MOLECULAR PHARMACOLOGY, 26:452-457

Further Characterization of Structural Requirements for Agonists at the Striatal Dopamine D_2 Receptor and a Comparison with Those at the Striatal Dopamine D_1 Receptor

Studies with a Series of Monohydroxyaminotetralins on Acetylcholine Release from Rat Striatum

M. P. SEILER AND R. MARKSTEIN

Preclinical Research, Sandoz-Ltd., CH-4002 Basel, Switzerland

Received July 30, 1984; Accepted September 4, 1984

SUMMARY

A series of phenolic hydroxy-2-aminotetralins with either a primary or a tertiary (*N,N*-di-*n*-propylated) amino group was investigated on electrically evoked acetylcholine release from striatal slices of reserpinized rats, a dopamine (DA) D_2 receptor model. 7-Hydroxy-2-aminotetralin (7-OH-AT) was found to be the most active inhibitor among the primary amines, whereas 5-hydroxy-2-(*N,N*-dipropylamino)tetralin (5-OH-DPAT) was the most potent compound among the tertiary amines; in the 7-OH series, the activity resided in the (2*R*)-enantiomers, in contrast to the 5-OH series, where the (2*S*)-enantiomers represented the effective form. A similar structure-activity pattern was earlier found for the same series of DA agonists at the striatal DA D_1 receptor. Differences between the effects of the compounds at the two DA receptor subtypes concerned the *N,N*-dipropyl substitution which influenced the D_2 activity much more pronouncedly, and an added 6-OH group (*i.e.*, a catechol function), which seemed to be of foremost importance at the D_1 site. These results suggest two similar major binding sites for the DA receptor subtypes, but differences with respect to additional binding sites. According to this model, DA would interact with both DA receptor subtypes in the β-rotamer conformation; however, *N,N*-dipropylation similarly should cause a change in preferred conformation toward the α-rotamer form. The potency with respect to acetylcholine release correlated with [^{3}H] spiroperidol binding, but not with [^{3}H]DA binding, confirming that the former binding involves the active site of the D_2 receptor.

INTRODUCTION

Among the different subtypes of DA[1] receptors proposed on the basis of binding data, only D_1 and D_2 receptors have also been well characterized functionally and their existence seems now well established (1, 2). Though structure-activity relationships have been described for many DA agonists, and despite the existence of relatively selective agonists and antagonists for both receptor subtypes, attempts at a comparative characterization of their active sites in terms of structural requirements for agonists have been rendered difficult, since comparable data are not available for many agents (3).

Recently, we studied the effects of a series of monohydroxyaminotetralin DA analogues with either a primary or a tertiary (*N,N*-di-*n*-propylated) amino group on DA-sensitive adenylate cyclase from rat striatum representing an *in vitro* model for a central D_1 receptor (4). In the present investigation, we tested the identical series of aminotetralins on a D_2 receptor model in order to obtain information about structural similarities and differences between the active sites of the two DA receptor subtypes. Since the hydroxyaminotetralins represent frozen conformations of the DA molecule (Fig. 1), we could hope to clarify whether DA would interact with the D_2 receptor in the so-called α- or β-rotameric conformation (3).

[1] The abbreviations used are: DA, dopamine; ACh, acetylcholine; 5-OH-AT, 5-hydroxy-2-aminotetralin; 6-OH-AT, 6-hydroxy-2-aminotetralin; 7-OH-AT, 7-hydroxy-2-aminotetralin; 8-OH-AT, 8-hydroxy-2-aminotetralin; 5-OH-DPAT, 5-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin; 6-OH-DPAT, 6-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin; 7-OH-DPAT, 7-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin; 8-OH-DPAT, 8-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin; 5,6-$(OH)_2$-AT, 5,6-dihydroxy-2-aminotetralin; 6,7-$(OH)_2$-AT, 6,7-dihydroxy-2-aminotetralin; 5,7-$(OH)_2$-AT, 5,7-dihydroxy-2-aminotetralin; 5,6-$(OH)_2$-DPAT, 5,6-dihydroxy-2-(*N,N*-di-*n*-propylamino)tetralin; 6,7-$(OH)_2$-DPAT, 6,7-di-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin; 5,7-$(OH)_2$-DPAT, 5,7-di-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin.

0026-895X/84/060452-06$02.00/0

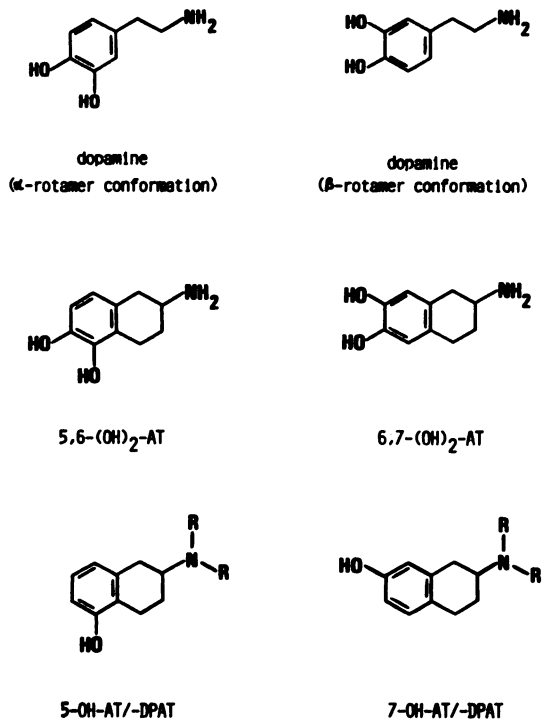


FIG. 1. *Chemical structures of the rotamers of dopamine, its aminotetralin correlates, and the aminotetralin analogues with a hydroxy group corresponding to the meta-hydroxy of dopamine (R═H, n-propyl)*

The DA D_2 receptor has functionally been classified as not enhancing adenylate cyclase activity upon receptor occupation (1, 2). Its activation has among others been linked to behavioral effects in the central nervous system (5), inhibition of prolactin release in the pituitary (6), emesis (7), and inhibition of noradrenaline release from peripheral noradrenergic nerve endings (8). In the striatum, ACh release has been shown to be regulated in an inhibitory manner by postsynaptic DA receptors of the D_2 type (9). Hence, in the present investigation, electrically evoked tritium outflow reflecting neuronal release of ACh from rat striatal slices preincubated with [^{3}H]choline was chosen as test system (10).

Radioligand-binding techniques are an excellent tool for a direct assessment of the events at the receptor level and hence a valuable complement to a functional test provided that a correspondence has been established. In our earlier studies, such a correlation could be shown between stimulation of DA-sensitive adenylate cyclase and [^{3}H]DA binding (calf caudate), implying that the latter involves binding to DA D_1 receptors (4). However, only a poor correlation between adenylate cyclase activity and [^{3}H]spiroperidol binding (calf caudate) was found. The question was therefore raised whether this was due to the antagonist character of the ligand or due to a binding to a different set of DA receptor subtypes. The results of the ACh release experiments will thus be compared with these earlier binding data in order to further clarify the role of these ligands with respect to the two DA receptor subtypes in the striatum and its corresponding functional models.

MATERIALS AND METHODS

Drugs. The aminotetralin derivatives were synthesized in our laboratories (4). Methyl[^{3}H]choline was purchased from the Radiochemical Centre, Amersham (U. K.).

Superfusion experiments. Male rats (Sandoz OFA strain, weighing approximately 150 g) were used. The animals were pretreated twice with reserpine (2.5 mg/kg subcutaneously) 18 and 12 hr before sacrifice and killed by decapitation, and the brains rapidly were removed and dissected over a chilled plate.

Tissue cylinders of rat striatum with a diameter of 3 mm were punched out from frontal sections approximately between the frontal planes A 9200-7200 (11) and cut into 0.3-mm thick slices (wet weight approximately 2 mg/slice), using a McIllwain tissue chopper. About 25 slices were incubated in 6 ml of Krebs medium containing 0.16 μM [^{3}H]choline at room temperature (~22°) for 30 min. Composition of Krebs medium was (millimolar): NaCl, 118; KCl, 5; $CaCl_2$, 1.2; $MgCl_2$, 2; $NaHCO_3$, 25; KH_2PO_4, 2; Na_2EDTA, 0.02; glucose, 11.1. It was saturated with oxycarbon (95% O_2/5% CO_2); the pH was 7.4. After incubation, the slices, two each, were transferred into superfusion chambers and superfused with Krebs medium at a rate of 1.2 ml/min at 30°.

Collections of 5-min fractions (6 ml) of the superfusate began after 60 min of superfusion. Two-minute periods of electric stimulation (frequency, 2 Hz; rectangular pulses of 2 msec with 12-mA current strength) were applied after 75 (S_1) and 150 (S_2) min of superfusion. Test substances were added 30 min before S_2 and were present in the medium between 120 and 170 min of superfusion. At the end of the experiment, the slices were solubilized in concentrated formic acid and total tritium was measured in superfusates and solubilized slices. Tritium outflow was expressed as the fractional rate per min (i.e., tritium outflow per 5 min/tritium content at the onset of the 5-min collection period).

Stimulation-evoked tritium overflow was calculated by subtracting the extrapolated basal outflow from the total outflow during the 2 min of stimulation and the following 13 min; the stimulation-evoked overflow was then expressed as percentage of the tritium content of the tissue at the onset of stimulation.

Drug effects on the stimulation-evoked overflow are expressed as the ratios of the overflows evoked by S_2 to that of S_1 (i.e., S_2/S_1) as percentage of controls. Each value is the mean of two (inactive compounds) and three (active compounds) independent experiments, respectively, performed in duplicate. Statistical significance of differences between means was calculated by the two-tailed Student's *t* test.

RESULTS

The effects of the aminotetralins on electrically evoked tritium overflow from rat striatal slices preincubated with [^{3}H]choline are shown in Fig. 2, indicating DA D_2 agonism (EC_{50} values and maximal drug effects for compounds with significant activities are given in Table 1).

In the series of racemic monohydroxyaminotetralins, variation of the position of the hydroxy group resulted in large differences in activities. Among the corresponding primary amines, only 7-OH-AT showed strong effects, 5-OH-AT and 6-OH-AT being only weakly active (maximal effects < 20%), while 8-OH-AT was found to be inactive. Introduction of *N,N*-di-*n*-propyl substituents markedly enhanced in this group of compounds potency and maximal inhibitory effects, except for 8-OH-DPAT which showed, like the corresponding primary amine, no activity. However, the increase in activity was much more pronounced in the case of the 5-hydroxy compound compared with that of the 7-hydroxy derivative, leaving 5-OH-DPAT slightly more potent than 7-OH-DPAT. Both compounds were considerably more potent than 6-OH-DPAT. All three compounds

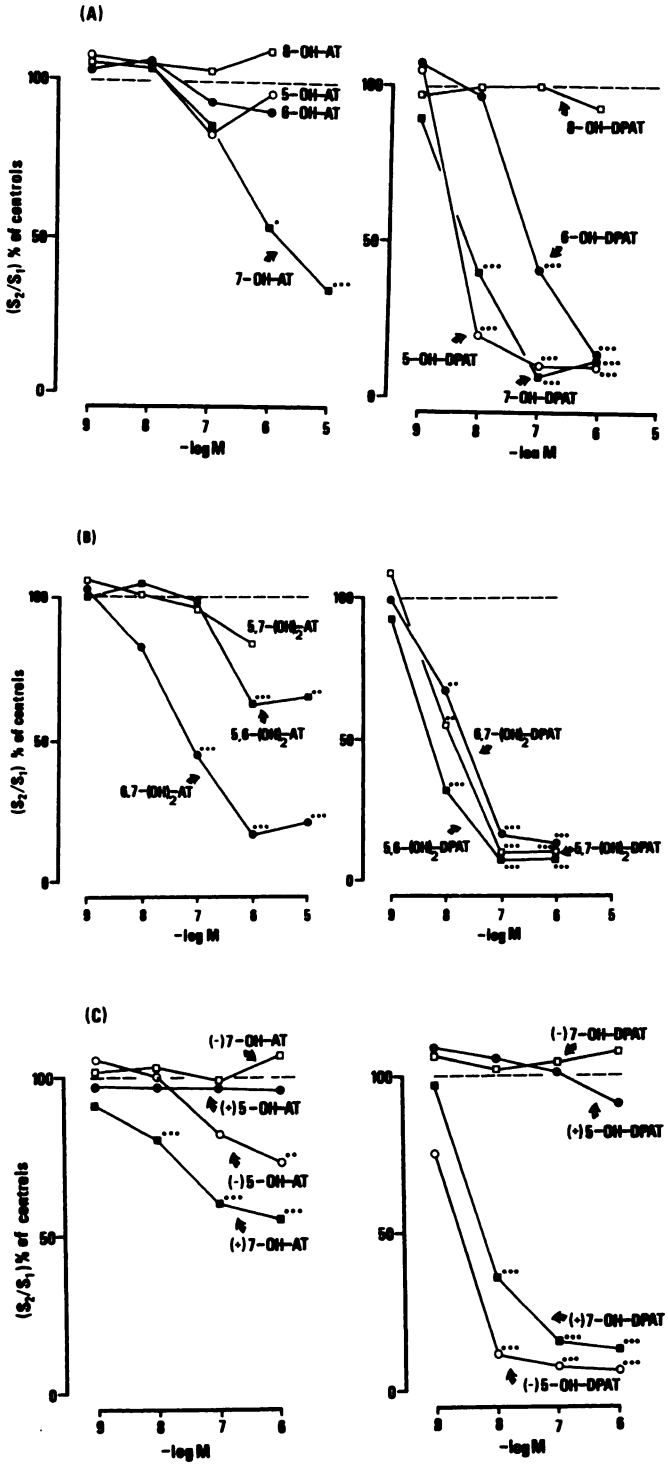


FIG. 2. *Effect of various concentrations of monohydroxyaminotetralins (A), dihydroxyaminotetralins (B), and enantiomers of 5- and 7-hydroxyaminotetralins (C) on electrically evoked tritium overflow from rat striatal slices preincubated with* [^{3}H]choline

Rats were pretreated with reserpine. After preincubation, slices were superfused and stimulated twice for 2 min each at 2 Hz (S_1, S_2). Compounds were added 30 min before S_2. Drug effects are expressed as percentage of control ratio. Control ratio was 0.78 ± 0.013 (n = 90). Significance of differences between means was calculated by the two-tailed Student's t test (*$2p < 0.05$; **$2p < 0.01$; ***$2p < 0.001$).

showed quite pronounced maximal effects in the 80–90% range.

Introduction of a second hydroxy group transforming the phenolic compounds into catechols affected primary and tertiary amines differently. In the series of primary amines, increases of both potency and maximal effects were observed, leaving 6,7-$(OH)_2$-AT, the β-rotamer DA analogue, as the most active compound, followed by 5,6-$(OH)_2$-AT. In the series of tertiary amines, however, the catecholic compounds showed similar effects concerning potency and maximal inhibition as the corresponding phenols; thus, the α-rotameric *N,N*-di-*n*-propyl-DA analogue 5,6-$(OH)_2$-DPAT and equiactive 5-OH-DPAT were slightly superior to 6,7.$(OH)_2$-DPAT and 7-OH-DPAT.

In the 5,7-dihydroxyaminotetralin series which contains the hydroxy groups in the optimal positions found in the monohydroxy series, 5,7-$(OH)_2$-AT and 5,7-$(OH)_2$-DPAT revealed a loss in activity compared with the corresponding optimal monohydroxy compounds 7-OH-AT and 5-OH-DPAT, which was more pronounced in the case of the primary amine, however. Accordingly, they were also weaker than the catecholic compounds of the 5,6- and 6,7-dihydroxyaminotetralin series.

The enantiomers of the most interesting monohydroxyaminotetralins with hydroxy groups in position 5 and 7 showed an excellent enantioselectivity. In the series of primary amines, the enantiomeric preference changed with the position of the hydroxy group: in 7-OH-AT, the activity resided in the (+)-enantiomer, whereas the (−)-form was found to be the active enantiomer of 5-OH-AT, leaving (+)-5-OH-AT and (−)-7-OH-AT inactive. *N,N*-Di-*n*-propyl substitution did not influence the enantiomeric preference. Accordingly, (−)-5-OH-DPAT and (+)-7-OH-DPAT were found as active enantiomers, (+)-5-OH-DPAT and (−)-7-OH-DPAT being inactive.

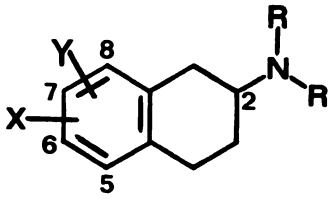
The potency of the DA agonists at the DA D_2 receptor modulating ACh release was compared with earlier reported data of the same series of compounds on inhibition of [^{3}H]DA and [^{3}H]spiroperidol binding from calf caudate nucleus (4). A correlation factor of $r = 0.86$ ($p < 0.01$) was found between inhibition of ACh release and [^{3}H]spiroperidol binding, whereas no significant relationship between inhibition of ACh release and [^{3}H]DA binding could be demonstrated (Fig. 3).

DISCUSSION

N,N-dialkylated monohydroxyaminotetralins have been reported to cause emesis and stereotyped behavior and to reduce striatal DA metabolism suggesting DA D_2 receptor activation (12, 13). It was therefore not surprising that 5-, 6-, and 7-hydroxyaminotetralins proved to be agonists at the striatal D_2 receptor modulating ACh release. In our previous investigation, these compounds were shown to stimulate the striatal DA D_1 receptor coupled with adenylate cyclase (4). They are therefore like the corresponding dihydroxy derivatives: nonselective with respect to the two established DA receptor subtypes. The inactivity of the two 8-hydroxyaminotetralins parallels the reported lack of effects of 8-OH-DPAT on striatal DA metabolism (13).

TABLE 1

Effects of aminotetralins on electrically evoked ACh release and on DA receptor binding



Compound	X,Y	R	ACh release[a]		Radioligand binding[b]	
			Potency EC_{50}	Maximal effect	[^{3}H]Dopamine IC_{50}	[^{3}H]Spiroperidol IC_{50}
			nM	%	*nM*	*nM*
Racemates						
5-OH-AT	5-OH	H			2,900	25,000
5-OH-DPAT	5-OH	*n*-Propyl	4	−90	33	1,100
6-OH-AT	6-OH	H			2,400	100,000
6-OH-DPAT	6-OH	*n*-Propyl	56	−88	1,200	5,900
7-OH-AT	7-OH	H	400	−66	210	8,400
7-OH-DPAT	7-OH	*n*-Propyl	5	−83	170	4,300
8-OH-AT	8-OH	H		0	26,000	100,000
8-OH-DPAT	8-OH	*n*-Propyl		0	10,000	17,000
5,6-$(OH)_2$-AT	5,6-$(OH)_2$	H	400	−38	230	21,000
5,6-$(OH)_2$-DPAT	5,6-$(OH)_2$	*n*-Propyl	5	−91	10	1,300
6,7-$(OH)_2$-AT	6,7-$(OH)_2$	H	40	−80	8.3	6,800
6,7-$(OH)_2$-DPAT	6,7-$(OH)_2$	*n*-Propyl	10	−89	23	4,400
5,7-$(OH)_2$-AT	5,7-$(OH)_2$	H			560	16,000
5,7-$(OH)_2$-DPAT	5,7-$(OH)_2$	*n*-Propyl	16	−86	420	2,800
Enantiomers						
(−)-(2*S*)-5-OH-AT	5-OH	H	63	−26	1,400	27,000
(+)-(2*R*)-5-OH-AT	5-OH	H		0	3,300	22,000
(−)-(2*S*)-5-OH-DPAT	5-OH	*n*-Propyl	2	−90	19	340
(+)-(2*R*)-5-OH-DPAT	5-OH	*n*-Propyl		0	1,200	3,600
(−)-(2*S*)-7-OH-AT	7-OH	H		0	13,000	100,000
(+)-(2*R*)-7-OH-AT	7-OH	H	400	−66	130	2,500
(−)-(2*S*)-7-OH-DPAT	7-OH	*n*-Propyl		0	52,000	28,000
(+)-(2*R*)-7-OH-DPAT	7-OH	*n*-Propyl	5	−86	180	2,000
Apomorphine			25	−68	11	500

[a] The maximal drug effect is expressed as the observed maximal change of S_2/S_1 ratio as a percentage of the control ratio. Control ratio was 0.78 ± 0.013 (n = 90). EC_{50} refers to the concentration required to give half-maximal effects. The EC_{50} values were estimatd graphically using four to five drug concentrations separated by 1 log unit (Fig. 2). Data are only given for compounds with significant effects.

[b] Data are taken from ref. 4.

It is interesting to find many similarities in the structure-activity relationship between the present results at the D_2 receptor and the earlier reported data at the D_1 receptor (4). 7-OH-AT is again the most active compound among the primary amines of the monohydroxy series. Upon *N,N*-di-*n*-propylation, again a switch in rank order has taken place between both *m*-hydroxy-DA analogues rendering 5-OH-DPAT superior to 7-OH-DPAT, a pattern which is also found in the catechol series with 6,7-$(OH)_2$-AT as the most active compound among the primary amines and 5,6-$(OH)_2$-DPAT as the most active compound among the corresponding tertiary amines. Similarly, a loss in activity of the 5,7-$(OH)_2$ derivatives with respect to the corresponding optimal 5-OH and 7-OH aminotetralins is observed. Finally, the enantiomers of the most interesting monohydroxy compounds showed identical enantioselectivities at both DA receptor subtypes with (*R*)-7-OH-AT, (*R*)-7-OH-DPAT, (*S*)-5-OH-AT, and (*S*)-5-OH-DPAT as the biologically active forms. To explain the change in absolute configuration between the β-rotameric 7-OH and the α-rotameric 5-OH stereoisomers, an analogous mode of interaction to the D_2 site is proposed, as already suggested for the D_1 (4) and a unspecified DA receptor site (14). One rotameric form is thereby oriented in a rotated fashion with *m*-hydroxy and amino group versus the proposed two major binding sites as depicted in Fig. 4. The much more pronounced increase in potency and maximal effect of the α-rotameric form upon *N,N*-di-*n*-propylation can again be explained by assuming that the *n*-propyl substituents of the α-rotameric 5-OH aminotetralins can more readily get access to an additional binding site than those of the β-rotameric 7-OH aminotetralins (4).

Beside all the similarities observed between the inter-

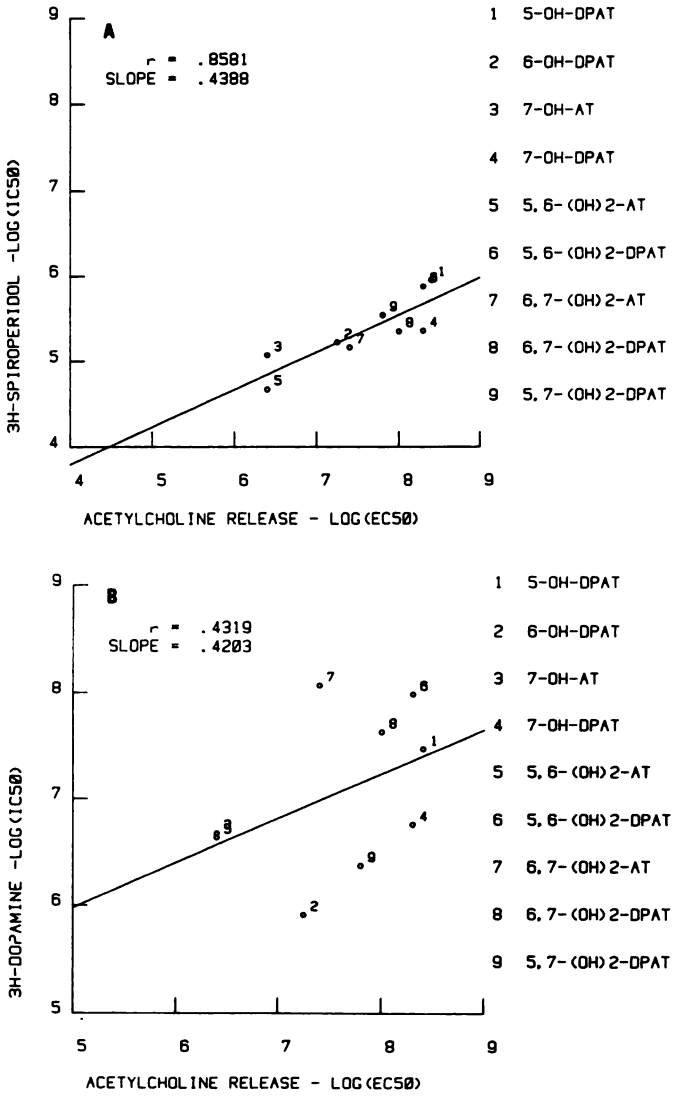


FIG. 3. *Relationship between EC_{50} values of racemic aminotetralins on acetylcholine release and their IC_{50} values at the [^{3}H]spiroperidol-binding site (A) and [^{3}H]DA-binding site (B)*

Data are taken from Table 1.

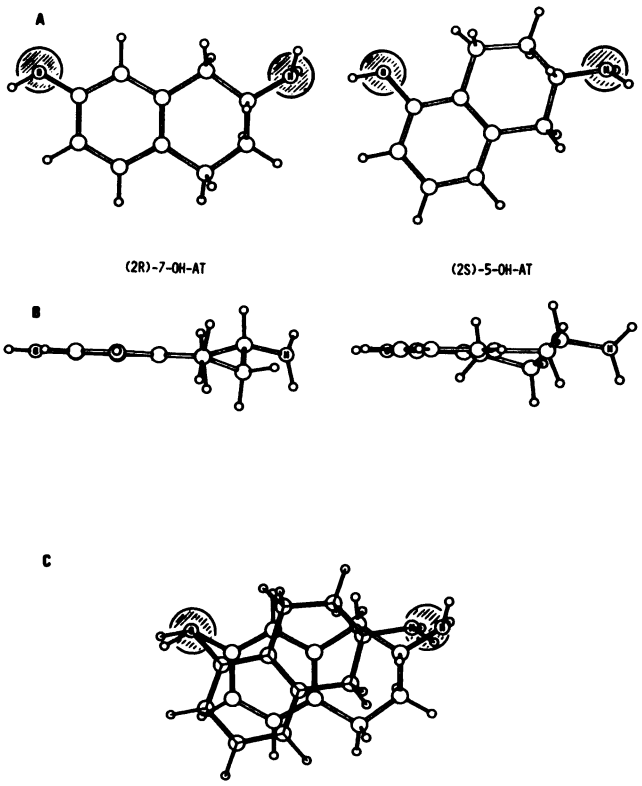


FIG. 4. *Orientation of (2R)-7-OH-AT and (2S)-5-OH-AT toward the proposed two major binding sites of the D_2 receptor*

Computer-generated perspective drawings of the aminotetralins are shown as displayed above the receptor represented by the two major binding sites: hatched circles (A), in a frontal view (B), and as superimposition above the receptor with common oxygen atom of the hydroxy groups (C). Computer-modeling was performed starting from the described X-ray coordinates of 5(OH)$_2$-DPAT (20) using the molecular mechanics program PIMM (21).

actions of the aminotetralins with the two DA receptor subtypes, some distinct differences should also be mentioned. At the D_2 receptor, *N,N*-di-*n*-propylation leads to a considerable increase in activity of all dopaminergic mono- and dihydroxyaminotetralins. At the D_1 site, on the other hand, transformation of 7-OH-AT into 7-OH-DPAT and of 6,7-(OH)$_2$-AT into 6,7-(OH)$_2$-DPAT causes a slight decrease in potency and maximal effect (4). It seems that at this DA receptor subtype, the additional binding site for the *N*-propyl substituents is not accessible for the β-rotameric DA analogues in contrast to the situation at the D_2 receptor. In general, this binding site appears to be of much greater importance for the D_2 than for the D_1 receptor interaction, since optimal activity at the D_2 site is only observed with *N,N*-di-*n*-propylated derivatives. Another dissimilarity in the structure-activity pattern at the two receptor subtypes concerns the relative importance of the additional binding site for the 6-hydroxy group corresponding to the *p*-hydroxy group of DA. Whereas it is of minor relevance at the D_2 receptor, as shown by practically equal activities of 5-OH-DPAT and 5,6-(OH)$_2$-DPAT, optimal agonist activity at the D_1 receptor is only granted by a catecholic partial structure (4).

From the structure-activity relationships discussed, the following conclusions seem to be justified. The DA D_2 and the Da D_1 receptor appear to possess similar major binding sites as demonstrated by the importance of the 5-OH and 7-OH group in the aminotetralins, the synergism lacking in the 5,7-(OH)$_2$ derivatives, and the observed enantioselectivities of the 5-OH and 7-OH stereoisomers. Binding to these sites involves the *m*-hydroxy and the amino group of DA. Differences between the two receptor subtypes seem to be related to additional binding sites. By the present investigation, this has been shown to be true for sites to which the *p*-hydroxy group and the *N*-*n*-propyl substituents of DA might attach. Though these additional binding sites are not sufficiently distinct in the two receptor subtypes to render the tested aminotetralins subtype-selective, this might be the case for another accessory site, to which the phenyl substituents of the D_1-selective benzazepine derivatives are supposed to bind (15, 16).

The high dopaminergic activity of apomorphine and

of the dihydroxyaminotetralin derivatives, containing the DA molecule in a fully extended *trans* conformation with the nitrogen atom close to the plane of the catechol ring (Fig. 4B), have reduced the question of the preferred conformation of DA at the receptor to the question of the preferred orientation of the catechol ring, α- or β-rotameric. It has been answered differently, favoring either the β-rotameric form, based on the strong activity of 6,7-$(OH)_2$-AT in *in vitro* tests (17), or the α-rotameric form, based on the high activity of 5,6-(OH)-DPAT in *in vitro* as well as in behavioral tests (18). The data of our investigations with the aminotetralins is based on *in vitro* models, thus eliminating possible influences of distribution and metabolism. It implies that DA itself cannot reach the accessory binding site for the *N*-alkyl substituents. Its preferred conformation at both DA receptor subtypes should therefore correspond to the β-rotameric form, as indicated by the superior activities of 7-OH-AT and 6,7-$(OH)_2$-AT on both receptor models. However, upon *N*,*N*-di-*n*-propylation, under the influence of the now accessible additional binding site for the *n*-propyl groups, it should adopt an α-rotameric conformation at both DA receptor subtypes, as demonstrated by the superb activities of 5-OH-DPAT and 5,6-$(OH)_2$-DPAT.

Butyrophenone-type neuroleptics, e.g., [^{3}H]spiroperidol, have been found to label preferentially DA D_2 receptors in the striatum (2). Recently, the potency of a series of DA agonists on electrically evoked [^{3}H]DA release from slices of cat caudate was shown to correlate with the inhibition of [^{3}H] spiroperidol binding from cat caudate, suggesting that the DA autoreceptor bears the characteristics of the D_2 receptor (19). The correlation found in our study between the potency of another series of DA agonists on electrically evoked ACh release from rat striatal slices and the inhibition of [^{3}H]spiroperidol binding from calf caudate parallels those results. It implys that the [^{3}H]spiroperidol binding involves in addition to the antagonist sites also the active site of the receptor. Together with the lack of correlation with the activity at the adenylate cyclase (4), it further supports the statement concerning the selectivity of this ligand for the striatal DA D_2 receptor (2). [^{3}H]DA binding, on the other hand, did correlate with the adenylate cyclase data (4), but not with the ACh release, pointing to the preference of this ligand to label DA D_1 receptors.

ACKNOWLEDGMENTS

The authors wish to thank Mr. A. Widmer and Dr. H. J. Tobler for the computer modeling and computer graphics, respectively.

REFERENCES

1. Kebabian, J. W., and D. B. Calne. Multiple receptors for dopamine. *Nature* **277**:93–96 (1979).
2. Creese, I., D. R. Sibley, M. W. Hamblin, and S. E. Leff. The classification of dopamine receptors: relationship to radioligand binding. *Annu. Rev. Neurosci.* **6**:43–71 (1983).
3. Cannon, J. G. Structure-activity relationships of dopamine agonists. *Annu. Rev. Pharmacol. Toxicol.* **23**:103–30 (1983).
4. Seiler, M. P., and R. Markstein. Further characterization of structural requirements for agonists at the striatal dopamine D_1 receptor: studies with a series of monohydroxyaminotetralins on dopamine-sensitive adenylate cyclase and a comparison with dopamine receptor binding. *Mol. Pharmacol.* **22**:281–289 (1982).
5. Seeman, P. Brain dopamine receptors. *Pharmacol. Rev.* **32**:229–313 (1980).
6. Caron, M. G., M. Beaulieu, V. Raymond, B. Gagne, J. Drouin, R. J. Lefkowitz, and F. Labrie. Dopaminergic receptors in the anterior pituitary gland. Correlation of [^{3}H]dihydroergocryptine binding with the dopaminergic control of prolactin release. *J. Biol. Chem.* **253**:2244–2253 (1978).
7. Cavero, I., R. Massingham, and F. Lefevre-Borg. Peripheral dopamine receptors, potential targets for a new class of antihypertensive agents. *Life Sci.* **31**:939–948 (1982).
8. Langer, S. Z. Presynaptic regulation of the release of catecholamines. *Pharmacol. Rev.* **32**:337–362 (1980).
9. Stoof, J. C., and J. W. Kebabian. Independent in vitro regulation by the D_2 dopamine receptor of dopamine-stimulated efflux of cyclic AMP and K^+-stimulated release of acetylcholine from rat neostriatum. *Brain Res.* **250**:263–270 (1982).
10. Stoof, J. C., R. E. Thieme, M. C. Vrijmoed-De Vries, and A. H. Mulder. In vitro acetylcholine release from rat caudate nucleus as a new model for testing drugs with dopamine receptor activity. *Naunyn-Schmiedebergs Arch. Pharmacol.* **309**:119–124 (1979).
11. Koenig, J. F. R., and R. A. Klippel (eds.). *The Rat Brain: a Stereotactic Atlas of the Forebrain and Lower Parts of the Brain Stem.* Williams and Wilkins, Baltimore (1970).
12. McDermed, J. D., G. M. McKenzie, and H. S. Freeman. Synthesis and dopaminergic activity of (±)-, (+)-, and (−)-2-dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene. *J. Med. Chem.* **19**:547–549 (1976).
13. Feenstra, M. G. P., H. Rollema, D. Dijkstra, C. J. Grol, A. S. Horn, and B. H. C. Westerink. Effect of non-catecholic 2-aminotetralin derivatives on dopamine metabolism in the rat striatum. *Naunyn-Schmiedebergs Arch. Pharmacol.* **313**: 213–219 (1980).
14. McDermed, J. D., H. S. Freeman, and R. M. Ferris. Enantioselectivity in the binding of (+)- and (−)-2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene and related agonists to dopamine receptors, in *Catecholamines: Basic and Clinical Frontiers* (E. Usdin, ed.). Pergamon Press, New York, 568–570 (1979).
15. Kaiser, C., P. A. Dandridge, E. Garvey, R. A. Hahn, H. M. Sarau, P. E. Setler, L. S. Bass, and J. Clardy. Absolute stereochemistry and dopaminergic activity of enantiomers of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine. *J. Med. Chem.* **25**:697–703 (1982).
16. Dandridge, P. A., C. Kaiser, M. Brenner, D. Gaitanopoulos, L. D. Davis, R. L. Webb, J. J. Foley, and H. M. Sarau. Synthesis, resolution, absolute stereochemistry, and enantioselectivity of 3′,4′-dihydroxynomifensine. *J. Med. Chem.* **27**:28–35 (1984).
17. Horn, A. S., and J. R. Rodgers. 2-Amino-6,7-dihydroxytetrahydronaphthalene and the receptor-site preferred conformation of dopamine—a commentary. *J. Pharm. Pharmacol.* **32**:521–523 (1980).
18. Costall, B., S. K. Lim, R. J. Naylor, and J. G. Cannon. On the preferred rotameric conformation for dopamine agonist action: an illusory quest? *J. Pharm. Pharmacol.* **34**:246–254 (1982).
19. Lehmann, J., M. Briley, and S. Z. Langer. Characterization of dopamine autoreceptors and [^{3}H]spiperone binding sites in vitro with classical and novel dopamine receptor agonists. *Eur. J. Pharmacol.* **88**:11–26 (1983).
20. Giesecke, J. The crystal structure of (+)-2-dipropylamino-5-hydroxytetralin hydrochloride. *Acta Crystallogr. B* **36**:110–114 (1980).
21. Lindner, H. J. Die Berechnung von Molekülgeometrien gespannter konjugierter Kohlenwasserstoffe. *Tetrahedron* **30**:1127–32 (1974).

Send reprint requests to: Dr. M. P. Seiler, Preclinical Research, Sandoz Ltd., Lichtstrasse, CH-4002 Basel, Switzerland.