Molecular Electrostatic Potential of D1 and D2 Dopamine Agonists

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The molecular electrostatic potential (MEP) of four selective D1, four nonselective D1/D2, and three selective D2 agonists has been calculated in a three-dimensional grid surrounding the molecules. The local density functional program DMol was used to evaluate the MEP. A comparison of the MEPs of all compounds revealed that while the electrostatic effects may be important for the affinity in both D1- and D2-selective ligands, it only appears to be a subtle modulator of the selectivity. Slight differences were found in the negative regions in the vicinity of the catechol ring that can account for the D1 versus D2 selectivity in the compounds studied.

Introduction

For over a decade, the dopaminergic receptors have been divided in two classes D1 and D2, on the basis of their pharmacological profiles.[1,2] More recently, five different dopamine receptors have been cloned and sequenced.[3-7] Very few compounds have been shown to recognize selectively these receptors. However, it is important that novel chemical probes are designed to enhance our understanding of the biochemistry of dopamine, particularly because of its proactive role in Parkinson's disease, schizophrenia, and drug abuse syndromes.

A significant body of literature exists for the D2-selective compounds, including the characterization of their electrostatic properties for different families of compounds. In this way, Testa et al. have found that dopamine,[8] zetidoline,[9] two indolones,[10] and a series of orthopramides[11-13] have similar features in their molecular electrostatic potentials (MEPs) on a plane over the aromatic ring, with two minima in one side of the molecules and a maximum in the opposite side. Kocjan and coworkers used the minima obtained in the MEP for apomorphine and several ergolines to superimpose the molecules and develop a pharmacophore of this receptor.[14] On the basis of the direction of a vector that links the position of the minima in the MEPs and the value of the LUMO, Chretien et al. have been able to explain the activity of a series of phenothiazines.[15] The relationship of the value of the LUMO with the activity in other families of selective D2 compounds have been shown by the same group.[16,17] Finally, Hogberg has proposed a nondemanding electronic interaction with the receptor in the region above the aromatic ring of the piquindone and a series of salicylamides.[18]

The number of studies on the properties of D1 receptor ligands or those aimed to explain receptor selectivity are rather small. Pettersson et al. tried to explain the lack of activity of a some benzazepine cyclohexyl derivatives on the basis of the importance of the electrostatic contribution of the aromatic ring present on most of them and absent in the cyclohexyl derivatives.[19] However, the recent discovery of potent compounds without a phenyl ring in a similar disposition seems to limit the validity of this hypothesis. Boudon and Chretien proposed that the position of the MEPs minima could account for D1 versus D2 selectivity based on the electrostatic properties of piquindone, SCH-23390, and dexclamol.[20] The existence of an electrostatic component to the selectivity is appealing; however, the hypothesis needs to be reexamined largely because of the small number of compounds used in that study.

In the present work, we analyze the MEP maps for 11 compounds, four D1 selective, four nonselective, and three D2 selective. Our study aims to test previous indications that the MEP might serve as a modulator of D1/D2 selectivity. The maps were calculated using the local density functional program DMol in a three-dimensional grid surrounding the molecules in their entirety, an advance over previous studies that computed this property in selected planes or in localized areas.

Methods

The compounds selected for this study are shown in Figure 1. Four of them, 1-4,[21-23] are D1-selective; while 5-8[21] are nonselective, and finally three of them, 9-11,[21,24] are D2-selective agonists.

The MEP maps for all molecules were analyzed using the bioactive form proposed for the compound according to a recently developed pharmacophore[25] which agrees with previous characterizations.[26-27]

The geometries were first optimized using local density functional calculations as implemented in the DMol package v. 2.2 and 2.3,[28] distributed by Biosym technologies. A double numerical basis set (DNP), including polarization, was used. The minimization was carried out until the maximum component of the gradient was smaller than 0.002. The MEPs were then calculated on a three-dimensional grid common for all the molecules that extends 4 Å from the largest molecule in each direction, being the number of points considered 6048 for each molecule.

The usefulness of the local density functional approach for the computation of MEPs has been stressed by a recent study[29] when DNP basis sets are used. The quality of the results appears to be comparable to the ab initio methods with a significant reduction in the computational cost.[29]

An in-house program was developed to characterize the grid points that are common to a set of compounds in a range of MEP values. For that range of MEP values the program characterizes points that are common to all ligands in a given group and absent in all the compounds from another group. These difference maps take into account not only the commonalties in each group but also the MEP maps of all the compounds included in each group.

Results and Discussion

The use of two-dimensional MEP maps has customarily been done because of the computational cost of the

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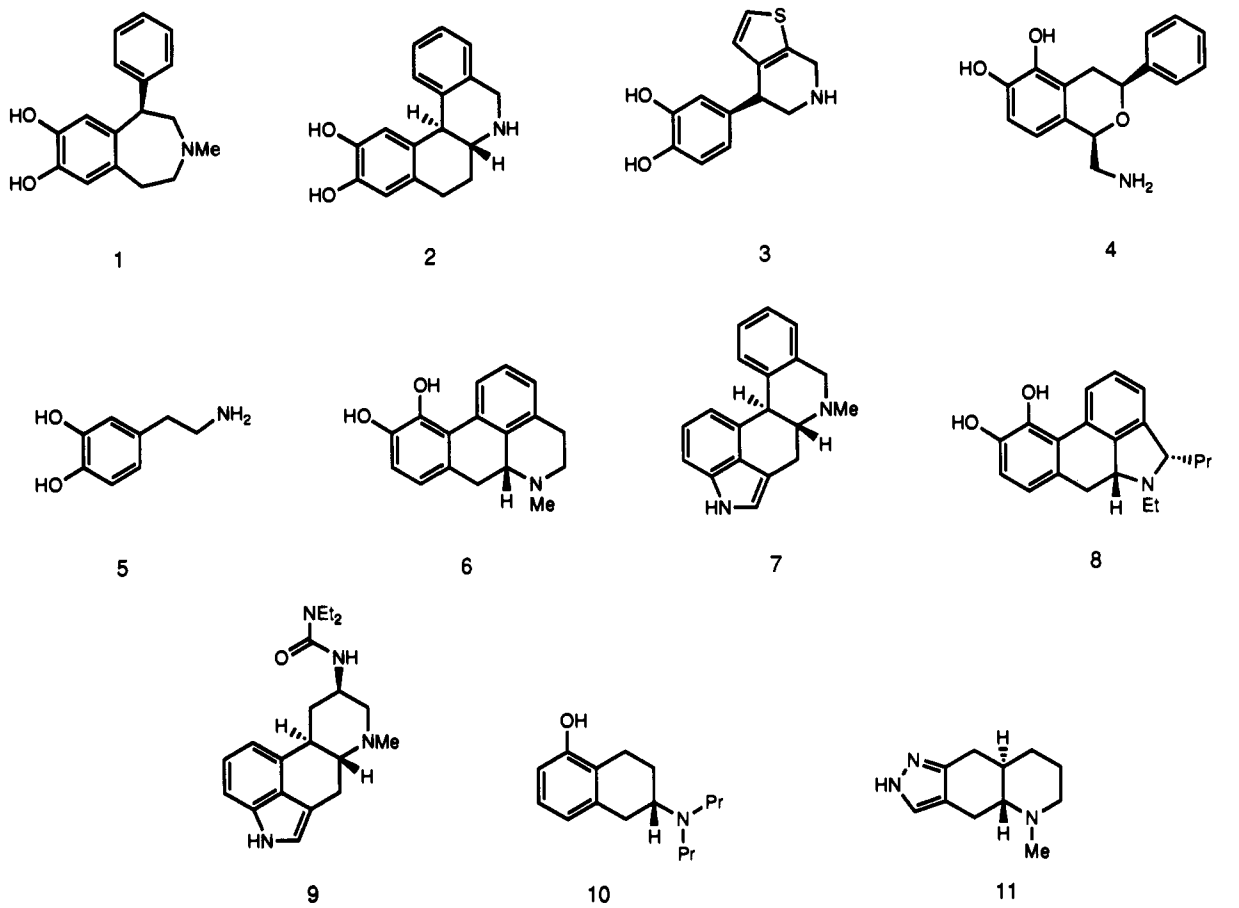

Figure 1. Chemical structure of the dopamine receptor ligands studied.

evaluation of this property. The initial applications of MEPs to drug design were done for planar systems, where the molecular plane provided a frame of comparison of different molecules.[30] The calculations presented here are a first effort to evaluate this property in its entirety for dopamine receptor ligands. Despite their computational cost, the evaluation of this property in three dimensions in the only manner in which the bias of selecting plane to carry out the analysis can be avoided. Some recent studies appear to recognize the importance of a the three-dimensional map; however, the map was only evaluated for a limited region in space.[19]

The structural overlap of the compounds in the conformation selected results in the overlap of all the similar topographical features of the MEP. The similar position of the maxima and minima in the maps for these diverse ligands enhances the reliability of the overlaps previously carried out based on structural commonalties.

Regions of low electrostatic potential for the D1 ligands can be found in the proximity of the lone pairs of the heteroatoms. One region is found in the proximity of the amine nitrogen, while another region of low potential is found in the proximity of the *m*-OH group of the dopamine or the corresponding hydroxy in the other compounds according to the structural overlap. Additional minima are found over both faces of the catechol ring, as well as the other aromatic group. Similar results have been described in previous studies showing a deep minimum generated by the common nitrogen and the rest of the heteroatoms present in the dopamine receptor ligands.[8,10,12,15,31] The minima generated by the aromatic rings have been described less intense and modulated by the substituents of the rings.[8,15,32]

The compounds selected can be divided in three groups: D1 or D2 selective and nonselective. We analyzed the commonalties of the MEPs for each of these groups of compounds, independently. We selected different values of this property, especially in the negative region. The positive regions correspond for the most part to points inside the van der Waals surface, where the nuclear repulsion interactions are dominant, and therefore the information that could be extracted is of limited value.

The compounds in each of the three groups that can be made according to selectivity have some features in common in their MEPs. Regardless of their selectivity, the compounds present negative regions due to the lone pair of the nitrogen and on both sides of the catechol ring as shown for the D1-selective agonists (Figure 2) and D2-selective agonists (Figure 3). These elements should be regarded as primary requirements for binding to any dopamine receptor ligand, as they are found in all ligands regardless of their affinity or selectivity. In addition to these characteristics common to all dopaminergic ligands, the D1-selective compounds have a negative region formed by contributions of the *m*-hydroxy group of the catechol ring, and another low potential area generated by the additional aromatic ring that connects to that generated by the nitrogen. The map in the neighborhood of the phenyl ring has been discussed in detail by Pettersson et al.;[27] however, since their study was limited to the zone in the immediacy of the rotatable phenyl group, they failed to see that this low potential region reaches up to the amine nitrogen for the D1 ligands. For the D2 ligands the maps are more fragmented in this region.

The three-dimensional MEP for the D2- and D1-selective ligands share important features in common,

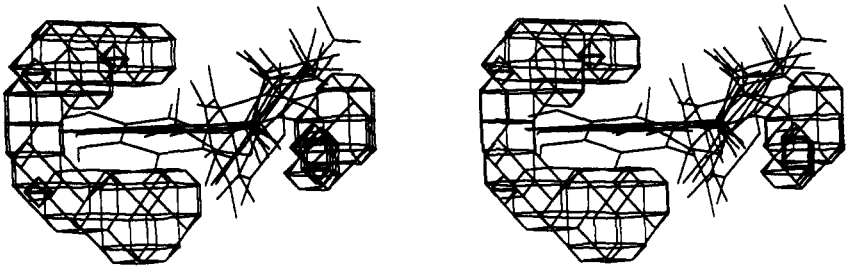

Figure 2. Isoenergy contours in common for all the D1-selective compounds studied in the range from −70 to −5 kcal/mol.

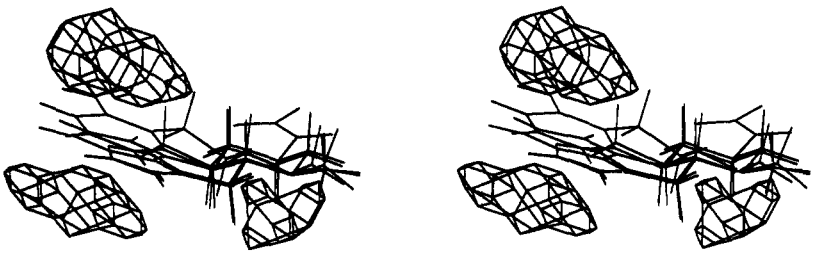

Figure 3. Isoenergy contours in common for all the D2-selective compounds studied in the range from −70 to −5 kcal/mol.

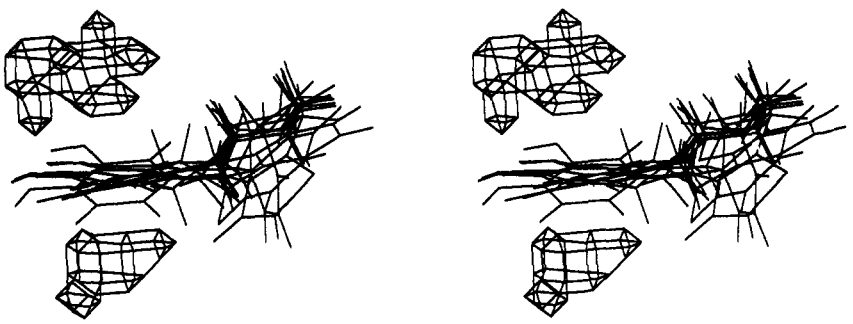

Figure 4. Isoenergy contours of the MEP points common to all D2-selective agonists but that are not common to all the D1-selective ligands in the range from −70 to −5 kcal/mol

which obscures the characteristics that may account for selectivity. The large number of compounds from different chemical classes that are able to bind equally well to either receptor suggests that the factors modulating selectivity are subtle. Therefore we resorted to the analysis of the map of the differences in MEPs for both groups. Only the negative regions are analyzed for this difference, i.e. regions where one of the maps is significantly lower than the other.

The major differences found in the MEPs between the D1- and D2-selective compounds are largely confined to the areas surrounding the catechol group. The values of the MEP in this region appear to be consistently lower for the D2-selective compounds, than for the D1 selective compounds, as can be seen in Figure 4. Note that this difference map only represents the negative regions of the differences. The nonselective compounds adopt intermediate values for the MEP in this region. Hence, the value of the MEP in the proximity of the catechol ring appears to be a modulator of selectivity. The differences in the MEP may indicate that this ring could be involved in the orientation step after the primary interaction of the nitrogen with the receptor as has been proposed for the phenothiazines.[25] In this way, this ring could interact with the D2 receptor requiring electron-rich π rings, such as charge transfer or dispersion interactions. Such interaction appears not to be so important for the D1 ligands.

The map of the difference between D2 and D1 ligands is less revealing since the D2 ligands appear to have systematically lower values of the MEP throughout. Hence, the map of this difference shows no features of any interest.

Conclusions

The general features observed in the MEP maps in three dimensions concur with the report of more fragmented studies. However, the results of a previous study that attempted the use of the MEP to account for the differences in selectivity observed[20] is inconsistent with our findings. The reason for this difference in the results could be the limited number of compounds used as well as the interpretation of the results obtained based on two-dimensional MEP computations.

Our results indicate that the electrostatic interactions are likely to be of importance in the binding to the dopamine receptors because of the presence of very low potential regions common to all dopamine receptor ligands. However, the MEP is unlikely to account, on its own, for the differences in D1/D2 selectivity. Nevertheless, the presence of a lower potential region in the proximity of the catechol ring could be a subtle modulator of affinity. Solely on the basis of the compounds currently available it is uncertain whether the difference in the MEP is a true modulator of selectivity or if the lower potential in D1 ligands is a mere consequence of other substituents that modulate the MEP values in this region. This question can be elucidated by the synthesis of additional probes to test this hypothesis, for instance introducing substituents in nonselective ligands, in other regions of the molecules that may modify the electron density of the catechol ring.

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