proven to offer clinical benefits.

### References

- Ahrens, R. & M. Weinberger: Levalbuterol and racemic albuterol: Are there therapeutic differences? *J. Allergy Clin. Immunol.* 2001, **108**, 681–684.
- Andersson, T., M. Hassan-Alin, G. Hasselgren, K. Röhss & L. Weidolf: Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin. Pharmacokinet.* 2001, **40**, 411–426.
- Ariëns, E. J.: Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. *Eur. J. Clin. Pharmacol.* 1984, **26**, 663–668.
- Ariëns, E. J.: Chirality in bioactive agents and its pitfalls. *Trends Pharmacol. Sci.* 1986, **7**, 200–205.
- Ariëns, E. J.: Stereoselectivity in the action of drugs. *Pharmacology & Toxicology* 1989, **64**, 319–320.
- Barlow, R. B., F. M. Franks & J. D. M. Pearson: The relation between biological activity and the degree of resolution of optical isomers. *J. Pharm. Pharmacol.* 1972, **24**, 753–761.
- Bernstein, P. R.: The challenge of drug discovery: Developing leukotriene antagonists. In: *SRS-A to leukotrienes, The dawn of a new treatment*. Ed.: S. Holgate & S.-E. Dahlén. Blackwell Science Ltd., Oxford, UK, 1997, pp. 171–186.
- Blaschke, G., H. P. Kraft, K. Fickentscher, & F. Köhler: Chromatographische Racemattrennung von Thalidomid und teratogene Wirkung der Enantiomere. *Arzneimittelforsch.* 1979, **29**, 1640–1642.
- Bonnert, R. V., R. C. Brown, D. Chapman, D. R. Cheshire, J. Dixon, F. Ince, E. C. Kinchin, A. J. Lyons, A. M. Davis, C. Hallam, S. T. Harper, J. F. Unitt, I. G. Dougall, D. M. Jackson, K. McKechnie, A. Young & W. T. Simpson: Dual  $D_2$ -receptor and  $\beta_2$ -adrenoceptor agonists for the treatment of airway diseases. 1. Discovery and biological evaluation of some 7-(2-aminoethyl)-4-hydroxybenzothiazol-2(3H)-one analogues. *J. Med. Chem.* 1998, **41**, 4915–4917.
- Boulton, D. W. & J. P. Fawcett: Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Brit. J. Clin. Pharmacol.* 1996, **41**, 35–40.



- Brittain, R. T. & G. P. Levy: A review of the animal pharmacology of labetalol, a combined  $\alpha$ - and  $\beta$ -adrenoceptor blocking drug. *Brit. J. Clin. Pharmacol.* 1976, **3**, (Supplement), 681–694.
- Brittain, R. T., G. M. Drew & G. P. Levy: The  $\alpha$ - and  $\beta$ -adrenoceptor blocking potencies of labetalol and its individual stereoisomers in anaesthetized dogs and in isolated tissues. *Brit. J. Pharmacol.* 1982, **77**, 105–114.
- Cahn, R. S., C. K. Ingold & V. Prelog: The specification of asymmetric configuration in organic chemistry. *Experientia* 1956, **12**, 81–94.
- Cushman, D. W., H. S. Cheung, E. F. Sabo & M. A. Ondetti: Design of potent competitive inhibitors of angiotensin-converting enzyme. Carboxyalkanoyl and mercaptoalkanoyl amino acids. *Biochemistry* 1977, **16**, 5484–5491.
- Cushny, A. R.: *Biological relations of optically isomeric substances*. Baillière, Tindall & Cox, London, 1926.
- De Camp, W. H.: The FDA perspective on the development of stereoisomers. *Chirality* 1989, **1**, 2–6.
- Easson, L. H. & E. Stedman: Studies on the relationship between chemical constitution and physiological action. *Biochem. J.* 1933, **27**, 1257–1266.
- Eichelbaum, M. & A. S. Gross: Stereochemical aspects of drug action and disposition. *Adv. Drug Res.* 1996, **28**, 1–64.
- Engelhardt, W.: Recovery and psychomimetic reactions following (S)-ketamine. *Anaesthesist* 1997, **46** Suppl.1, 38–42.
- Eriksson, T., S. Björkman, B. Roth, Å. Fyge & P. Höglund: Stereospecific determination, chiral interconversion *in vitro* and pharmacokinetics in humans of the enantiomers of thalidomide. *Chirality* 1995, **7**, 44–52.
- Eriksson, T., S. Björkman, B. Roth & P. Höglund: Intravenous formulations of the enantiomers of thalidomide: pharmacokinetic and initial pharmacodynamic characterization in man. *J. Pharm. Pharmacol.* 2000, **52**, 807–817.
- Fabro, S., R. L. Smith & R. T. Williams: Toxicity and teratogenicity of optical isomers of thalidomide. *Nature* 1967, **215**, 296.
- Green, S. A., A. P. Spasoff, R. A. Coleman, M. Johnson & S. B. Liggett: Sustained activation of a G protein-coupled receptor via “anchored” agoist binding. *J. Biol. Chem.* 1996, **271**, 24029–24035.
- Handley, D. A., J. R. McCullough, S. D. Cowther & J. Morley: Sympathomimetic enantiomers and asthma. *Chirality* 1998a, **10**, 262–272.
- Handley, D. A., J. Morley & L. Vaickus: Levalbuterol hydrochloride. *Exp. Opin. Invest. Drugs* 1998b, **7**, 2027–2041.
- Handley, D. A., C. H. Senanayake, W. Dutczak, J. L. Benovic, T. Walle, R. B. Penn, H. S. Wilkinson, G. J. Tanoury, R. G. G. Andersson, F. Johansson & J. Morley: Biological actions of formoterol isomers. *Pulm. Pharmacol. Ther.* 2002, **15**, 135–145.
- Hirota, K., T. Sato, S. F. Rabito, E. K. Zsigmond & A. Matsuki: Relaxant effect of ketamine and its isomers on histamine-induced contractions of tracheal smooth muscle. *Brit. J. Anaesth.* 1996, **76**, 266–270.
- Hitzl, M., K. Klein, U. M. Zanger, P. Fritz, A. K. Nüssler, P. Neuhaus & M. F. Fromm: Influence of omeprazole on multidrug resistance protein 3 expression in human liver. *J. Pharmacol. Exp. Therap.* 2003, **304**, 524–530.
- Honda, K., T. Takenaka, A. Miyata-Osawa & M. Terai: Adrenoceptor blocking properties of the stereoisomers of amosulalol (YM-09538) and the corresponding desoxyderivative (YM-11133). *J. Pharmacol. Exp. Therap.* 1986, **236**, 776–783.
- Ihmsen, H., G. Geisslinger & J. Schüttler: Stereoselective pharmacokinetics of ketamine: R(-)-ketamine inhibits the elimination of S(+)-ketamine. *Clin. Pharmacol. Therap.* 2001, **70**, 431–438.
- Jackson, E. K.: Renin and angiotensin. In: *Goodman & Gilman's The Pharmacological Basis of therapeutics*, 10th edn. Eds.: J. G. Hardman, L. E. Limbird & A. Goodman Gilman. McGraw-Hill, New York, USA, 2001, pp.809–841.
- Jamali, F., R. Mehvar & F. M. Pasutto: Enantioselective aspects of drug action and disposition: Therapeutic Pitfalls. *J. Pharmaceut. Sci.* 1989, **78**, 695–715.
- Johnson, M.: Salmeterol. *Med. Res. Rev.* 1995, **15**, 225–257.
- Jones, T. R., M. Labelle, M. Belley, E. Champion, L. Charette, J. Evans, A. W. Ford-Hutchinson, J. Y. Gauthier, A. Lord, P. Masson, M. McAuliffe, C. S. McFarlane, K. M. Metters, C. Pickett, H. Piechuta, C. Rochette, I. W. Rodger, N. Sawyer, R. N. Young, R. Zamboni & W. M. Abraham: Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D4 receptor antagonist. *Can. J. Physiol. Pharmacol.* 1995, **73**, 191–201.
- Jost, P., M. Fasshauer, C. R. Kahn, M. Benito, M. Meyer, V. Ott, B. B. Lowell & H. H. Klein: Atypical  $\beta$ -adrenergic effects on insulin signalling and action in  $\beta_3$ -adrenoceptor-deficient brown adipocytes. *Amer. J. Physiol. Endocrinol. Metabol.* 2002, **283**, E146–E153.
- Kenakin, T. P.: An *in vitro* quantitative analysis of the alpha adrenoceptor partial agonist activity of dobutamine and its relevance to inotropic selectivity. *J. Pharmacol. Exp. Therap.* 1981, **216**, 210–219.
- Kikkawa, H., K. Naito & K. Ikezawa: Tracheal relaxing effect and  $\beta_2$ -selectivity of TA-2005, a newly developed bronchodilating agent, in guinea-pig tissues. *Jap. J. Pharmacol.* 1991, **57**, 175–185.
- Klepstad, P., A. Maurset, E. R. Moberg & I. Øye: Evidence of a role for NMDA receptors in pain perception. *Eur. J. Pharmacol.* 1990, **187**, 513–518.
- Knoche, B. & G. Blaschke: Investigations on the *in vitro* racemization of thalidomide by HPLC. *J. Chromatogr.* 1994, **A666**, 235–240.
- Krell, R. D., D. Aharony, C. K. Buckner, R. A. Keith, E. J. Kusner, D. W. Snyder, P. R. Bernstein, V. G. Matassa, Y. K. Yee, F. J. Brown, B. Hesp & R. G. Giles: The preclinical pharmacology of ICI 204,219. A peptide leukotriene antagonist. *Amer. J. Resp. Dis.* 1990, **141**, 978–987.
- Lehmann, P. A.: Stereoisomerism and drug action. *Trends Pharmacol. Sci.* 1986, **7**, 281–285.
- Lindberg, P., D. Keeling, J. Fryklund, T. Andersson, P. Lundborg & E. Carlsson: Review article: esomeprazole – bio-availability, specificity for the proton pump and inhibition of acid secretion. *Aliment. Pharmacol. Therap.* 2003, **17**, 481–488.
- Lötvall, J., M. Palmqvist, P. Arvidsson, A. Maloney, G. P. Ventresca & J. Ward: The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. *J. Allergy Clin. Immunol.* 2001, **108**, 726–731.
- Mason, S.: The origin of chirality in nature. *Trends Pharmacol. Sci.* 1986, **7**, 20–23.
- Mazzoni, L., R. Naef, I. D. Chapman & J. Morley: Hyperresponsiveness of the airways following exposure of guinea-pigs to racemic mixtures and distomers of  $\beta_2$ -selective sympathomimetics. *Pulm. Pharmacol.* 1994, **7**, 367–376.
- McClellan, K. J. & D. Faulds: Ropivacaine: An update of its use in regional anaesthesia. *Drugs* 2000, **60**, 1065–1093.
- Montpetit, C. J. & S. F. Perry: Adrenergic regulation of catecholamine secretion from trout (*Oncorhynchus mykiss*) chromaffin cells. *J. Endocrinol.* 2002, **173**, 187–197.
- Murase, K., T. Mase, H. Ida, K. Takahashi & M. Murakami: Absolute configuration of four isomers of 3-formamido-4-hydroxy- $\alpha$ -[[N-(p-methoxy- $\alpha$ -methylphenethyl)amino]methyl]benzylalcohol, a potent  $\beta$ -adrenoceptor stimulant. *Chem. Pharm. Bull.* 1978, **26**, 1123–1129.
- Nelson, H. S., G. Bensch, W. W. Pleskow, R. DiSantostefano, S. DeGraw, D. S. Reasner, T. E. Rollins & P. D. Rubin: Improved bronchodilation with levoalbuterol compared with racemic albuterol in patients with asthma. *J. Allergy Clin. Immunol.* 1998, **102**, 943–952.
- Pabelick, C. M., K. Rehder, K. A. Jones, R. Shumway, S. G. E. Lindahl & D. O. Warner: Stereospecific effects of ketamine enantiomers on canine tracheal smooth muscle. *Brit. J. Pharmacol.* 1997, **121**, 1378–1382.
- Patil, P. N.: A use of the isomeric ratio as a criterion to differentiate adrenergic receptors. *J. Pharm. Pharmacol.* 1969, **21**, 628–629.

- Patil, P. N., D. D. Miller & U. Trendelenburg: Molecular geometry and adrenergic drug activity. *Pharmacol. Rev.* 1975, **26**, 323–392.
- Pauwels, R. A., C.-G. Löfdahl, D. S. Postma, A. E. Tattersfield, P. O'Byrne, P. J. Barnes & A. Ullman: Effect of inhaled formoterol and budesonide on exacerbations of asthma. *New Engl. J. Med.* 1997, **337**, 1405–1411.
- Persson, J., J. Hasselström, A. Maurset, I. Øye, J.-O. Svensson, O. Almqvist, H. Scheinin, L. L. Gustafsson & O. Almqvist: Pharmacokinetic and non-analgesic effects of S- and R-ketamines in healthy volunteers with normal and reduced metabolic capacity. *Eur. J. Clin. Pharmacol.* 2002, **57**, 869–875.
- Pfeiffer, C. C.: Optical isomerism and pharmacological action, a generalisation. *Science* 1956, **124**, 29–31.
- Reading, S. A. & J. K. Barclay: The inotropic effect of nitric oxide on mammalian papillary muscle is dependent on the level of  $\beta_1$ -adrenergic stimulation. *Can. J. Physiol. Pharmacol.* 2002, **80**, 569–577.
- Roth, M., P. R. A. Johnson, J. J. Rüdiger, G. G. King, Q. Ge, J. K. Burgess, G. Anderson, M. Tamm & J. L. Black: Interaction between glucocorticoids and  $\beta_2$  agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. *Lancet* 2002, **360**, 1293–1299.
- Ruffolo, R. R., Jr. & K. Messick: Inotropic selectivity of dobutamine enantiomers in the pithed rat. *J. Pharmacol. Exp. Therap.* 1985, **235**, 344–348.
- Ruffolo, R. R., Jr. & E. L. Yaden: Vascular effects of the stereoisomers of dobutamine. *J. Pharmacol. Exp. Therap.* 1983, **224**, 46–50.
- Ruffolo, R. R., Jr., T. A. Spradlin, G. D. Pollock, J. E. Waddell & P. J. Murphy: Alpha and beta adrenergic effects of the stereoisomers of dobutamine. *J. Pharmacol. Exp. Therap.* 1981, **219**, 447–452.
- Ruffolo, R. R., Jr., K. Messick & J. S. Horng: Interactions of the enantiomers of 3-O-methyldobutamine with  $\alpha$ - and  $\beta$ -adrenoceptors *in vitro*. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1985, **329**, 244–252.
- Sampaio, E. P., E. N. Sarno, R. Galilly, Z. A. Cohn & G. Kaplan: Thalidomide selectively inhibits tumor necrosis factor- $\alpha$  production by stimulated human monocytes. *J. Exp. Med.* 1991, **173**, 699–703.
- Samuelsson, B.: The discovery of the leukotrienes and the structure elucidation of SRS-A. In: *SRS-A to leukotrienes, The dawning of a new treatment*. Eds.: S. Holgate & S.-E. Dahlén. Blackwell Science Ltd., Oxford, UK, 1997, pp. 39–49.
- Sanjar, S. & J. Morley: Airway hyperreactivity. *Lancet* 1988, **2**, 160–161.
- Schmidt, D., B.-L. Källström, B. Waldeck, D. Branscheid, H. Magnusson & K. F. Rabe: The effect of the enantiomers of formoterol on inherent and induced tone in guinea-pig trachea and human bronchus. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 2000, **361**, 405–409.
- Sheskin, J.: Thalidomide in the treatment of lepra reactions. *Clin. Pharmacol. Therap.* 1965, **6**, 303–306.
- Smith, D. F.: The stereoselectivity of drug action. *Pharmacology & Toxicology* 1989, **65**, 321–331.
- Testa, B., P.-A. Carrupt & J. Gal: The so-called “interconversion” of stereoisomeric drugs: An attempt at clarification. *Chirality* 1993, **5**, 105–111.
- Trofast, J., K. Österberg, B.-L. Källström & B. Waldeck: Steric aspects of agonism and antagonism at  $\beta$ -adrenoceptors: Synthesis of and pharmacological experiments with the enantiomers of formoterol and their diastereomers. *Chirality* 1991, **3**, 443–450.
- Tucker, G. T.: Chiral switches. *Lancet* 2000, **355**, 1085–1087.
- Tuttle, R. R. & J. Mills: Development of a new catecholamine to selectively increase cardiac contractility. *Circ. Res.* 1975, **36**, 185–196.
- Vidal-Beretervide, K.: Effects of ( $\pm$ ) dobutamine and its (+) and (–) enantiomers in the isolated rat portal vein. *Fundam. Clin. Pharmacol.* 1991, **5**, 237–244.
- Voss, H.-P.: *Long-acting  $\beta_2$ -adrenoceptor agonists in asthma: molecular pharmacological aspects*. Thesis, Vrije Universiteit, Amsterdam, 1994.
- Voss, H.-P., D. Donnell & A. Bast: Atypical molecular pharmacology of a new long-acting  $\beta_2$ -adrenoceptor agonist, TA-2005. *Eur. J. Pharmacol.* 1992, **227**, 403–409.
- Waldeck, B.: Biological significance of the enantiomeric purity of drugs. *Chirality* 1993, **5**, 350–355.
- Waldeck, B.: Enantiomers of bronchodilating  $\beta_2$ -adrenoceptor agonists: Is there a cause for concern? *J. Allergy Clin. Immunol.* 1999, **103**, 742–748.
- Waldeck, B.:  $\beta$ -Adrenoceptor agonists and asthma – 100 years of development. *Eur. J. Pharmacol.* 2002, **445**, 1–12.
- Walle, U. K., G. R. Pesola & T. Walle: Stereoselective sulphate conjugation of salbutamol in humans: comparison of hepatic, intestinal and platelet activity. *Brit. J. Clin. Pharmacol.* 1993, **35**, 413–418.
- Wallin, J. D. & W. H. Frishman: Dilevalol: a selective beta-2 adrenergic agonist vasodilator with beta adrenergic blocking activity. *J. Clin. Pharmacol.* 1989, **29**, 1057–1068.
- Weiner, N.: Drugs that inhibit adrenergic nerves and block adrenergic receptors. In: *Goodman & Gilman's The pharmacological Basis of Therapeutics*, 6th edn. Eds.: A. Goodman Gilman, L. S. Goodman & A. Gilman. MacMillan Publishing Co, New York, USA, 1980, pp.176–210.
- White, P. F., W. I. Way & A. J. Trevor: Ketamine – its pharmacology and therapeutic uses. *Anesthesiology* 1982, **56**, 119–136.
- Wnendt, S., M. Finkam, W. Winter, J. Ossig, G. Raabe & K. Zwingenberger: Enantioselective inhibition of TNF- $\alpha$  release by thalidomide and thalidomide analogues. *Chirality* 1996, **8**, 390–396.
- Zeilhofer, H. U., D. Swandulla, G. Geisslinger & K. Brune: Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. *Eur. J. Pharmacol.* 1992, **213**, 155–158.
- Äbelö, A., T. Andersson, M. Antonsson, A. Naudot, I. Skånberg & L. Weidolf: Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab. Dispos.* 2000, **28**, 966–972.