J. Pharm. Pharmacol. 1991, 43: 481–485
Received January 10, 1991

5-Oxygenated *N*-Alkyl- and *N,N*-Dialkyl-2-amino-1-methyltetralins. Effects of Structure and Stereochemistry on Dopamine-D_2-receptor Affinity

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Abstract—The ability of a series of stereochemically well-defined 5-oxygenated 2-aminotetralins, consisting of dopamine-receptor agonists and antagonists, to displace [^{3}H]spiperone and [^{3}H]*N*-propylnorapomorphine (NPA) from calf-caudate dopamine receptor sites has been evaluated in-vitro. In addition, the partition coefficients of the compounds were determined to measure their lipophilicity. The data were compared with previously obtained in-vivo biochemical data (dopa accumulation in reserpine pretreated or non-pretreated rats). Compounds with 2*S*-configuration and a C^5-hydroxy substituent have the highest affinity for NPA-binding sites and such derivatives also have the highest potency in-vivo. The 2*R*-derivatives are less efficacious and their affinity for NPA- and spiperone binding sites is influenced by their lipophilicity. On the basis of these results, a model is proposed in which the antagonists form two, and the agonists form three, strong intermolecular bonds with the D_2-receptor. According to this model, the agonists, but not the antagonists, are able to donate a hydrogen bond from the phenolic hydroxyl to the receptor.

Dopamine D_1- and D_2-receptors have been well characterized functionally and, today, their existence is commonly accepted (Andersen et al 1990). In addition, both D_1- and D_2-receptors have been cloned and expressed but the three-dimensional structures of these receptors have not yet been elucidated. It should be possible to identify differences in topology between the D_1- and D_2-receptor sites by structural analysis of compounds that bind preferentially to either of these sites (Billard et al 1985; Waddington 1986). It is more complicated to use the structures of agonists with preference for presynaptic D_2-receptors in attempts to deduce topographical differences between pre- and postsynaptic D_2-receptors since this class of compounds is structurally heterogeneous (for a recent review, see Seyfried & Boettcher (1990)). In addition, a preferential action for pre- or postsynaptic dopamine receptor sites might well be explained in terms of a difference in receptor reserve (Meller et al 1986, 1987) or in the responsiveness of the receptor (Carlsson 1983). Thus, although considerable progress has been made in the distinction and localization of dopamine receptor sites and states, the structural requirements for selective agonists and antagonists have not been established in such detail that the topography of these receptor sites can be described accurately. Therefore, there is still a need for novel and pharmacologically well-characterized agonists and antagonists with small structural differences.

The compounds studied in the present investigation (*1-13*; Fig. 1) are 2-aminotetralin derivatives substituted with a hydroxy or a methoxy group in the 5-position (that is, meta to the phenethylamine moiety), and with a methyl group at the C^1-position of the alicyclic ring in a well-defined stereochemical relationship to the nitrogen atom (Johansson et al 1985, 1987). The nitrogen has been substituted with various alkyl groups. In a previous report, these compounds were classified as pre- or postsynaptic agonists and antagonists based on in-vivo pharmacological data (Johansson et al 1987). However, in-vivo data are obtained from a very

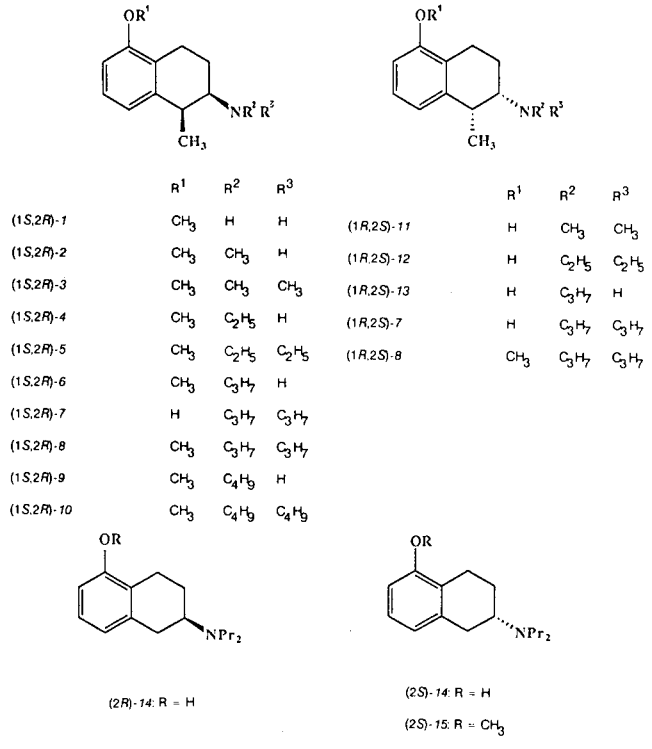

FIG. 1. Structures of the compounds studied.

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complex system and are, therefore, difficult to interpret. In addition, it is now recognized that many behavioural dopaminergic effects result from complementary effects of D_1- and D_2-receptor activation (Molloy et al 1986; Robertson & Robertson 1987). This complicates the interpretation further.

In contrast to in-vivo pharmacology, the radioligand binding technique is an excellent tool for direct assessment of the events at the receptor level. Therefore, we have determined the affinities for D_2-receptors of the substituted 2-aminotetralins *1-13*. In addition, we have measured the binding affinities of *S-* and *R-14* and *S-15* for comparative purposes. Since the lipophilicity of the ligand (or part of it) may affect the affinity when hydrophobic interactions stabilize or destabilize the receptor-ligand complex, we have also assessed the lipophilicity of the compounds by determining their partition coefficients in an n-octanol-buffer system. The results have been used to discuss the topological requirements for the various pharmacological effects at the molecular level.

Materials and Methods

Determination of partition coefficients

From a standard solution of the compounds (1 mg/10 mL) an amount of 50–500 μL was added to 5·00 mL of an n-octanol saturated phosphate buffer (pH = 7·4, 20°C). The resulting solution was shaken for 5–10 min with 0·05–1·0 mL n-octanol and centrifuged. A sample from the water phase was injected into a 20 μL loop and chromatographed on a 20 cm CPSphere C8 column with a phosphate-citrate buffer (pH = 4) using 8–20% isopropanol as an organic modifier. Finally, tetrabutylammonium sulphate (0·02–0·10%) was added to prevent tailing. The concentration was measured with UV or electrochemical detection against the standard solution. In this way it was often possible to determine the partition coefficient of two to three compounds in one HPLC run.

Binding experiments

Membrane preparation. Calf striatal tissue was obtained from a local slaughter house and stored at −80°C until use. The tissue was homogenized with 40 vol of ice-cold salt buffer (50 mM Tris, 1 mM EDTA, 5 mM HCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, pH 7·4) using an Ultraturrax (1000 rev min^{-1}). The homogenate was centrifuged at 43 000 *g* for 20 min at 5°C. The pellet was resuspended in 40 vol of salt buffer and preincubated for 30 min at 35°C, centrifuged at 43 000 *g* for 20 min at 5°C and resuspended and centrifuged once more. The pellet thus obtained was resuspended in 10 vol of salt buffer. Samples (2·35 mL) of tissue homogenate were frozen in plastic tubes (liquid nitrogen) and stored at −20°C.

[^{3}H]Spiperone binding. The tissue homogenate was suspended in 3 v/v of ice-cold incubation buffer (50 mM Tris-HCl, 1 mM EDTA, 50 mM NaCl, 5 mM KCl, 1·5 mM $CaCl_2$, 4 mM $MgCl_2$, pH 7·2). Triplicate determinations were conducted in borosilicate glass tubes. Each tube (final volume 1 mL) included 100 μL of 10 nM [^{3}H]spiperone (20 Ci $mmol^{-1}$, NEN) and the competitor drug (50–100 μL) both in Tris-salt buffer. Non-specific binding was defined using 1 μM (+)-butaclamol (Ayerst) in buffer. In saturation experiments, the specific binding of [^{3}H]spiperone was obtained as a function of its concentration (0·025–1·5 nM). Non-specific binding was defined as binding in the presence of 1 μM (+)-butaclamol. Eadie-Hofstee plots indicated a single binding site with a K_d of 0·16 ± 0·006 nM and a capacity of 21·5 ± 0·8 pmol (g tissue)$^{-1}$.

The reaction was initiated by the addition of 100 μL of the membrane suspension (1·5–2 mg/tube) and incubated at 37°C for 40 min. Bound ligand was separated from free by rapid vacuum filtration over GF/B filters with 4 × 3·5 mL washes of the filters with ice-cold Tris-salt buffer. The filters were placed in glass vials with 6 mL of Plasmasol (Packard). After at least 6 h of equilibration, the vials were counted by liquid scintillation spectroscopy using a Beckman LS 1800 (47% efficiency).

[^{3}H]NPA binding. This assay ([^{3}H]NPA, 55·8 Ci $mmol^{-1}$, NEN) was performed essentially as described above for the [^{3}H]spiperone binding. The buffer used was a 50 mM Tris-HCl buffer with 1 mM EDTA, 4 mM $MgCl_2$ and 0·01% ascorbic acid (pH 7·2). In the assay, each tube (1 mL final volume) included 100 μL of 5 nM radioligand, 50–100 μL of the competitor drug and 100 μL of membrane suspension (1·5–2 mg/tube), all dissolved in buffer. Non-specific binding was defined using 1 μM (+)-butaclamol and the incubation was performed at 25°C for 45 min, followed by vacuum filtration and scintillation counting as described above. Saturation experiments were performed using 0·1–3 nM [^{3}H]NPA. Nonspecific binding was defined as binding in the presence of 1 μM (+)-butaclamol. Eadie-Hofstee plots indicated a single binding site with a K_d of 0·71 ± 0·02 nM and a capacity of 18·3 ± 2·1 pmol (g tissue)$^{-1}$.

Analysis of binding data

In saturation experiments with calf striatum, the K_d and B_{max} values for [^{3}H]spiperone were found to be 0·16 nM and 21·5 pmol g^{-1}, respectively. For [^{3}H]NPA a K_d of 0·71 nM and a B_{max} of 18·3 pmol g^{-1} were found. In both cases, the Eadie-Hofstee plots were linear with a Hill coefficient around 1 revealing only one binding site under our conditions (alternatively, two sites or states for which the ligands have equipotent affinity might have been present). The displacements of [^{3}H]spiperone or [^{3}H]NPA were performed with the 2-aminotetralin concentration ranging from 10^{-9} to 10^{-4} M. Throughout the experiments, the concentration of the radiolabelled ligand was kept constant at 1 nM ([^{3}H]spiperone) or 0·5 nM ([^{3}H]NPA).

An analysis of binding data to deduce inhibition constants of compounds for one or two sites or states is quite common, if not routine. However, such an approach may be subject to unwanted or unrecognized circumstantial factors and it may be too simple to give reliable data that describe the molecular events (Abramson et al 1987; Strange 1987; Urwyler 1987). Thus, although we have analysed the displacement curves with a curve-fitting program and tabulated, when appropriate, the high and low affinity dissociation constants, we consider the binding data as an overall value of the affinity of the compounds to D_2 high and/or low (spiperone) and to D_2 high (NPA) receptors.

Results

Physicochemical properties

In order to assess the lipophilicity of the compounds we determined their partition coefficients in an n-octanol-buffer system (Table 1).

The present results correlate reasonably well with published hydrophobic fragmental constants (Hansch & Leo 1979). A methyl group has a π value of 0·7 and the difference in π between a hydroxy and a methoxy group is 0·6. By comparing two pairs of compounds, *8* vs *15* and *14* vs *15*, we found the corresponding changes in log P to be 0·52 and 0·66, respectively. Starting with the observed values for *1* (-0·14) and *11* (0·30) we calculated the respective log P values for the methoxy and the hydroxy compounds using the hydrophobic fragmental constants. The correlation between the calculated and observed values for the two sets of compounds (having OCH_3 and OH groups, respectively) is depicted in Fig. 2.

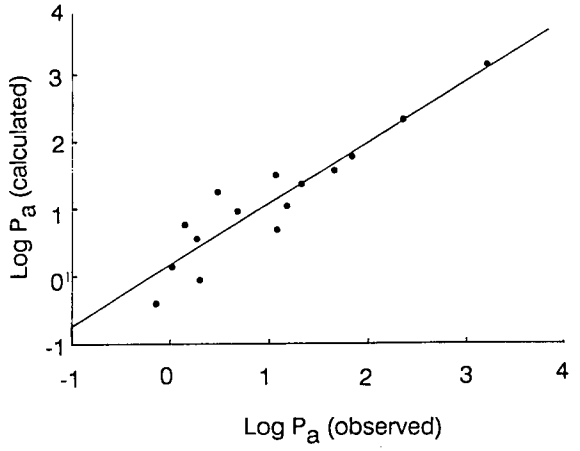

FIG. 2. Lipophilicity of compounds *1-15* expressed as their apparent partition coefficient P_a determined in octanol-buffer vs their calculated values.

Receptor binding

The affinities of the compounds were determined with [^{3}H]spiperone as a ligand for D_2-receptors and with ^{3}H-labelled *N*-propylnorapomorphine ([^{3}H]NPA), being an agonist with affinity for D_1- and D_2-receptor sites. The results are summarized in Table 1, which also presents ED50 values obtained in previous in-vivo studies.

Discussion

The compounds under study have previously been classified as pre- or postsynaptic agonists or antagonists based on in-vivo data (Johansson et al 1987). In the biochemical screening assay used for these compounds, a classical D_2-receptor agonist is expected to decrease striatal and limbic dopa levels in reserpinized as well as in normal animals, due

Table 1. 5-Oxygenated 2-aminotetralins: experimentally determined apparent partition coefficients (log P_a values) and abilities to displace [^{3}H]*N*-propylnorapomorphine ([^{3}H]NPA) or [^{3}H]spiperone from dopamine receptors in calf caudate in-vitro IC50 values; means ± s.e.m. n = 2–4; n_H values = Hill coefficients). The binding data were fitted to a one- and a two-site model and compared for statistical differences. Values for a two-site model are presented if an F-test showed a significant improvement of the fit over a one-site model. Previously reported (Johansson et al 1986, 1987) abilities to produce a half-maximal decrease or increase of the dopa levels in striata of reserpinized (R) or non-reserpinized (NR) rats in-vivo (ED50 values) are included for comparison.

		[^{3}H]NPA		[^{3}H]Spiperone		Dopa accumulation: ED50, μmol kg^{-1} s.c.	
	log P_a	pIC50	n_H	pIC50	n_H		
(1*S*, 2*R*)-*1*	−0·14	5·30 ± 0·08	1·31 ± 0·19	4·30 ± 0·11	0·99 ± 0·22	4·2	(NR)
(1*S*, 2*R*)-*2*	0·021	5·94 ± 0·09	1·14 ± 0·26	5·42 ± 0·05	0·79 ± 0·26	1·8	(NR)
				8·44 ± 0·72	12%		
				5·37 ± 0·04	88%		
(1*S*, 2*R*)-*3*	1·08	5·74 ± 0·10	0·93 ± 0·20	5·56 ± 0·11	0·59 ± 0·12	2·9	(NR)
				6·38 ± 0·45	37%		
				5·07 ± 0·35	63%		
(1*S*, 2*R*)-*4*	0·27	5·25 ± 0·11	0·73 ± 0·18	5·05 ± 0·05	0·89 ± 0·15	4·8	(NR)
(1*S*, 2*R*)-*5*	1·07	6·15 ± 0·04	0·91 ± 0·08	5·28 ± 0·06	0·88 ± 0·14	2·9	(NR)
(1*S*, 2*R*)-*6*	0·68	5·32 ± 0·09	0·79 ± 0·16	4·53 ± 0·21	0·88 ± 0·16	4·4	(NR)
(1*S*, 2*R*)-*7*	1·66	6·49 ± 0·04	0·81 ± 0·02	5·17 ± 0·19	0·75 ± 0·43	9·4	(NR)
				6·75 ± 0·08	73%		
				5·71 ± 0·24	27%		
(1*S*, 2*R*)-*8*	2·36	6·60 ± 0·07	1·07 ± 0·15	6·29 ± 0·13	0·77 ± 0·27	9·6	(NR)
(1*S*, 2*R*)-*9*	1·33	4·74 ± 0·10	1·88 ± 0·41	4·83 ± 0·11	0·94 ± 0·34	20·0	(NR)
(1*S*, 2*R*)-*10*	3·21	5·73 ± 0·05	0·92 ± 0·11	5·47 ± 0·15	0·74 ± 0·10	> 52	
(1*R*, 2*S*)-*11*	0·30	6·49 ± 0·13	0·82 ± 0·32	4·47 ± 0·07	1·04 ± 0·17	25·0	(R)
(1*R*, 2*S*)-*12*	0·15	6·17 ± 0·09	0·65 ± 0·19	4·96 ± 0·09	1·04 ± 0·29	1·6	(R)
(1*R*, 2*S*)-*13*	0·48	6·36 ± 0·12	0·75 ± 0·23	3·92 ± 0·13	0·43 ± 0·18	5·0	(R)
(1*R*, 2*S*)-*7*	1·66	7·43 ± 0·14	0·57 ± 0·05	5·38 ± 0·11	0·96 ± 0·27	0·34	(R)
		7·86 ± 0·11	73%				
		6·08 ± 0·27	27%				
(1*R*, 2*S*)-*8*	2·36	4·99 ± 0·14	0·68 ± 0·33	4·10 ± 0·10	2·13 ± 1·16	5·8	(R)
(2*S*)-*14*	1·18	8·90 ± 0·25	0·41 ± 0·07	6·42 ± 0·12	0·67 ± 0·17	0·0037	(R)
		10·87 ± 0·11	45%				
		8·09 ± 0·08	55%				
(2*R*)-*14*	1·18	6·37 ± 0·10	0·79 ± 0·22	< 4		*	
(2*S*)-*15*	1·84	6·60 ± 0·08	0·79 ± 0·16	5·28 ± 0·05	0·85 ± 0·10		

*The reported value (Wikström et al 1985) is not reliable due to contamination with the potent *S*-enantiomer. Compare Karlsson et al (1990).

to negative feedback mechanisms (Andén et al 1969). A dopamine receptor antagonist, on the other hand, should increase striatal and limbic dopa levels in non-reserpinized but not in reserpinized animals. In behavioural tests, classical dopamine receptor agonists induce hypermotility in reserpinized rats. In contrast, dopamine receptor antagonists or selective presynaptic dopamine receptor agonists are not expected to antagonize the reserpine-induced hypomotility. In non-reserpinized rats, classical dopamine receptor agonists induce hypomotility after low doses and hypermotility after high doses, by stimulation of first presynaptic and then postsynaptic receptors. Classical dopamine receptor antagonists produce hypomotility at high doses. However, (1*R*, 2*S*)-*11* and (1*R*, 2*S*)-*12* decreased dopa formation in reserpinized rats, without antagonizing the hypomotility induced by reserpine (Johansson et al 1987). In non-reserpinized rats, on the other hand, (1*R*, 2*S*)-*11* increased dopa formation, whereas (1*R*, 2*S*)-*12* was inactive. Both compounds induced hypomotility in non-reserpinized rats. These results showed that (1*R*, 2*S*)-*11* and (1*R*, 2*S*)-*12* behave as agonists or antagonists depending on the test system. Therefore they were classified as partial dopamine receptor agonists. It is, however, not obvious how to differentiate the compounds according to their pharmacological profiles based on the present in-vitro data. This might indicate that the structural requirements (and, therefore, the receptor topography) of the pre- and postsynaptic dopamine receptors are comparable (or even identical). Previously observed selectivity differences might have been caused by spare receptors and the density or occupation of these receptors, rather than by differences in receptor topography (Meller et al 1987; Cox & Waszcak 1989). The affinities of the compounds for D_2-receptors are fairly low as compared to that of the non-methyl substituted *S-14*. Most likely, this is due to the introduction of the pseudoaxial C^1-methyl group which may prevent a close interaction with the receptor due to its steric bulk (Johansson et al 1986). The most potent of the C^1-methylated tetralins are (1*R*, 2*S*)-*7* and (1*S*, 2*R*)-*8*. This indicates that a tertiary amine with at least one *N*-propyl substituent is optimal for D_2-receptor affinity and agrees with previous in-vivo data (Hacksell et al 1979).

A comparison of *N,N*-dipropyl derivatives [(1*R*, 2*S*)-*7* vs (1*S*, 2*R*)-*7* and (1*R*, 2*S*)-*8* vs (1*S*, 2*R*)-*8*] reveals that the absolute stereochemistry of the C^1-methylated derivatives is important for activity. It has been previously shown that *cis* C^1-methyl substituted 2-aminotetralins are more potent than the *trans* diastereoisomers (Hacksell et al 1984; Johansson et al 1987). Thus, both relative and absolute stereochemistries are important for D_2-receptor activity.

Based on results obtained in this and other studies the following trends are apparent: a hydroxy substituent appears to confer the greatest affinity in the 2*S*-series; in contrast methoxy substituted derivatives seem to bind more tightly in the 2*R*-series (Table 1). When the pharmacological profiles are taken into account it appears that the factors contributing the most to the pharmacological differentiation are the absolute configuration at C^2 and the presence of a hydroxy or a methoxy group. It appears that compounds with the 2*S* configuration and a hydroxyl substituent tend to have a higher efficacy (based on their influence on the dopa levels). They also have a significantly higher affinity to the NPA binding sites and, thus, to the high affinity sites. The 2*R* derivatives, on the other hand, are less efficacious (Johansson et al 1987) and their receptor interaction is strongly influenced by their lipophilicity (compare (1*S*, 2*R*)-*7* and (1*S*, 2*R*)-*8*; Table 1). The importance of the OH-group donating a hydrogen bond to the receptor, was stressed in a molecular modelling study in which a good correlation was found between the affinities and the position of the oxygen lone pair (Tonani et al 1987).

One of the phenols in the present series is an antagonist but this compound has the 1*S*,2*R* configuration. As suggested by Neumeyer et al (1988) and Froimowitz & Baldessarini (1987), the orientation of the ammonium hydrogen (or lone electron pair) determines the agonist or antagonist activities at the D_2-receptor. A similar conclusion was drawn by Liljefors & Wikström (1986) who proposed an agonistic position of the C-N bond and an antagonistic position, 'above' and 'below' the plane of the aromatic ring of tetralins and related derivatives. According to these models, the methoxy and hydroxy substituted (1*S*, 2*R*)-enantiomers would be antagonists due to the "antagonistic" orientation of the ammonium hydrogen. However, these models do not explain the very poor affinity of the methoxy substituted (1*R*, 2*S*)-*8* which easily adopts an optimal "agonistic" N-H orientation.

We wish to rationalize the above results for the methoxy-2*S* series by assuming that the hydrogen bond-accepting

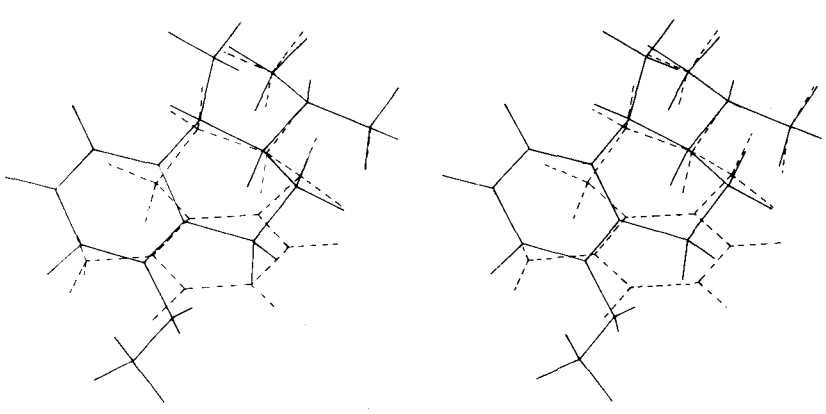

FIG. 3. Computer generated stereo pair of the best fit of the "agonist conformation" of (2*S*)-*14* (dashed lines) and the minimum energy conformation of (1*S*, 2*R*)-*8* (solid lines). Mean distance between fitted atoms (N, N-electron pair, Cα, and Cα′) is 0·003 Å. For clarity only the dimethylamino moieties are shown.

domain of the D_2-receptor can accomodate a hydroxy group but not a methoxy group. For the 2*R* series the (1*S*, 2*R*)-enantiomers are turned in such a way as to give the N-H moieties identical positions (Fig. 3). In such a model, the N-H pharmacophore of the 2*R*-enantiomers adopts an optimal position but the position of the methoxy/hydroxy groups will differ from that of the 2*S*-enantiomers. Nevertheless, the overall stereochemical and electronic properties of the (1*S*, 2*R*)-derivatives should enable binding to the D_2-receptor. Since the hydroxy group of the (1*S*, 2*R*)-enantiomers would be too far away to interact with the hydrogen-bonding site, they will behave as antagonists. Thus, in this model, both agonists and antagonists have the same orientation towards the cationic binding site of the receptor. According to the model, a 2-aminotetralin derivative needs a properly positioned hydroxy group to be an agonist. Thus, the present model stresses the crucial role of the phenolic group or the isosteric indole N-H functionality (Asselin et al 1986; Wikström et al 1989), in the process activating the D_2-receptor. The role of the charged nitrogen would primarily be to anchor the agonist/antagonist to the receptor by long range coulombic forces.

Interest in the present series of compounds will probably be heightened as a result of the recent report that (1*S*,2*R*)-*6* [(+)-AJ-76] and (1*S*,2*R*)-*8* [(+)-UH-232] have higher affinities for D_3- than for D_2-receptors (Sokoloff et al 1990).

Acknowledgement

Support for this study was provided by grants from the Swedish Natural Science Research Council and "Centrala Försöksdjursnämnden".

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