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Considerations on the recognition of the D1 receptor by agonists

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SUMMARY

A model of the mechanism for recognition of the D1 receptor has been developed. Conformational analysis for 10 agonists from diverse chemical families was carried out as a first step toward the characterization of the bioactive form. First, maximum structural overlap of the features common to all ligands allowed a simple identification of the candidate bioactive form for each ligand. At a second level of characterization, steric and electronic properties were computed for all accessible structures to analyze those properties that may modulate receptor recognition.

INTRODUCTION

Dopamine receptors have been primary targets for drugs used in the treatment of psychomotor disorders, such as Parkinson's disease [1], schizophrenia [2] and in the pharmacotherapeutic treatment of the abstinence syndrome elicited by some drugs of abuse [3]. Unfortunately, all these drugs have very serious side effects which may eventually be reduced if they were to act on more specific populations of dopamine receptor.

Two distinct dopamine receptors have been characterized pharmacologically in the central nervous system [4]. The major biochemical difference between these two receptors, D1 and D2, is in their ability to stimulate the enzyme adenylate cyclase [5]. Activation of the D1 receptor produces an increase in the production of cyclic adenosine monophosphate (cAMP), while the activation of the D2 receptor leads to the inhibition of the catalytic properties of adenylate cyclase [6].

It is only recently that a family of highly selective D1 agonists and antagonists [7] was characterized. The discovery of the benzazepines (BZP) and other D1-selective families [8–10] has provided the tools required for an in-depth study of the specific behavioral responses elicited by activation of each receptor type. Equally important, D1-selective ligands allow the development

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of pharmacophores unique to this receptor and the understanding of processes that govern D1-receptor recognition and activation that could lead to the rational design of other selective families.

For several years, simple inspection of the ligands that interact with the dopamine receptor led to the belief that D1-receptor ligands must contain a phenolic ring system and an amino group, with an optimal spacing between the two elements equivalent to two methylene groups [11]. In particular, the catechol group was believed to be essential for activation of the D1 receptor. The requirement that a catechol ring be present for activation, however, has been disproved by the identification of a family of D1-selective agonists that lacks both a catechol and a phenol group [12].

Several models for D1-receptor recognition, including three-dimensional criteria have been proposed each using only one or two families of compounds. Examples of this approach are models developed for the BZPs [13] and tetrahydroisoquinolines [14]. In each case, extensive conformational analysis of the compounds being considered was carried out using molecular-mechanics methods. Then, based on comparisons of the conformations accessible for each ligand with their receptor affinities, a candidate bioactive conformer was suggested for each compound. For the BZPs, the bioactive conformer deduced was a chair with the phenyl ring in equatorial position. In the isoquinolines family, the biostructure proposed, based on the comparison with a BZP compound in the conformation previously mentioned, was a half-chair (twist) with the phenyl ring in pseudoequatorial orientation.

Models based on quantum-mechanical descriptions have only been used to find discriminants of D1 versus D2 selectivity [15]. The position of the minimum of the molecular electrostatic potential appeared to discriminate among compounds with different selectivity. For the nonselective ligands, two minima were found in the molecular electrostatic potential surface, in close proximity to the minima found for each selective analog.

The structural similarity of the D1 agonists and antagonists can lead one to think that both interact with the same residues in the active site of the receptor. However, mutation experiments in another G-coupled receptor, the β-adrenergic receptor, have provided evidence that suggests that the agonists and antagonists do not interact with the same residues [16]. Similar hypotheses have been proposed for the binding mode of other G-coupled receptors, such as the histamine H-2 and serotonine 5-HT-2 receptors [17]. Even though in the case of the dopamine D1 receptor there are no data to confirm this theory, some recent experiments show that a point mutation in this receptor, Ala^{198}, eliminates all the affinity for the antagonist SCH-23388. However, the mutated receptor can still be activated by agonists like dopamine or SKF-38393 [18].

In the present paper, we use quantum-mechanical methods to define an initial model for recognition of the D1 agonists. First, maximum structural overlap of 10 D1 agonists was determined. The superpositions allow the definition of a candidate bioactive structure for each ligand. For the first time, a non-catechol-containing analog in the study of the D1 receptor is included, which provides valuable information regarding the function of that group present in all other analogs. The structural overlaps are validated by evaluation of steric and electronic properties for all conformers.

METHODS

The compounds selected for this study are shown in Fig. 1. Table 1 shows their inhibition

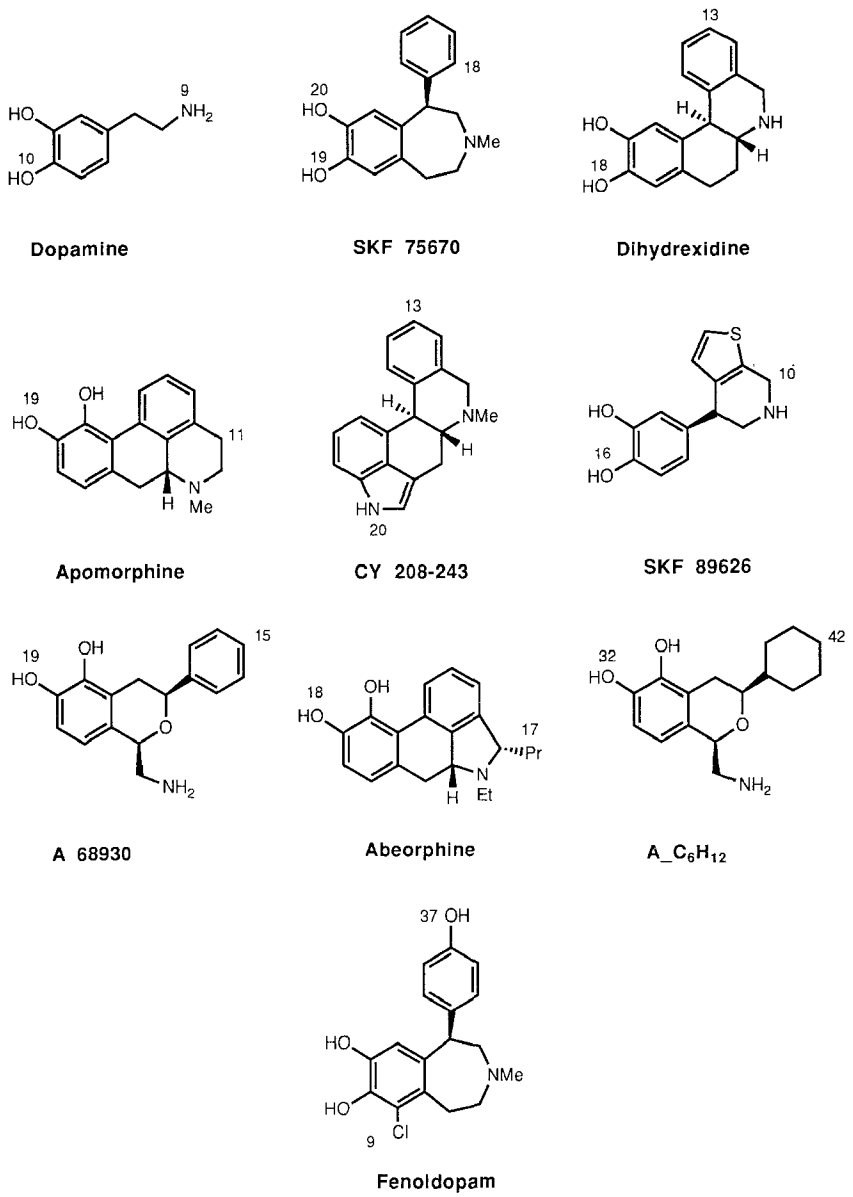

Fig. 1. Chemical structures of the compounds used in the development of the model for recognition.

constants, K_i, at the D1 and D2 receptors obtained from literature data. All the K_i values were from experiments using [^{3}H] SCH 23390 and rat striatum membranes, with consistent protocols.

Initial geometries for all the compounds were generated using the standard distances and angles in the QUANTA program [22]. These geometries were then optimized using the CHARMm force field [23] with atomic charges computed using the Gasteiger method [24]. These structures served as starting points in an extensive conformational analysis of each compound used to define the model for recognition.

TABLE 1
DOPAMINE RECEPTOR AFFINITIES K_i (nM) OF THE COMPOUNDS STUDIED

	D1	D2	D1/D2
Dopamine	380	660	0.58[a]
Apomorphine	87	92	0.89[a]
SKF 89626	80	>10000	<0.008[a]
CY 208-243	55	92	0.60[a]
Dihydrexidine	10[b]	122[b]	0.1[c]
SKF 75670	1.9	1130	0.0017[a]
A 68930	1.6	807	0.002[d]
Abeorphine	7	5.2	1.35[a]
A_C6H12	5.4	1120	0.005[d]
Fenoldopam	3.1	170	0.018[a]

[a] From Ref. 19.
[b] IC_{50} (nM) values.
[c] From Ref. 20.
[d] From Ref. 21.

The conformational space was scanned using a combination of high-temperature molecular-dynamics simulations and energy minimization with the CHARMm force field. Molecular dynamics is a method used to overcome energy barriers, systematically sampling the conformational space [25].

The molecules were thermalized to 1500 K increasing the temperature 2 K every 0.01 ps. The heating stage was followed by 10 ps equilibration, which was sufficient to uniformly distribute the kinetic energy and stabilize the structures after thermalization. Finally, 75 ps simulation were done, during which 300 structures were stored at equal intervals. All structures were optimized using CHARMm during 50 cycles of steepest descents followed by Adopted Basis Newton-Raphson minimization until the gradient was below 0.001 kcal/Å. The minima obtained were compared to eliminate those previously encountered. Unique structures were subjected to further minimization with the AM1 semiempirical Hamiltonian [26], included in the MOPAC 6.0 package [27], using the PRECISE keyword. No significant differences were found for the structural parameters after reoptimization with AM1. Detailed structural parameters for all compounds are available from the authors upon request.

For A_C6H12 no systematic reoptimization of the conformations has been done using AM1, due to the large number of unique conformations obtained in the molecular-dynamics step. The conformation used for the superposition has been built substituting the aromatic ring of A68930 by a cyclohexyl group and reoptimizing only this structure with AM1.

The AM1-optimized structures were used to evaluate steric and electronic properties for all conformers of all compounds. Steric characterization of all conformers of these compounds was done by computing the STERIMOL parameters [28] using the radii reported by Gavezotti [29]. We will mainly focus on the parameter L that depicts the maximum separation between any two points on the van der Waals molecular surface.

The fulfilment of certain steric criteria is necessary but not sufficient for an effective interaction between the ligand and the receptor. Complementarity in the electronic properties of the receptor to those of the ligand is also required. We used the AM1 semiempirical method to compute several electronic properties including atomic charges, dipole moments, frontier orbitals and superdelocalizabilities for each ligand.

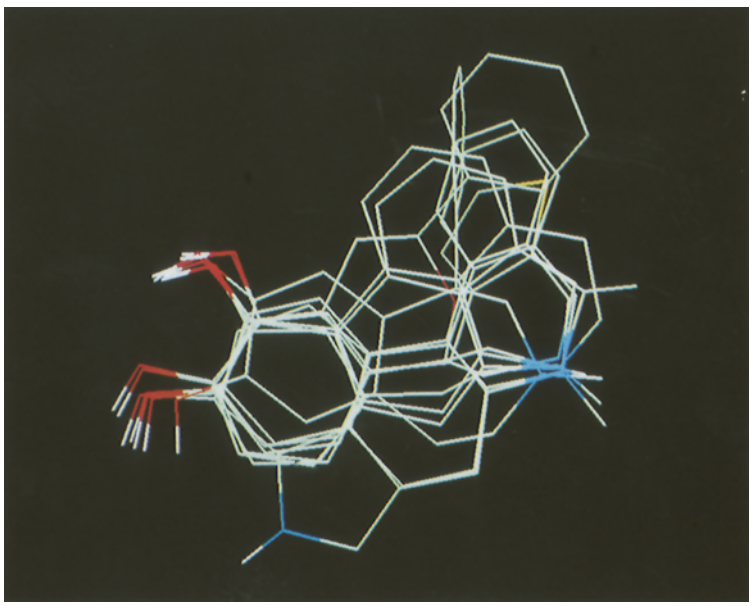

Fig. 2. Structural overlap of the D1 agonists. The figure includes SKF 75607, dihydrexidine, apomorphine, CY 208-243, SKF 89626, A 68930, abeorphine and dopamine.

RESULTS AND DISCUSSION

Since the development of the pharmacophore is based on the structures found in the conformational search, this step must be carried out using a technique that assures finding as many minima as possible in an objective and efficient manner. For this reason, we have used molecular dynamics at high temperature followed by minimization which provides a rapid way to scan the conformational space of those compounds that are considerably conformationally restrained. As a validation of the strategy, the conformers characterized for SKF 75670 have been compared with a conformational study published earlier [30]. In the past, 12 conformers have been described for the bicyclic portion of the molecule [31]. The procedure adopted for this study found the same 12 conformers and six additional ones corresponding to axial and equatorial pairs of twist and boat conformers. The comparison of results from two different methods gave us confidence in the effectiveness of the methodology employed in exploring the conformational space.

In Table 2 the number of minima characterized for the basic molecular skeleton of the molecules are reported, without including the possible conformational differences in the hydroxyl groups.

Once the conformational search was completed the model for recognition was developed at two levels. First, we proceeded to characterize the bioactive form by maximum overlap of the molecules. Later on, steric and electronic properties of the compounds have been studied to define common characteristics that can modulate their affinity for the receptor.

The common substructural elements present in all ligands should play a similar role in receptor recognition. Three key structural elements are present in all of these D1 ligands and were used to overlap the molecules: (1) the amine nitrogen atom; (2) the catechol-containing ring or the

aromatic ring attached to the pyrrole moiety in the case of CY 208-243; and (3) the unsubstituted aromatic ring.

The presence of these substructural elements in all the agonists suggests that they should play a similar role in receptor recognition. Thus, the conformer that maximized similarities in the spatial position of the three key structural elements and occupied a similar space region should be the bioactive structure for all high-affinity analogs. For the substituted aromatic ring, the presence of the substituents was considered when the overlaps were carried out, and their orientation was preserved. For the amine nitrogen, the overlap of the atom was not sufficient to define its position in the binding site, since its lone pair of electrons is likely to be involved in a more stringent directional interaction with residues at the receptor cavity. Therefore, the overlaps were carried out with the lone pair of electrons of the amine nitrogen pointing in the same direction for all analogs and a similar orientation between the substituted and unsubstituted aromatic rings in all ligands. The structural overlaps were done automatically using the algorithms in the QUANTA package, minimizing the RMS deviation for the position of the amine nitrogens and the atoms on both the substituted and nonsubstituted aromatic rings. Maximum structural overlap quantified by the RMS deviations, together with the visual inspection of the similarity of the volume occupied by the molecules, allowed the selection of the bioactive form.

Figures 2 and 3 show two views of the final overlaps obtained, using the bioactive forms. The energy difference between the lowest-energy structure characterized and the candidate bioactive form for each compound using AM1 are given in Table 3. The bioactive structure selected for each compound is in most cases not the lowest-energy one but is energetically accessible from it.

Some of the general features of the superposition are the planar disposition of the compounds (Fig. 3), the axial direction of the lone pair of the nitrogen, and the lack of a well-defined position for the additional aromatic ring.

The planar disposition of the molecules is violated only by the additional aromatic ring of the BZPs (SFK 75670 and fenoldopam) which is almost orthogonal to the rest of the structure. However, the energy required to bring the rotatable ring of these compounds to an orientation similar to that of other analogs is only 2 kcal/mol.

The most significant overlap for these compounds was obtained when the lone pair of the nitrogen atom was in an axial disposition, which agrees with previous models in this respect [31]. In all the conformations selected, the angle between the center of the substituted aromatic ring, the nitrogen atom and the direction of the lone pair is approximately constant for the diverse chemical families considered, ranging from 90° to 110°. It can be considered as an element necessary for recognition.

TABLE 2
TOTAL NUMBER OF MINIMA FOUND FOR EACH COMPOUND WITHOUT CONSIDERING THE DIFFERENT CONFORMATIONAL POSSIBILITIES FOR THE PHENOL HYDROXYL GROUPS

Compound	Total number of minima	Compound	Total number of minima
Dopamine	5	SKF 89626	8
SKD 75670	18	A 68930	13
Dihydrexidine	6	Abeorphine	2
Apomorphine	5	Fenoldopam	18
CY 208-243	7		

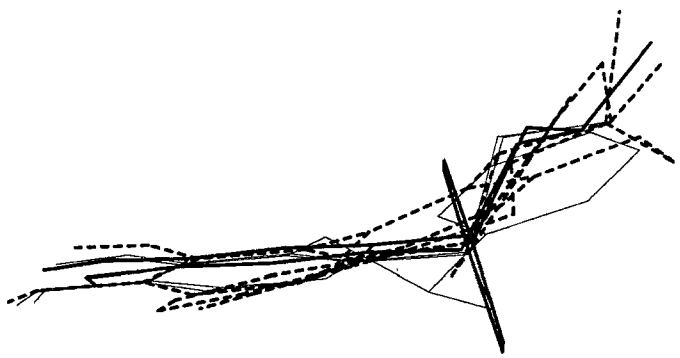

Fig. 3. Lateral view of the overlap.

The inclusion of A_C6H12 indicates that the role of the unsubstituted aromatic moiety in the rest of the compounds is likely to be part of a lipophilic pocket in the binding site. This theory contradicts previous work that explained the lack of activity of the cyclohexyl derivative of SKF 75670 based on the electrostatic influence of the aromatic ring in the neighborhood of one of the hydroxyl groups [32]. However, a steric problem could be a better explanation. Indeed, when the cyclohexyl derivative of SKF 75670 was included in the overlap, part of the aliphatic moiety occupied a significantly different region than the aliphatic ring in A_C6H12 or the equivalent aromatic ring of the other compounds, which can be seen in Fig. 4.

Other characteristics shown in the superposition are the significant overlap of the hydroxyl groups in the phenol-containing compounds and the possible hydrogen-bond interaction with the receptor, approximately at 2 Å of the hydrogens of one of the hydroxyl groups and corresponding to the NH of CY 208-243.

TABLE 3
RELATIVE AM1 ENERGIES OF THE CANDIDATE BIOACTIVE FORM AND ITS MAXIMUM MOLECULAR SPAN, L[a]

Compound	ΔE (kcal/mol)	L (Å)	
Dopamine	2.28	11.0	(9,10)
SKF 75670	2.33	12.4	(18,19)
Dihydrexidine	3.80	12.7	(13,18)
Apomorphine	1.00	12.5	(11,19)
CY 208-243	2.98	13.0	(13,20)
SKF 89626	2.75	12.2	(10,16)
A 68930	2.11	14.2	(15,19)
Abeorphine	0.00	13.2	(17,18)
fenoldopam	2.34	13.7	(9,37)
A_C6H12	[b]	14.3	(32,42)

[a] In parentheses the atoms at the extremes of each parameter. The numeration corresponds to that in Fig. 1. In all cases the atom is the hydrogen attached to the heavy atom whose number is given.

[b] See Methods section in the text.

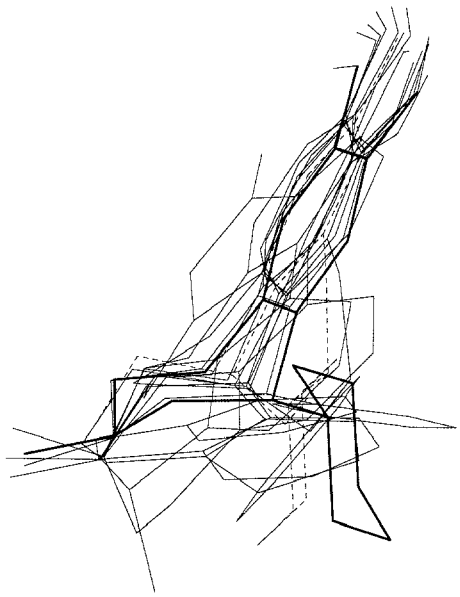

Fig. 4. Superposition of the cyclohexyl derivative of SKF 75670 (bold) with the rest of the molecules (A_C6H12 is shown in dashed line).

Even though the hydroxyl groups in the compounds studied display good overlap, it is not clear whether either of these groups is necessary for recognition. Replacing the hydroxyl groups equivalent to OH19 of SKF 75670 (see Fig. 1) by another substituent of totally different nature, such as a halogen, does not result in any significant decrease in affinity, as is the case for the antagonists SCH 23390 [33]. The second OH group equivalent to OH20 in SKF 75670, that has been previously reported to function as a proton acceptor, also appears not to be essential for recognition since the high-affinity CY 208-243 does not have a hydrogen acceptor group in a similar spatial orientation.

The inclusion of CY 208-243 in this study demonstrates that the catechol moiety is not necessary for the receptor activation as previously proposed [34]. However, the presence of a polar hydrogen is needed. Our model suggests that this proton donor could interact with a receptor group placed approximately at 2 Å from the polar hydrogen and approximately at the intersection of the direction of the OH bonds, like OH19 of SKF 75670, and the NH bond of CY 208-243. This finding is in agreement with experimental results that show that the replacement of OH19 of SKF 75670 with another group eliminates its agonist activity even when the oxygen is preserved, as is the case with the methoxy derivative [33], which proves that this group is actually interacting with the receptor.

In order to obtain more quantitative information about the steric characteristics of the binding site, the STERIMOL parameter has been calculated for all of the ligands. An analysis of these parameters shows that L, the maximum molecular span (Table 3), offers some interesting insights. For all high-affinity compounds the L direction is at least one-and-a-half times longer than any of the orthogonal directions and has as its extremes the substituted and unsubstituted aromatic rings. These two findings stress the importance of this parameter in the recognition process.

Since L defines the maximum extension of these analogs and is significantly longer than any other direction in the molecules studied, all ligands must be accommodated along this direction, which makes the most stringent demands on the binding-site cavity.

Moreover, the chemical equivalence across diverse chemical families for the extremes of L in high-affinity analogs allows an interaction with similar complementary groups in the receptor. For the compounds studied, one of the extremes of L is located on one of the hydroxyl groups, equivalent to OH19 of SKF 75670 and, in the case of CY 208-243 on the NH of the pyrrole ring, supporting the idea that both groups have the same function.

Hence, the development of pharmacophores consistent with the experimental evidence should have the direction of the maximum molecular span aligned for different ligands. Interestingly, the substituted and unsubstituted aromatic rings, that are the extremes of L, were two of the three elements considered in the maximum structural overlap studies. Therefore, it is not surprising that the same overlaps as those shown in Fig. 2 have also been found aligning the L segment for the diverse ligands and the amine nitrogen lone pair as requirements for recognition.

Among all the electronic properties computed, the direction of the dipole moment appears to be another modulator of recognition. Figure 5 shows the angle of the dipole vectors for the agonists. All the compounds have their dipole vectors pointing within a very close range despite their structural diversity, which suggests that the dipole moment may be a significant modulator of recognition. If the dipole moment is considered a modulator of activation, this can be due to the presence of an internal field at the binding site, caused by highly polar and charged groups.

The other electronic properties computed, such as frontier orbitals and charges or superdelocalizabilities were not indicative of additional modulators.

Finally, Fig. 6 schematically represents the pharmacophore proposed in this study. The separation between the amine nitrogen and the substituted aromatic rings is 4.7 ± 0.4 Å for all ligands in their bioactive form. The amine nitrogen lies only approximately 1.2 Å below the plane of the substituted phenyl ring making them almost coplanar and defining a flat region between them. The planarity of this region contrasts with the more accommodating lipophilic zone, which shows larger dispersions in its separation to the other two points on the pharmacophore. For instance, the lipophilic center is separated by 4.2 ± 0.8 Å and 4.6 ± 0.8 Å from the amine nitrogen and the other aromatic ring, respectively. The larger tolerance for the separations involving the lipophilic center can be due to the fact that it is involved in hydrophobic interactions and therefore that its precise location is not critical for the recognition process.

CONCLUSIONS

Recent investigations in several disciplines have suggested that the D1/D2 classification scheme may no longer be adequate. In particular, a D1-like receptor might exist that does not affect adenylate cyclase but phosphoinositide turnover [6]. Moreover, in addition to the D1 [35] and D2 [36] receptor several other dopamine receptors, D3 [37], D4 [38] and D5 [39], have been cloned and sequenced.

Attempts to use protein sequences obtained from molecular biology to derive models for the receptor are emerging [40–43], based on modeling by homology to bacteriorhodopsin, the only protein with seven transmembrane helical regions whose structure has been reported to date. However, the models can at this point be regarded as heuristic at best, since the homology

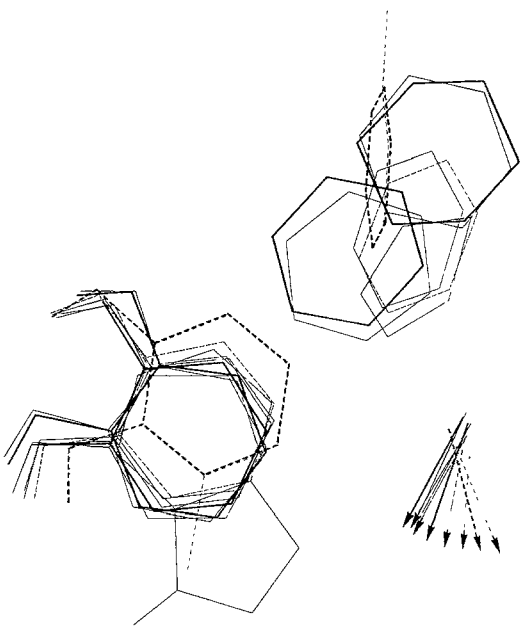

Fig. 5. Overlap of the phenol-containing ring, the second aromatic moiety and the orientation of the dipole moment for all the compounds studied. The origin of the dipole moment is at the location of the amine nitrogen atom. Parts of the structures have been omitted for clarity.

between bacteriorhodopsin and the other cloned receptors is extremely small. This disparity leads to disagreement even about fundamental questions such as the way in which the helices are packed. These models will certainly be refined and become more elaborate as results from point mutations and chimers for these receptors become available.

Molecular determinants of receptor recognition, such as the one proposed here, provide an additional means of validation of the explicit models of the binding sites reported for the receptors. For instance, the binding site proposed in any model should span approximately 12 to 14 Å with a hydrophobic pocket at one end. Moreover, it is very likely that the binding-site cavity has a large internal field, since all ligands have their dipole moments constrained to a certain orientation, possibly because of the presence of charged residues in the cavity.

In the past the efforts aimed at the characterization of D1-receptor recognition have been based on findings for a single or very few chemical families. This study is more comprehensive since it involves many different chemical classes. Moreover, the study resulted in a pharmacophore that is independent of the actual chemical structure, and it is expressed in terms of molecular properties. The studies carried out permit the gaining of some insights into the process of receptor recognition of D1 receptors by agonists. The structural overlaps allowed the identification of bioactive forms for several different chemical classes of ligands. The receptor cavity has three well-defined areas. One of these areas accommodates an amine nitrogen which is present in all ligands, probably involved in a polar interaction with the receptor. The second area is a lipophilic pocket and the third region is formed by a substituted aromatic ring. We have calculated the average distances between these three regions. Additionally, the presence of a polar hydrogen has been characterized as being important for activation of the receptor.

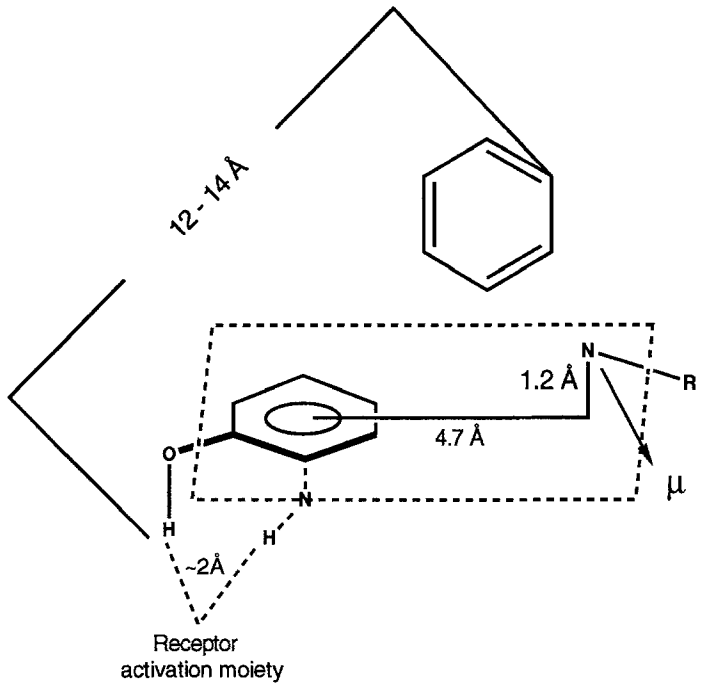

Fig. 6. Schematic representation of the pharmacophore.

The pharmacophore developed, based on the structural overlaps, suggests that the binding-site cavity is extremely planar. We have demonstrated that this planarity can be found even when several families are considered simultaneously. We found that the orientation of the dipole moment may be a modulator of receptor recognition; however, this point requires further analysis. No other electronic properties were found to correlate with the affinity.

The L STERIMOL parameter, which accounts for the maximum separation between any two points on the molecular surface, is a very important quantity. The extremes of L for all D1 ligands are consistently located on the highly lipophilic region and the substituted aromatic ring. For the compounds studied, the extreme of L corresponds to the proton-donating group responsible for the activity of the agonists.

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