J. Pharm. Pharmacol. 1997, 49: 169–177
Received April 11, 1996
Accepted August 8, 1996

Pharmacodynamic and Pharmacokinetic Studies in Rats of *S*-8-(2-Furyl)- and *R*-8-Phenyl-2-(di-*n*-Propylamino)Tetralin, Two Novel 5-HT_{1A} Receptor Agonists In-vitro with Different Properties In-vivo

HONG YU, YE LIU*, HONG B. LI†, ARNOLD R. MARTIN†, ULI HACKSELL* AND TOMMY LEWANDER

*Department of Psychiatry (Ulleråker), Uppsala University, S-750 17 Uppsala, *Department of Organic Pharmaceutical Chemistry, Box 574, Uppsala University, S-751 23 Uppsala, Sweden and †Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, Arizona 85721, USA*

Abstract

R- and *S*-8-(2-Furyl)- and *R*- and *S*-8-phenyl-2-(di-*n*-propylamino)tetralins (*R*- and *S*-LY-55 and *R*- and *S*-LY-49, respectively), novel enantiopure dipropylaminotetralins, have been screened as 5-HT_{1A} receptor ligands.

All had nanomolar affinities for 5-HT_{1A} receptors and fully inhibited forskolin-stimulated adenylyl cyclase in-vitro (i.e. the four compounds appeared to be 5-HT_{1A} agonists). It was also found that the enantiomers of LY-55 behaved as typical 5-HT_{1A} receptor agonists in rats in-vivo by inducing a typical behavioural 5-HT syndrome, hypothermia and a decrease in 5-HT synthesis and turnover, indicating effects both on postsynaptic 5-HT_{1A} receptors and somatodendritic 5-HT_{1A} autoreceptors. In contrast, *R*- and *S*-LY-49 did not cause any 5-HT_{1A} receptor-related effects in-vivo except for a partial inhibition of 5-HT synthesis after high doses. The 5-HT_{1A} receptor antagonist WAY-100635 was shown to attenuate the *R*-LY-49-induced inhibition of 5-HT synthesis, indicating the compound to be a weak agonist at somatodendritic 5-HT_{1A} autoreceptors. *R*-LY-49 at a high dose and with a long pre-treatment time interval inhibited the hypothermic and behavioural effects, but not the inhibition of 5-HT synthesis induced by the 5-HT_{1A} receptor agonist *R*-8-hydroxy-(dipropylamino)tetralin (*R*-8-OH-DPAT). Taken together, these findings seem to indicate, that *R*-LY-49 is a weak partial agonist at 5-HT_{1A} receptors. A comparative pharmacokinetic study showed that the enantiomers of LY-55 entered the brain rapidly after subcutaneous administration and reached peak brain tissue/plasma concentration ratios within 15–30 min of injection, whereas the brain concentrations of *R*-LY-49 increased slowly, reaching a relatively low peak brain tissue/plasma concentration ratio 90 min after injection despite their similar lipophilicity.

The differences between the pharmacological activity of the two compounds in-vivo seem to be explained by their different abilities to cross the blood-brain barrier, and a weak agonistic activity of *R*-LY-49 on 5-HT_{1A} receptors, both pre- and postsynaptically, compared with *S*-LY-55. Further studies are, however, needed for a deeper understanding of these differences.

The 5-HT_{1A} receptor has attracted considerable attention as a target in the development of novel therapeutic principles for treatment of depression and anxiety disorders (Blier & de Montigny 1994; De Vry 1995; Temple 1995). It is, therefore, of interest to understand fully the functional role of this 5-HT receptor subtype. Starting from the original finding of the 5HT-ergic action of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; Arvidsson et al 1981; Hjorth et al 1982), we have studied enantiopure dipropylaminotetralin derivatives to further the understanding of the interaction between the 5-HT_{1A} receptor and its ligands and to find new chemical entities of interest for drug development (Liu et al 1993, 1995; Hacksell et al 1993). In the process of screening a series of C8-substituted dipropylaminotetralins, we identified compounds that had nanomolar affinity for the 5-HT_{1A} receptor in a receptor-binding assay in-vitro, but lacked the ability to stimulate or block 5-HT_{1A} receptors in-vivo (Liu et al 1993, 1995). It was concluded that additional pharmacodynamic and pharmacokinetic studies were needed to enable understanding of these paradoxical findings. In this study, four C8-substituted 2-(dipropylamino)tetralins, *R*- and *S*-8-(2-furyl)-2-(di-*n*-propylamino)tetralin (*R*- and *S*-LY-55) and *R*- and *S*-8-phenyl-2-(di-*n*-propylamino)tetralin (*R*- and *S*-LY-49) were selected for detailed investigation. Both *R*-LY-49 and *S*-LY-55 have < 10 nM affinity for the 5-HT_{1A} receptor in-vitro. Whereas *S*-LY-55 has the expected 5-HT_{1A} receptor agonist-like effects in-vivo, *R*-LY-49 showed weak or no 5-HT_{1A} receptor-mediated effects. Hence, these two compounds were subjected to a comparative pharmacodynamic and pharmacokinetic study.

Correspondence: T. Lewander, Department of Psychiatry (Ulleråker), Uppsala University, S-750 17 Uppsala, Sweden.

Materials and Methods

Materials

The enantiopure compounds (Fig. 1), (+)-*R*- and (−)-*S*-8-phenyl-2-(di-*n*-propylamino)tetralin (*R*- and *S*-LY-49) oxalate, (+)-*R*- and (−)-*S*-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin (*R*- and *S*-LY-55) hydrochloride and (+)-*R*-8-hydroxy-2-(di-*n*-propylamino)tetralin (*R*-8-OH-DPAT) hydrochloride, were synthesized at the Department of Organic Pharmaceutical Chemistry, Uppsala University, Sweden. 3-Hydroxybenzylhydrazine hydrochloride (NSD1015) was purchased from Sigma. WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexamide trihydro-

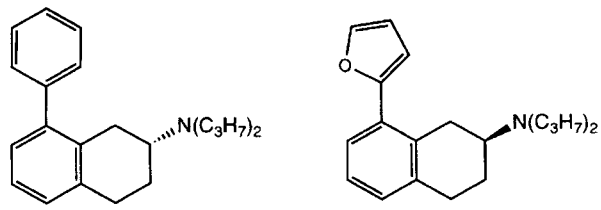

FIG. 1. Chemical structures of *R*-LY-49 and *S*-LY-55.

chloride monohydrate) was a gift from Astra Arcus AB, Södertälje, Sweden. All compounds were dissolved in saline (0·9% NaCl), occasionally with gentle warming and stirring and were injected subcutaneously. Injection volumes were 2 mL kg^{-1}.

Animals

Male Sprague–Dawley rats (Alab, Stockholm), 250–280 g, were kept at 23 ± 1°C with lights on between 0600 and 1800 h. Four rats were housed in each cage (55 × 35 × 20 cm) and were acclimatized in the laboratory for at least a week before being used. They were allowed free access to food and water. All experiments were performed between 0900 and 1500 h. Each animal was used only once. Whenever feasible, behavioural symptoms, body temperature, and 5-HT turnover were studied sequentially in the same animal at different time-points.

Behavioural observations

The behavioural observations were made 30–60 min after injection of test compounds or saline, and each animal was observed for 30 s at pre-determined intervals, usually 6, 12, 30 and sometimes 60 min. Saline-treated controls and *R*-8-OH-DPAT-treated animals (a positive control for 5-HT_{1A} receptor-induced effects) were run in parallel in the same experiment. The investigators were not blind to the drugs given. Particular attention was paid to the 5-HT syndrome (flat body posture and forepaw treading). Such behaviour was reported as absent or present.

Body temperature

Body temperature was determined by insertion of a thermistoprobe (Ellab Instruments, Copenhagen) into the colon, 2·5–3·0 cm from the anal orifice. Baseline values were measured before the injections and recordings were made 30 min after the injections of the test compounds or vehicle at room temperature (22 ± 1°C).

Determination of 5-HT turnover

Rats were decapitated within 5–10 min of the last behavioural rating and body temperature measurement, i.e. 35–45 min after drug administration. The hippocampus was rapidly dissected out and frozen (− 20°C) until assayed. Changes in the 5-hydroxyindoleacetic acid/5-HT ratio were taken as indications of changes in 5-HT turnover.

Determination of 5-HT synthesis

5-HT synthesis was estimated by measuring the accumulation of 5-hydroxytryptophan after inhibition of aromatic L-amino acid decarboxylase by NSD1015 (Carlsson et al 1972). NSD1015 (60 mg kg^{-1}, i.e. 287 μmol kg^{-1}, s.c.) was injected 30 min after administration of the test compounds and the rats were decapitated at 30 min after NSD1015. The hippocampus, the hypothalamus, the corpus striatum and the cortex were rapidly dissected out and stored at − 20°C until assayed.

Bioanalysis of 5-hydroxytryptophan, 5-HT and 5-hydroxyindoleacetic acid

All samples were stored at − 20°C for not more than one week before analysis. The frozen samples were weighed and homogenized in perchloric acid (0·1 M; 1 mL) using α-methyl-5-hydroxytryptophan as internal standard. The homogenate was centrifuged (18 600 *g*, 4°C, 10 min) and filtered, and levels of 5-hydroxyindoleacetic acid, 5-HT and 5-hydroxytryptophan in the supernatant were determined by HPLC. The HPLC system consisted of a PM-48 pump (Bioanalytical Systems) with a CMA/240 autoinjector (injection volume 20 μL), a 100 × 4·6 mm, 5 μm Spheri-5 RP-18 column (and 15 × 3·2 mm, 7 μm RP-18 Newguard precolumn), and an amperometric detector (LC-4B, BAS, equipped with an Ag/AgCl reference electrode and an MF-2000 cell) operating at a potential of +0·85 V. The mobile phase (pH 2·6) was freshly prepared phosphate-citric acid buffer (7·5 mM K_2HPO_4, 26 mM citric acid) containing sodium octylsulphate (40 mg L^{-1}), EDTA (4 drops of 10% solution) and 3–10% methanol (depending on the condition of column). The mobile phase was filtered and degassed before use. The flow rate was 1 mL min^{-1} and the temperature of the column was kept constant at 35°C. Standard curves for each analysis were prepared for each experiment and standards were run intermittently for continuous monitoring of the accuracy of the analyses.

Inhibition of forskolin-stimulated adenylate cyclase in-vitro

The effect of the enantiomers of LY-55 and LY-49 on forskolin-stimulated adenylate cyclase from rat hippocampal tissue was studied by use of methods adapted from De Vivo & Maayani (1986) as described in detail elsewhere (Cornfield et al 1991).

Bioanalysis of R-, S-*LY-55 and* R-*LY-49*

Parallel groups of rats were used for determination of brain and plasma concentrations of *S*- or *R*-LY-55 (because of limited availability of the substances, *R*-LY-55 was used to study the time course and *S*-LY-55 to study the relationship between dose and concentration) and *R*-LY-49. Rats were decapitated at pre-determined intervals, 5, 15, 30, 45, 60, 90, 120 or 240 min after administration. Blood samples were collected and plasma was separated from blood cells by centrifugation within 5 min of sampling. The brains were rapidly removed and cut sagittally in the midline. One half of the brain was taken for determination of the average brain tissue concentration. In another parallel study, the hippocampus, the hypothalamus, the striatum, the brain stem (mesencephalon, pons, medulla oblongata) and the cortex (cerebral neocortex) were rapidly dissected out for determination of drug concentrations after different doses. Both the plasma and the brain parts were frozen (− 20°C) until assayed. The frozen brain tissue parts were weighed and homogenized in perchloric acid (0·1 M; 1·0 mL) adding *R*-LY-55 as an internal standard when studying *R*-LY-49, and adding *R*-LY-49 as internal standard when

studying *S*- or *R*-LY-55. After centrifugation (18 600 *g*, 4°C, 10 min), the supernatant was collected. The brain tissue supernatant (1 mL) or plasma (1 mL) was added to saturated $NaHCO_3$ (pH 8–9; 1 mL) and diethyl ether (4 mL). After automatic shaking of the capped test tubes (in upright position) for 10 min and centrifugation (3500 rev min^{-1} for 10 min), the organic phase (3 mL) was concentrated to dryness under nitrogen gas. The residue was dissolved in methanol (300 μL), evaporated again and redissolved in mobile phase (100 μL); 20 μL was analysed by HPLC (analytical column YMC-pack, ODS-A, 100 × 4·6 mm i.d., *S*-3 μm, 120 A; mobile phase: phosphate buffer (pH 2·0): acetonitrile = 64 : 36, flow rate 0·7 mL min^{-1}) with UV-detector (BAS, UV-116; wavelength 200 nm). Standard curves were produced by use of standard samples of *R*-LY-49 or *S*-LY-55 at concentrations from 0·1 to 5 μg mL^{-1} and the internal standard added to brain tissue homogenate or plasma before extraction. *S*-LY-55 was measured with an accuracy of 100% and a precision of ±0·6% (coefficient of variation; n = 10) in brain tissue (750 ng of the compound added to 1 mL of brain homogenate) and 100% ±3% (n = 10) in plasma (250 ng added to 1 mL of plasma). The accuracy and precision values for *R*-LY-49 in brain homogenate (100 ng added) were 98% ±0·6% (n = 10), and in plasma (200 ng added) 100% ±3% (n = 10), respectively.

Determination of log D values

Log D values were determined as the distribution of *R*-LY-49 or *S*-LY-55 between *n*-octanol saturated with phosphate buffer and phosphate buffer (pH 7·4) by measuring *R*-LY-49 or *S*-LY-55 concentrations in the two phases in-vitro (Grol et al 1991). The concentrations of *R*-LY-49 or *S*-LY-55 were determined by HPLC-UV (see above).

Statistical methods

The behavioural syndromes described as present or absent were analysed by Fisher's exact probability test. Parametric statistics (analysis of variance followed by Tukey's studentized range (HSD) test; Base SAS Software, SAS Institute Inc., Cary, NC, USA) was used for all other measurements.

Results

5-HT_{1A} receptor affinities and activities in-vitro

The receptor affinities for rat brain 5-HT_{1A} receptors for the four aminotetralins are shown in Table 1. It was observed that *S*-LY-55 and *R*-LY-49 have the higher affinities within the respective enantiomeric pairs. Although all four compounds inhibited forskolin-stimulated adenylate cyclase in-vitro, and appeared to be full agonists (approximately 100% inhibition relative to 5-HT; Cornfield et al 1991) in this test, *S*-LY-55 and *R*-LY-49 were more potent than the respective opposite enantiomer. Pindolol, used as a 5-HT_{1A} antagonist, caused a rightward shift of the concentration vs effect curves with a corresponding increase of the EC50 values. Pindolol (10 nM) shifted the EC50 values 5-6-fold for the *S* enantiomers, 28-fold for *R*-LY-49 and 41-fold for *R*-LY-55. The *S* enantiomers appeared to have a lower coupling efficiency ($EC50/K_i$ ratio) in this test as compared with the *R* enantiomers and *R*-8-OH-DPAT.

R- *and* S-*LY-55*

S-LY-55 (3·2–32 μmol kg^{-1}) elicited dose-dependent forepaw treading and flat body posture and a decrease in body temperature and 5-HT turnover (Table 2). At 32 μmol kg^{-1} these effects were similar to those of 1 μmol kg^{-1} *R*-8-OH-DPAT. The effect of *R*-LY-55 appeared to be equivalent to that of *S*-LY-55, except that no forepaw treading was observed. Synthesis of 5-HT, i.e. 5-hydroxytryptophan accumulation after inhibition of aromatic amino acid decarboxylase, was dose-dependently reduced by *S*-LY-55 (3·2–32 μmol kg^{-1}) in all brain regions tested (Table 3). The compound appeared, however, to be less effective in the hippocampus than in the cortex and the striatum.

R- *and* S-*LY-49*

In contrast with *R*-8-OH-DPAT (1·0 μmol kg^{-1}) and both enantiomers of LY-55, at the doses tested, none of the enantiomers of LY-49 induced the 5-HT behavioural syndrome, changed body temperature or reduced 5-HT turnover (Table 2). Even after intravenous (32 μmol kg^{-1}) or intracerebroventricular administration (accumulated doses 1·14 nmol $animal^{-1}$), there were no effects of *R*-LY-49 on behaviour or on body temperature (data not shown). Pretreatment with *R*-LY-49 (100 μmol kg^{-1}) at 90 min before *R*-8-OH-DPAT (0·32 μmol kg^{-1}) attenuated the behavioural symptoms and completely abolished the hypothermia induced by *R*-8-OH-DPAT. *R*-LY-49, 32 μmol kg^{-1}, given 10 min before 1·0 μmol kg^{-1} *R*-8-OH-DPAT did not, however, antagonize responses to the 5-HT_{1A} agonist (Table 4).

R-LY-49 significantly reduced 5-hydroxytryptophan accumulation in different brain regions 60 min after doses of 32 and 100 μmol kg^{-1} (Table 3). This effect of *R*-LY-49 appeared to be weaker in some brain regions, such as in the hippocampus and the hypothalamus. In other experiments, however, a statistically significant decrease in 5-HT synthesis was observed in all brain regions both 120 min (Table 5) and 60 min (Table 6) after *R*-LY-49.

Table 1. Inhibition of 5-HT-sensitive forskolin-stimulated adenylyl cyclase by the enantiomers of LY-55 and LY-49.

Compound	5-HT_{1A} K_i (nM) (n = 2)	Potency EC50 (nM)	Inhibition (%)	$EC50/K_i$
R-8-Hydroxy-2-(di-*n*-propylamino)tetralin	4·1	57·4 ± 11	101 ± 8	14·0
R-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin	9·3 (8·0–11)[a]	149 ± 58	102 ± 2	16·0
S-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin	1·8 (1·6–2·1)[a]	82 ± 8	98 ± 2	45·6
R-8-Phenyl-2-(di-*n*-propylamino)tetralin	7·7 (7·2–8·3)[a]	190 ± 77	103 ± 3	24·7
S-8-Phenyl-2-(di-*n*-propylamino)tetralin	24 (22–26)[a]	913 ± 370	101 ± 3	38·0

[a][^{3}H]8-OH-DPAT as a ligand and data from Liu et al (1993, 1995).

Table 2. Effects of the enantiomers of LY-55 and LY-49 on 5-HT behavioural syndrome displayed between 0 and 30 min, on body temperature at 30 min and on 5-HT turnover 35–45 min after drug administration.

Compound	Dose (μmol kg^{-1}, s.c.)	Forepaw treading[a]	Flat body posture[a]	Body temperature (Δ°C)	5-Hydroxyindole-acetic acid/5-HT ratio (hippocampus)
Saline	–	0/12	0/12	0·2 ± 0·01	100 ± 4
R-8-hydroxy-2-(di-*n*-propylamino)tetralin	1·0	12/12*	12/12*	−2·5 ± 0·05**	68 ± 2**
R-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin	3·2	0/8	0/8	−0·7 ± 0·2	99 ± 15
	10	0/3	3/3*	−1·5 ± 0·2**	81 ± 2***
	32	0/4	4/4*	−2·8 ± 0·1**	68 ± 7**
S-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin	3·2	0/4	1/4	−0·6 ± 0·2	85 ± 4***
	10	0/4	4/4*	−1·7 ± 0·3**	79 ± 2***
	32	4/4*	4/4*	−2·6 ± 0·1**	63 ± 5**
R-8-Phenyl-2-(di-*n*-propylamino)tetralin	32	0/8	0/8	0·1 ± 0·2	94 ± 3
	100	0/4	0/4	−0·1 ± 0	–
S-8-Phenyl-2-(di-*n*-propylamino)tetralin	32	0/8	0/8	0·3 ± 0·1	93 ± 7

[a]The number of the rats displaying the behavioural symptom out of the number of the rats tested are shown. *$P < 0·005$, **$P < 0·01$, ***$P < 0·05$ compared with saline-treated rats. The value of 5-hydroxyindoleacetic acid/5-HT ratio is shown as percentage of control and control level is 1·13 ± 0·04 in the hippocampus.

Table 3. Effects of *R*-LY-49 and *S*-LY-55 on 5-HT synthesis 60 min after administration.

Compound	Dose (μmol kg^{-1}, s.c.)	5-Hydroxytryptophan accumulation (% of control)				
		Hippocampus	Hypothalamus	Striatum	Brain stem	Cortex
S-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin	3.2	93 ± 3	82 ± 3	71 ± 2*	78 ± 1*	79 ± 2*
	10	71 ± 5*	70 ± 2*	51 ± 3*	62 ± 4*	57 ± 5*
	32	74 ± 9**	58 ± 3*	52 ± 4*	61 ± 3*	54 ± 2*
R-8-Phenyl-2-(di-*n*-propylamino)tetralin	10	97 ± 3	92 ± 6	98 ± 4	85 ± 4	93 ± 3
	32	88 ± 9	75 ± 5**	85 ± 5	72 ± 6*	74 ± 6
	100	81 ± 5	73 ± 6*	68 ± 3*	67 ± 5*	57 ± 5*

Values are means ± s.e.m., n = 5–6. The control levels (ng g^{-1}) of 5-hydroxytryptophan accumulation for *S*-LY-55 were 135 ± 7, 306 ± 20, 130 ± 13, 254 ± 14 and 116 ± 4 in the hippocampus, the hypothalamus, the striatum, the brain stem and the cortex, respectively. For *R*-LY-49 the levels were 126 ± 7, 317 ± 36, 120 ± 7, 287 ± 9 and 123 ± 3 in the hippocampus, the hypothalamus, the striatum, the brain stem and the cortex, respectively. *$P < 0·01$, **$P < 0·05$ compared with saline-treated rats.

Table 4. Effects of *R*-LY-49 on the 5-HT$_{1A}$ agonistic actions induced by *R*-8-OH-DPAT.

Compound	Dose (μmol kg^{-1}, s.c.)	Forepaw treading[a]	Flat body posture[a]	Body temperature[b] (Δ°C)
10 min between injections				
Saline + saline	–	0/8	0/8	0·3 ± 0·2
Saline + *R*-8-hydroxy-2-(di-*n*-propylamino)tetralin	1·0	8/8*	8/8*	−2·7 ± 0·3**
R-8-phenyl-2-(di-*n*-propylamino)tetralin + saline	32	0/8	0/8	0·3 ± 0·1
R-8-phenyl-2-(di-*n*-propylamino)tetralin + *R*-8-hydroxy-2-(di-*n*-propylamino)tetralin	32 + 1·0	12/12*	12/12*	−3·3 ± 0·1**
90 min between injections				
Saline + saline	–	0/9	0/9	0·1 ± 0·1
Saline + *R*-8-hydroxy-2-(di-*n*-propylamino)tetralin	0·32	1/6	6/6*	−1·9 ± 0·3**
R-8-phenyl-2-(di-*n*-propylamino)tetralin + saline	100	0/4	0/4	−0·4 ± 0
R-8-phenyl-2-(di-*n*-propylamino)tetralin + *R*-8-hydroxy-2-(di-*n*-propylamino)tetralin	100 + 0·32	0/6	3/6	−0·5 ± 0·1***

[a]The number of rats displaying the behavioural symptom out of the number of the rats tested are shown. [b]Change in body temperature, i.e. difference between the value 30 min after the last injection and the pre-injection value. *$P < 0·005$, **$P < 0·01$ compared with saline-treated rats; ***$P < 0·01$ compared with saline + *R*-8-OH-DPAT.

The decrease in 5-hydroxytryptophan accumulation induced by *R*-8-OH-DPAT was not attenuated by pretreatment with *R*-LY-49 given 60 min before *R*-8-OH-DPAT, i.e. 120 min before the animals were killed (Table 5). On the contrary, there was a 30–40% reduction in 5-hydroxytryptophan accumulation induced by *R*-8-OH-DPAT in rats pretreated with *R*-LY-49, i.e. approximately the same effect as in saline-treated controls. WAY-100635, a 5-HT$_{1A}$ receptor antagonist, in a dose (0·55 μmol kg^{-1}, s.c.) not changing 5-HT synthesis by itself, partially antagonized the reduction in 5-hydroxytryptophan

Table 5. Effects of *R*-LY-49 (LY-49) on the *R*-8-OH-DPAT (8-OH)-induced decrease in 5-HTP accumulation in four brain regions.

	5-HTP accumulation (ng(g tissue)$^{-1}$)			
	Saline + saline	LY-49 + saline	Saline + 8-OH	LY-49 + 8-OH
Hippocampus	140 ± 7	101 ± 5**	88 ± 3**	68 ± 6**††
Hypothalamus	325 ± 16	272 ± 17	231 ± 20**	190 ± 10**†
Striatum	127 ± 5	91 ± 5**	86 ± 7**	64 ± 5**†
Cortex	132 ± 4	90 ± 5**	64 ± 2**	54 ± 3**††

R-LY-49 (32 μmol kg^{-1}, s.c.) or saline was given to the rats 60 min before *R*-8-OH-DPAT (0·32 μmol kg^{-1}, s.c.) or saline. NSD1015 (60 mg kg^{-1}, s.c.) was injected 30 min after *R*-8-OH-DPAT or saline and the rats were killed 30 min after NSD1015. Results are means ± s.e.m., $^{**}P < 0.01$ (n = 5–6) compared with saline + saline; $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$ compared with *R*-LY-49 + saline.

Table 6. Antagonism by WAY-100635 (WAY) of the *R*-LY-49 (LY-49)-induced decrease in 5-HTP accumulation in four brain regions.

	5-HTP accumulation (ng(g tissue)$^{-1}$)			
	Saline + saline	Saline + LY-49	WAY + saline	WAY + LY-49
Hippocampus	126 ± 4	95 ± 5**	114 ± 3	106 ± 5*
Hypothalamus	385 ± 24	249 ± 16**	413 ± 23	343 ± 13†
Striatum	139 ± 6	100 ± 6**	148 ± 4	126 ± 5††
Cortex	151 ± 4	106 ± 6**	154 ± 4	138 ± 9††

WAY-100635 (0·55 μmol kg^{-1}, s.c.) or saline was given to the rats 15 min before *R*-LY-49 (100 μmol kg^{-1}, s.c.) or saline. NSD1015 (60 mg kg^{-1}, s.c.) was injected 30 min after *R*-LY-49 or saline and the rats were killed 30 min after NSD1015. Results are means ± s.e.m., n = 5–6. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline + saline; $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$ compared with saline + *R*-LY-49.

accumulation induced by *R*-LY-49 (Table 6). This effect of WAY-100635 was statistically significant in the hypothalamus, striatum and cortex, but not in the hippocampus.

Brain and plasma concentrations of LY-55 and LY-49

Brain and plasma concentrations of *R*-LY-55 (Fig. 2) and *R*-LY-49 were measured at predetermined time-points after subcutaneous administration of 32 μmol kg^{-1} of the two compounds in separate experiments. As shown in Fig. 2a the mean plasma concentration of *R*-LY-55 was approximately 1·2 nmol mL^{-1} within 5 min after drug administration and remained fairly constant at that level throughout the 4 h experiment. The brain concentration of *R*-LY-55 equalled that in plasma during the first 15 min, thereafter there was a steep increase to a peak brain concentration of 4·4 nmol g^{-1} 30 min after injection. The brain/plasma concentration ratio was then 3·7. Two hours after injection brain and plasma concentrations were similar. The time-course of *R*-LY-49 in plasma (Fig. 2b) was similar to that of *R*-LY-55. Within 5 min after injection the mean plasma concentration was approximately 1 nmol mL^{-1}; it peaked at 1·2 nmol mL^{-1} after 15 min and then decreased slowly to approximately 0·6 nmol mL^{-1} at 6 h. In contrast to *R*-LY-55, the brain concentrations of *R*-LY-49 increased slowly, peaked at 1·8 nmol mL^{-1} 2 h after injection, with a brain/plasma concentration ratio of 2·5, and then returned slowly towards the plasma concentration level. *R*-LY-49 could be detected in both brain and plasma 24 h after injection (data not shown).

The next set of experiments was designed to study the dose-related brain and plasma concentrations and the regional distribution of *S*-LY-55 and *R*-LY-49 within the brain 60 min after injection of the compounds. Fig. 2c shows that there was an approximately linear relationship between dose and brain and plasma concentrations of *S*-LY-55 within the 3·2–32 μmol kg^{-1} dose-range 60 min after injection. There were, however, large and dose-dependent variations in the drug concentrations between brain regions with brain/plasma ratios varying from 5·3 in the cortex to 1·6 in the hypothalamus at 32 μmol kg^{-1} (Table 7). At the 3·2 μmol kg^{-1} dose level, however, hippocampus had a brain/plasma concentration ratio of 29, and again the value was lowest for the hypothalamus (6·4). Because of the apparently lower potency of *R*-LY-49 in pharmacodynamic experiments, the dose range 10–100 μmol kg^{-1} was chosen for study. As shown in Fig. 2d the relationship between dose and brain and plasma concentration was not linear for plasma and hypothalamus, whereas the relationship was apparently linear for other brain regions, e.g. striatum and cortex. The maximum brain tissue/plasma concentration ratio was 2·9–3·3 in the hypothalamus after both 32 and 100 μmol kg^{-1}, whereas in this instance the ratio was lowest for the hippocampus (1·0–2·2, Table 7).

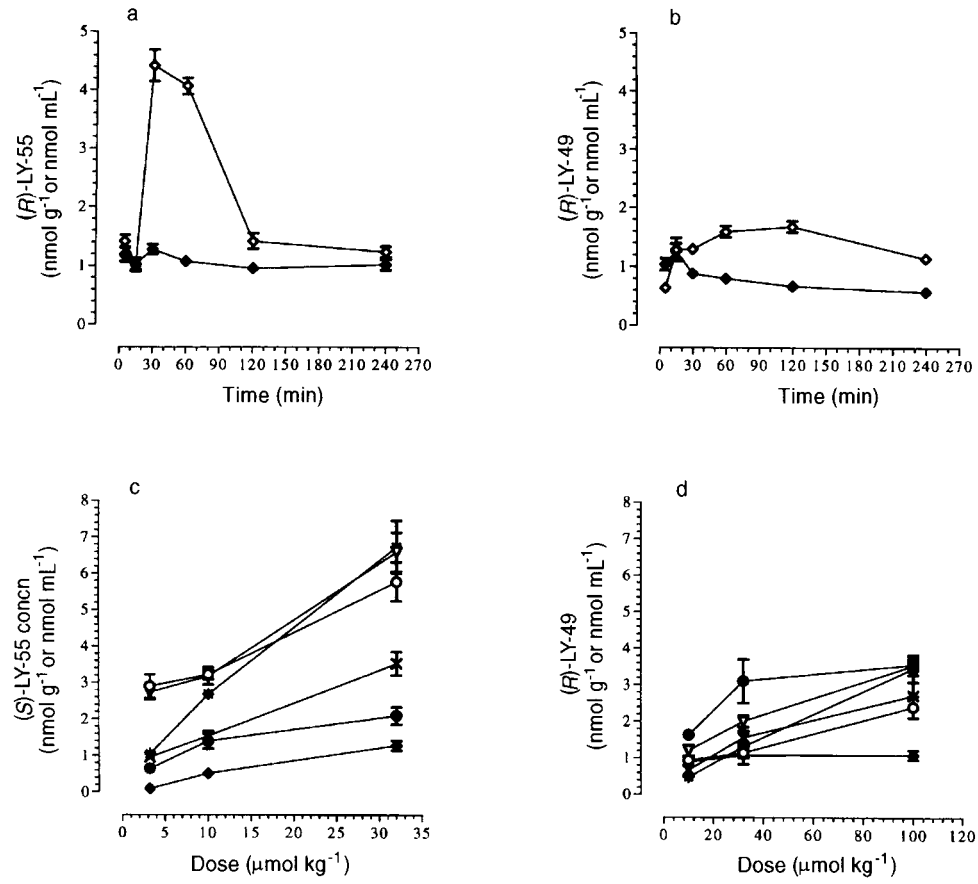

FIG. 2. The concentrations of the test compounds at different time-points after single doses (32 μmol kg^{-1}, s.c.) of *R*-LY-55 or *R*-LY-49 in whole rat brain (◇) and in plasma (◆) are shown in a and b, respectively. The concentrations of *S*-LY-55 or *R*-LY-49 at 60 min after different doses of the drugs in hippocampus (○), hypothalamus (●), striatum (△), brain stem (×), cortex (*) and plasma (◆) are shown in c and d, respectively. Values are expressed as means ± s.e.m. (n = 5–6). Because of limited availability of the *S*-enantiomer experiment a was performed with *R*-LY-55 instead of *S*-LY-55.

Table 7. Brain tissue/plasma concentration ratio for *S*-LY-55 and *R*-LY-49 in five brain regions 60 min after administration of different doses of the compounds.

	Dose (μmol kg^{-1}, s.c.)			
	3·2	10	32	100
S-8-(2-Furyl)-2-(di-*n*-propylamino)tetralin				
Hippocampus	29·0	6·3	4·5	
Hypothalamus	6·4	2·7	1·6	
Striatum	27·4	6·2	5·1	
Brain stem	9·6	3·0	2·2	
Cortex	10·4	5·3	5·3	
R-8-phenyl-2-(di-*n*-propylamino)tetralin				
Hippocampus		1·0	1·0	2·2
Hypothalamus		1·8	2·9	3·3
Striatum		1·3	1·8	3·2
Brain stem		0·7	1·5	2·5
Cortex		0·5	1·2	3·2

Log D values of S-*LY-55 and* R-*LY-49*

The octanol/water distribution coefficients, log D, of *S*-LY-55 and *R*-LY-49 at pH 7·4 were 2·35 and 2·41, respectively. *R*-8-OH-DPAT has a log D value of 1·3 (Yu & Lewander 1997) with the present method.

Discussion

These studies of the enantiomers of LY-55 and LY-49 confirm and extend previous data from in-vitro and in-vivo pharmacological screening of these compounds (Liu et al 1993, 1995). Thus, in addition to having nanomolar affinity for the 5-HT_{1A} receptor, they all inhibit forskolin-stimulated adenylate cyclase in-vitro and appear as full agonists in this respect, being similar to 5-HT and the prototypical 5-HT_{1A} agonist, *R*-8-OH-DPAT (Cornfield et al 1991). In addition, the pindolol-induced shifts of the EC50 values indicate that the inhibition of adenylate cyclase is primarily a 5-HT_{1A} receptor-mediated event. The less than complete pindolol-induced shift (5–6 fold) for *S*-LY-49 and *S*-LY-55, in contrast with that obtained for the *R* enantiomers (28- to 41-fold), might indicate that some other receptor is involved in the inhibition of the enzyme induced by these compounds.

The results from the original in-vivo screening (Liu et al 1993, 1995) have been confirmed by the findings of dose-dependent typical 5-HT_{1A} agonist-like effects induced by *R*- and *S*-LY-55. Thus, these two compounds elicited flat body posture, hypothermia and a reduction in 5-HT turnover. The two enantiomers appeared to be equipotent and had similar effects at 32 μmol kg^{-1} as 1 μmol kg^{-1} of *R*-8-OH-DPAT, with the exception that *R*-LY-55, in contrast to *S*-LY-55, did not elicit forepaw treading. The enantiomers of LY-49, however, did not have any 5-HT_{1A} agonist-like behavioural effects or hypothermia, typical postsynaptic effects of 5-HT_{1A} agonists, after subcutaneous administration of up to 100 μmol kg^{-1} and there was no reduction in 5-HT turnover. Not even after intravenous or intraventricular administration did *R*- or *S*-LY-49 induce behavioural effects or changes in body temperature, excluding poor absorption as an explanation for the apparent lack of efficacy. *R*-LY-49 and *S*-LY-55 were, however, found to induce a dose-dependent reduction in 5-HT synthesis, indicating a stimulation of somatodendritic 5-HT_{1A} autoreceptors (Arvidsson et al 1981; Hjorth et al 1982; Hjorth & Magnusson 1988). *R*-LY-49 seemed to be less potent than *S*-LY-55 in this respect, because *S*-LY-55 reduced 5-HT synthesis maximally in most brain regions at 10 μmol kg^{-1}, whereas at least 100 μmol kg^{-1} of *R*-LY-49 had to be given to achieve similar inhibition of 5-HT synthesis.

The apparently paradoxical finding that *R*-LY-49 has high affinity for the 5-HT_{1A} receptor and appears to be a full agonist in-vitro, but was shown to be devoid of agonist activity on post-synaptic 5-HT_{1A} receptors in-vivo, might be explained if the drug behaves as a weak partial agonist, or an antagonist, at this receptor. *R*-LY-49, 32 μmol kg^{-1}, given 10 min previously produced no sign of antagonism of effects on behaviour or body temperature induced by 1 μmol kg^{-1} of *R*-8-OH-DPAT, however. Having studied the time-course of *R*-LY-49 in brain tissue after subcutaneous administration, however, a second experiment was performed in which a dose of 0·32 μmol kg^{-1} of *R*-8-OH-DPAT was given 90 min after 100 μmol kg^{-1} of *R*-LY-49, i.e. when the brain concentrations of *R*-LY-49 should be close to maximum. Under these conditions, *R*-LY-49 fully antagonized *R*-8-OH-DPAT-induced hypothermia, and partially antagonized forepaw treading and flat body posture.

The *R*-LY-49-induced decrease in 5-HT synthesis in different brain regions was further studied in two separate experiments. Firstly, we sought to determine whether or not *R*-LY-49 might antagonize the *R*-8-OH-DPAT-induced reduction in 5-HT synthesis. It was found, however, that in all brain regions the inhibitory effect of *R*-8-OH-DPAT was similar in size in rats pre-treated with *R*-LY-49 and in saline-treated controls. Thus these results would suggest that *R*-LY-49 is not an antagonist at the somatodendritic 5-HT_{1A} autoreceptors. WAY-100635, a 5-HT_{1A} antagonist (Fletcher et al 1994; Forster et al 1995), reduced the *R*-LY-49-induced reduction in 5-HT synthesis in cortex, striatum and hypothalamus, but not, however, in the hippocampus. This additional result suggests that the *R*-LY-49-induced effect on 5-HT synthesis might be mediated, at least partly, by 5-HT_{1A} receptors.

An important finding of these comparative studies of *S*-LY-55 (or *R*-LY-55; Fig. 2) and *R*-LY-49 is the apparent differences in their pharmacokinetic characteristics. Both compounds seem to be absorbed equally well from the subcutis, because equimolar doses result in similar plasma concentrations of the two compounds even as soon as 5 min after injection, and the time-courses in plasma over 6 h are also similar. The brain concentrations of *R*-LY-55, however, increased rapidly to about 4·5 nmol g^{-1} within 30 min and returned to 1 nmol g^{-1} after 2 h. In studies of the effect of dose on the concentration in various brain regions it was found that the concentrations of *S*-LY-55 varied considerably between brain regions with the highest levels (5·5–6·5 nmol g^{-1}) in the hippocampus, striatum and cortex. This pharmacokinetic pattern resembles recent findings with *R*-8-OH-DPAT (Yu & Lewander 1997). In contrast, the average brain concentration of *R*-LY-49 increased gradually up to a maximum of 1·8 nmol g^{-1} at 2 h followed by a gradual decrease. Again in contrast with *S*-LY-55, the concentrations of *R*-LY-49 in different brain regions were similar with only a 2-fold variation in brain tissue/plasma concentration ratios and with the highest levels (3 nmol g^{-1}) in the hypothalamus rather than hippocampus. It is possible that the gradual increase and relatively low brain-concentrations of the drug contribute to its low potency in-vivo. The small difference between the log D values of *S*-LY-55 and *R*-LY-49 at physiological pH (Manners et al 1988) indicates that they are of similar lipophilicity and that both compounds are more lipophilic than *R*-8-OH-DPAT. Thus, *S*-LY-55 and *R*-LY-49 should be distributed to the brain to a similar extent. A difference in influx to the brain by active transport across the blood-brain barrier (Pardridge & Oldendorf 1977), or possibly efflux from the brain by P-glycoprotein (Tsuji et al 1993; Ruetz & Gros 1994) might be avenues for further investigation. Obviously, additional studies of the pharmacokinetics of the two tetralin derivatives would be of interest.

The findings with the four aminotetralins can be summarized as follows. Both *R*- and *S*-LY-55 have high affinity for the 5-HT_{1A} receptor, inhibit forskolin-stimulated adenylate cyclase in-vitro, and elicit behavioural effects, hypothermia and biochemical changes in 5-HT neurons in-vivo typical of 5-HT_{1A} receptor agonists such as *R*-8-OH-DPAT. These findings

would, therefore, suggest that both enantiomers of LY-55 are 5-HT_{1A} agonists both presynaptically on somatodendritic autoreceptors (inhibition of 5-HT turnover and synthesis) and postsynaptically (behaviour, hypothermia). There are, however, two caveats: firstly, the less than complete pindolol shift for *S*-LY-55 and, secondly, the absence of forepaw treading for *R*-LY-55 might indicate that more than one receptor is involved, and that the profiles of the two enantiomers are not exactly similar. *R*- and *S*-LY-49 both have high affinity for the 5-HT_{1A} receptor and inhibit forskolin-stimulated adenylate cyclase in-vitro to the same extent as *R*-8-OH-DPAT (Cornfield et al 1991), an effect apparently mediated via 5-HT_{1A} receptors (De Vivo & Maayani 1986). In-vivo, however, neither enantiomer has 5-HT_{1A}-like action on behaviour, body temperature or 5-HT turnover. *R*-LY-49 does, however, inhibit 5-HT synthesis, indicative of an agonistic action on somatodendritic 5-HT_{1A} autoreceptors, as supported by the attenuation of this effect by the 5-HT_{1A} receptor antagonist WAY-100635. Taken together, these findings indicate that *R*-LY-49 is a weak partial agonist. Such a conclusion is supported by the antagonism of *R*-8-OH-DPAT-induced hypothermia and flat body posture upon adjustment of the dose and pre-treatment time according to the pharmacokinetics of the compound. *R*-LY-49 did not, however, antagonize the inhibitory action of *R*-8-OH-DPAT on 5-HT synthesis. A high density of autoreceptors might explain the apparent absence of an antagonistic effect of a weak partial agonist on somatodendritic 5-HT_{1A} receptors (Hjorth et al 1989; Sharp et al 1989; Gartside et al 1990; Meller et al 1990; Björk et al 1991). Other explanations might be the existence of different subtypes of 5-HT_{1A} receptors presynaptically compared with postsynaptically (Blier et al 1993; Peroutka 1994; Nénonéné et al 1994; Artigas 1995) or the fact that 5-HT_{1A} receptors are coupled to different second messengers in different neuronal populations (Boess & Martin 1994; Hoyer et al 1994; De Vry 1995).

The apparent lack of pharmacological activity of *R*-LY-49 as reported from in-vivo screening of the compounds, despite high affinity and activity in-vitro, might be explained by a weak partial agonist activity of the compound in-vivo in combination with a slow and limited transport of the compound across the blood-brain barrier. In contrast, the enantiomers of LY-55 appear to be better agonists at 5-HT_{1A} receptors both pre- and postsynaptically in-vivo and they seem to be transported more readily across the blood-brain barrier. It is possible that other C8-aryl and heteroaryl substituted 2-(dipropylamino)tetralins devoid of pharmacological effects in-vivo (Liu et al 1995) might have pharmacodynamic and pharmacokinetic properties similar to *R*-LY-49.

Acknowledgements

These investigations were supported by the Swedish Board for Industrial Technical Development, the Swedish Natural Science Research Council, Astra Arcus AB and the Medical Faculty, University of Uppsala, Sweden. The authors are grateful to Dr Göran Sundholm for scientific advice and Pharm. Lic. Yan Hongmei for contributing to the bioanalytical methods. Ms Anne-Maj Gustavsson is acknowledged for excellent technical assistance.

References

Arvidsson, L. E., Hacksell, U., Nilsson, J. L. G., Hjorth, S., Carlsson, A., Lindberg, P., Sanchez, D., Wikström, H. (1981) 8-Hydroxy-2-(di-*n*-propylamino)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. J. Med. Chem. 24: 921–923

Artigas, F. (1995) 5-Hydroxytryptamine and antidepressant augmentation. Arch. Gen. Psychiatry 52: 969–971

Björk, L., Cornfield, L. J., Nelson, D. L., Hillver, S. E., Andén, N. E., Lewander, T., Hacksell, U. (1991) Pharmacology of the novel 5-hydroxytryptamine$_{1A}$ receptor antagonist (*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)tetralin: inhibition of (*R*)-8-hydroxy-2-(dipropylamino) tetralin-induced effects. J. Pharmacol. Exp. Ther. 258: 58–65

Blier, P., De Montigny, C. (1994) Current advances and trends in the treatment of depression. Trends Pharmacol. Sci. 15: 220–226

Blier, P., Lisa, A., De Montigny, C. (1993) Differential properties of pre- and postsynaptic 5-hydroxytryptamine$_{1A}$ receptors in the dorsal raphe and hippocampus: I. Effect of spiperone. J. Pharmacol. Exp. Ther. 265: 7–15

Boess, F. G., Martin, I. L. (1994) Molecular biology of 5-HT receptors. Neuropharmacology 33: 275–317

Carlsson, A., Davis, J. N., Kehr, W., Lindqvist, M., Atack, C. V. (1972) Simultaneous measurement of tyrosine and tryptophan hydroxylase activities in brain in vivo using an inhibitor of the aromatic amino acid decarboxylase. Naunyn Schmiedebergs Arch. Pharmacol. 275: 153–168

Cornfield, L. J., Lambert, G., Arvidsson, L. E., Mellin, C., Vallgårda, J., Hacksell, U., Nelson, D. L. (1991) Intrinsic activity of enantiomers of 8-hydroxy-2-(di-*n*-propylamino)tetralin and its analogs at 5-hydroxytryptamine$_{1A}$ receptors that are negatively coupled to adenylate cyclase. Mol. Pharmacol. 39: 780–787

De Vivo, M., Maayani, S. (1986) Characterization of 5-hydroxytryptamine$_{1A}$ receptor-mediated inhibition of forskolin-stimulated adenylyl cyclase activity in guinea-pig and rat hippocampal membranes. J. Pharmacol. Exp. Ther. 238: 248–253

De Vry, J. (1995) 5-HT_{1A} receptor agonists: recent developments and controversial issues. Psychopharmacology 121: 1–26

Fletcher, A., Bill, D. J., Cliffe, I. A., Forster, E. A., Jones, D., Reilly, Y. (1994) A pharmacological profile of WAY-100635, a potent and selective 5-HT_{1A} receptor antagonist. Br. J. Pharmacol. 112: 92P

Forster, E. A., Cliffe, I. A., Bill, D. J., Dover, G. M., Jones, D., Reilly, Y., Fletcher, A. (1995) A pharmacological profile of the selective silent 5-HT_{1A} receptor antagonist, WAY-100635. Eur. J. Pharmacol. 281: 81–88

Gartside, S. E., Cowen, P. J., Hjorth, S. (1990) Effects of MDL 73005EF on central pre- and postsynaptic 5-HT_{1A} receptor function in the rat in vivo. Eur. J. Pharmacol. 191: 391–400

Grol, C. J., Nordvall, G., Johansson, A. M., Hacksell, U. (1991) 5-Oxygenated *N*-alkyl- and *N,N*-dialkyl-2-amino-1-methyltetralins. Effects of structure and stereochemistry on dopamine-D_2-receptor affinity. J. Pharm. Pharmacol. 43: 481–485

Hacksell, U., Liu, Y., Yu, H., Vallgårda, J., Backlund Höök, B., Johansson, A. M., Lewander, T. (1993) Neuromedicinal chemistry of 5-HT_{1A}-receptor agonists and antagonists. Drug Des. Discov. 9: 287–297

Hjorth, S., Magnusson, T. (1988) The 5-HT_{1A} receptor agonist, 8-OH-DPAT, preferentially activates cell body 5-HT autoreceptors in rat brain in-vivo. Naunyn Schmiedebergs Arch Pharmacol. 338: 463–471

Hjorth, S., Carlsson, A., Lindberg, P., Sanchez, D., Wikström, H., Arvidsson, L. E., Hacksell, U., Nilsson, J. L. G. (1982) 8-Hydroxy-2-di-*n*-propylaminotetralin, 8-OH-DPAT, a potent and selective simple ergot congener with 5-HT-receptor stimulating activity. J. Neural Transm. 55: 1690–1188

Hjorth, S., Sharp, T., Hacksell, U. (1989) Partial postsynaptic 5-HT_{1A} agonist properties of the novel stereoselective 8-OH-DPAT analogue (+)*cis*-8-hydroxy-1-methyl-2-(di-*n*-propylamino) tetralin, (+)ALK-3. Eur. J. Pharmacol. 170: 269–274

Hoyer, D., Clarke, D. E., Fozard, J. R., Hartig, P. R., Martin, G. R., Mylecharane, E. J., Saxena, P. R., Humphrey, P. P. A. (1994) International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol. Rev. 46: 157–203

Liu, Y., Yu, H., Svensson, B. E., Cortizo, L., Lewander, T., Hacksell, U. (1993) Derivatives of 2-(dipropylamino)tetralin: effect of the C8-

substituent on the interaction with 5-HT_{1A} receptors. J. Med. Chem. 36: 4221–4229

Liu, Y., Cortizo, L., Yu, H., Svensson, B. E., Lewander, T., Hacksell, U. (1995) C8-Substituted derivatives of 2-(dipropylamino)tetralin: exploration of the effect of C8-aryl and heteroaryl substituents on the interaction with 5-HT_{1A}-receptors. Eur. J. Med. Chem. 30: 277–286

Manners, C. N., Payling, D. W., Smith, D. A. (1988) Distribution coefficient, a convenient term for the relation of predictable physicochemical properties to metabolic processes. Xenobiotica 18: 331–350

Meller, E., Goldstein, M., Bohmaker, K. (1990) Receptor reserve for 5-hydroxytryptamine$_{1A}$-mediated inhibition of serotonin synthesis: possible relationship to anxiolytic properties of 5- hydroxytryptamine$_{1A}$ agonists. Mol. Pharmacol. 37: 231–237

Nénonéné, E. K., Radja, F., Carli, M., Grondin, L., Reader, T. A. (1994) Heterogeneity of cortical and hippocampal 5-HT_{1A} receptors: a reappraisal of homogenate binding with (^{3}H)8-hydroxydipropylaminotetralin. J. Neurochem. 62: 1822–1834

Pardridge, W. M., Oldendorf, W. H. (1977) Transport of metabolic substrates through the blood-brain barrier. J. Neurochem. 28: 5–12

Peroutka, S. J. (1994) Molecular biology of serotonin (5-HT) receptors. Synapse 210: 88–90

Ruetz, S., Gros, P. (1994) A mechanism for P-glycoprotein action in multidrug resistance: are we there yet? Trends Pharmacol. Sci. 15: 260

Sharp, T., Bramwell, S. R., Hjorth, S., Grahame-Smith, D. G. (1989) Pharmacological characterization of 8-OH-DPAT-induced inhibition of rat hippocampal 5-HT release in vivo as measured by microdialysis. Br. J. Pharmacol. 98: 989–997

Temple, D. L. (1995) Antidepressants: clinical and neuropharmacologic considerations relevant to future drug discovery and development. Exp. Opin. Invest. Drugs 4: 909–914

Tsuji, A., Tamai, I., Sakata, A., Tenda, Y., Terasaki, T. (1993) Restricted transport of cyclosporin A across the blood-brain-barrier by a multidrug transporter, P-glycoprotein. Biochem. Pharmacol. 46: 1096–1099

Yu, H., Lewander, T. (1997) Pharmacodynamic and pharmacokinetic studies of *R*-8-hydroxy-2-(di-*n*-propylamino)tetralin in the rat. Eur Neuropsychopharmacol. In press