On the Interaction of the Aromatic Part of Dopaminergic Agonists with the Receptor

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Structure–activity analysis of some selected, structurally diverse dopaminergic agonists that interact presumably with the D-2 receptor subtype was based on matching the minima of molecular electrostatic potential. Congruent superimpositions may indicate that the aromatic or heterocyclic portions of the structure interact with the receptor via π- or lone pair electron density. The interaction of the aromatic or heterocyclic XH (X = O, N) group or substituent as a hydrogen bond proton donor seems not to be essential for binding and activating the dopamine receptor.

Introduction

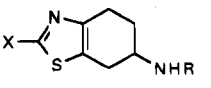
Several studies on dopaminergic action of ergolines have been directed toward elucidation of which part or fragment confers dopamine-mimetic activity upon the molecule. Different parts of the ergoline skeleton have been claimed to represent the dopaminergic pharmacophore based on superimpositions of ergolines and rigid dopamine (DA) congeners like apomorphine. Superimpositions differ with respect to whether chiral centers were matched[1,2] or not[3,4] in view of pronounced stereoselectivity of DA receptor agonists. The central point of most superimpositions is the correspondence between the XH groups—"*m*-OH" of DA analogues and indole NH of ergolines implying the hypothesis that the aromatic part of DA agonists interacts with the receptor site as a proton donor.

We reported previously on the use of molecular electrostatic potential (MEP) as a means for characterizing the interaction profile of aromatic (heterocyclic) moieties of DA agonists.[5] We concluded that ergoline and its partial analogues can share the same receptor site as rigid DA congeners since satisfactory agreement was obtained between the positions of MEP minima with respect to the amine N atom. We proposed therefore that the congruent MEP minima represent a part of dopaminergic pharmacophore. Congruent MEP minima may imply that the aromatic portions interact via π- or lone pair electron density with the receptor site.

DA receptor agonists having the phenol or indole ring as an aromatic moiety are not most appropriate for studying the mode of interaction because they can interact with the receptor site as a proton donor and/or proton acceptor. Heterocyclic analogues of ergolines and of rigid DA congeners are much more promising in this respect. Some of them such as 6-aminobenzothiazole derivatives of general structural formula 1 (X = NH_2, R = alkyl) can be considered, in view of the potent dopaminergic agonist action, as heterocyclic bioisosteres of the catechol ring. The 2-aminothiazole moiety is particularly interesting as it is a constituent part of several potent agonists, some of which have pronounced selectivity for DA autoreceptors. In the 4-(1,2,5,6-tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamine series of derivatives, the 2-NH_2 substituent of the thiazole ring was ascribed the role of the *m*-OH group of DA analogues.[6] It was demonstrated that the methyl replacement of the 2-NH_2 substituent gave practically an inactive compound. However, the suggestion about the role of the thiazole 2-NH_2 substituent is in contradiction with the results of Maillard et al.[7] They claimed that the 6-aminobenzothiazole derivatives of general formula 1 (X = H, Me; R = H, Me) elicited strong effects in the assay on contralateral rotations in rats with a unilateral 6-OHDA-induced lesion of the nigrostriatal DA pathway, thus indicating interaction with postsynaptic DA receptors. Since stereotyped behavior induced by **1a** was inhibited by haloperidol, pimozide, and also sulpiride, the effects of the 6-aminobenzothiazole derivatives had to be transmitted by the D-2 subtype of DA receptors. These results suggest that the 2-NH_2 substituent of the thiazole ring is not essential for the dopaminergic activity of 6-aminobenzothiazole derivatives.

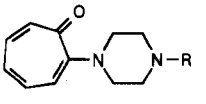
The same conclusion on the role of the thiazole 2-NH_2 substituent can be drawn from the results reached by the Behringer's group on 6-(propylamino)benzothiazole in DA autoreceptor assays. Schneider and Mierau found that **1b** exhibited a pronounced selectivity for DA autoreceptors.[8a] Later, it was also found by the Behringer's group that **1c** was equipotent to **1b** in the inhibition of GBL accelerated DA synthesis.[8b]

It is now widely accepted that DA autoreceptors are closely related to D-2 receptors eventually forming a common family of receptors[9a] according to the D-1/D-2 DA receptor classification due to Kebabian and Calne.[9b] This classification is not necessarily in contradiction to that of recently cloned DA receptor proteins since they can be also classified as "D_1-like" and "D_2-like".[9c]



1

1a X=H, R=Me
1b X=NH_2, R=n-Pr
1c X=H, R=n-Pr



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2a R=CH_2CH_2OH
2b R=Me

There are some other, structurally unrelated compounds that lack the aromatic XH yet attain high

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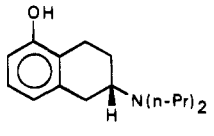
dopaminergic activities. Some *N*-(alkyltroponyl)piperazine derivatives of general formula **2** were demonstrated by Bagli et al. to be potent postsynaptic DA receptor agonists in the assay on turning behavior in rats with unilateral 6-OHDA-induced lesion of the nigrostriatal pathway.[10] In this model both D-1 and D-2 agonists can produce contralateral rotations that are mediated via distinct but interacting D-1 and D-2 receptor subtypes.[11] The action of **2a** was attenuated only by haloperidol, a nonselective D-1/D-2 antagonist. However, it has been demonstrated that haloperidol binds preferentially to D-2 receptors,[12] and moreover, it failed to block contralateral rotations induced by a selective D-1 agonist.[13] It could be therefore concluded that an appreciable part of the effects elicited by *N*-alkyl derivatives of **2** had to be transmitted via D-2 receptors.

The hypothesis on π-electron interaction of DA agonists does not necessarily exclude the proton-donor interaction of the aromatic XH groups. However, the reports on the potent DA agonist activity of drugs that are devoid of the XH group strongly disfavors the XH proton-donor interaction as an important recognition element at the receptor site. They give support to the π- or lone pair electron density interaction since these compounds, as it will be shown below, optimally fit MEP minima with other DA agonists.

The MEP maps of **1b,c** and **2b** will be compared to that of *N,N*-di-*n*-propyl-5-hydroxyaminotetralin (**3**), a potent D-2 agonist. **3** is a monohydroxy semirigid DA analogue. It is well-known from the SAR studies on phenethylamine, 2-aminotetralin, and aporphine derivatives that only a *m*-OH substituent of the phenethylamine fragment is essential for DA receptor agonist activity.[14] The MEP-based superimpositions of **1b** onto apomorphine (**4**), a nonselective D-1/D-2 agonist, and quinpirole (**5**), a selective D-2 DA agonist, will serve to illustrate the correspondence between the σ-electron lone pair heteroatoms of the aromatic moieties and the matching of the chiral centers.



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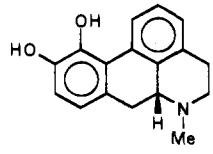

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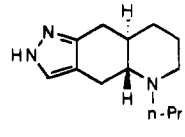

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The selected DA agonists belong to different chemical classes of compounds. They are fairly rigid molecules that make consideration of stereochemical similarity effected by three-dimensional structure superimpositions straightforward. Most of SAR studies on DA receptor agonists pertain to (semi)rigid DA analogues and were directed toward the conformational requirements at the receptor site. The present compounds have been assayed for pharmacological activity in different laboratories using different assay methods. Despite the potential risk of comparing such compounds, I believe that this subset of structurally diverse dopaminergic agonists can be employed in an attempt to deduce the interaction mode of aromatic moieties.

Results and Discussion

Molecular Geometries. Molecular geometries of **1b,c**, **3**, **4**, and **5** were calculated by the Discover molecular mechanics methods. The conformation of **3**, including the *N,N*-dipropylamino orientation, corresponds to one of two molecules (A) in the crystal unit cell.[15] The conformation of **4**, a rigid DA analogue, also corresponds to that observed by X-ray crystallography.[16] Both structures have congruent chiralities (*S*-**3**, *R*-**4**) and congruent conformations of the phenylethylamine fragment, as well as the N atom electron lone pair orientations that are almost perpendicular to the plane of the aromatic ring. These conformational features are part of the model for agonist DA receptor interation established by several studies that carried out conformational analysis of various rigid DA analogues.[17,18]

Compound **5** has a trans ring junction and is therefore very rigid. Crystal structure determination revealed that the chiral center C-4a in the active enantiomer has the same configuration (*R*) as the corresponding one in natural ergolines.[2b] The conformation of the active enantiomer and the N-lone pair orientation fits perfectly the agonist receptor interaction model quoted above. It has to be noted that **5** can exist in two tautomeric forms. The 1*H*-tautomer was found in the crystal. Our semiempirical and ab initio MO calculations on smaller analogue molecules showed that the tautomeric energy difference was rather small, ~1 kcal/mol, in favor of the 1*H*-tautomer.[19]

The chirality of the (−)-enantiomer **1b** was determined by X-ray crystallography to be *S* and is the same as that in **3**.[8a] The conformation of the thiazolylethylamine fragment in **1b** corresponds to the phenethylamine one in **3**.

For determining the molecular geometry of **2b**, data from the X-ray crystal structure of AY-27110 were preferably used[20] as the conformational profile of the bond between the tropone moiety and the piperazine ring is not easily amenable to a molecular mechanics method. This bond can have a partially double bond character due to the piperazine N-lone pair delocalization, and such effects would demand a more complex potential energy function. The crystal structure of **2b** fits well the agonist DA receptor interaction model. The N atom is located closely to the plane of the aromatic ring (0.2 Å); the N lone pair direction makes an angle of 35° with the normal to the plane. The torsional flexibility around the bond connecting the piperazine and the tropone ring was estimated by the ab initio MO method using 3-21G basis set in the rigid rotor approximation with a step of 30°. Two minima were found within the energy difference of ~1 kcal/mol; one of them corresponds to the crystal structure conformation.

MEP Maps. A characteristic feature of the MEP patterns shown in Figure 1 is disposition of two minima. The global minimum corresponds to the amine N atom and is probably related to the interaction with the carboxylic group of the Asp residue that is common to aminergic receptors. The other minimum is generated by the electron density distribution of the aromatic moiety.

The isopotential contours calculated above the thiazole moiety in **1b** and **1c** indicate a dominant contribu-

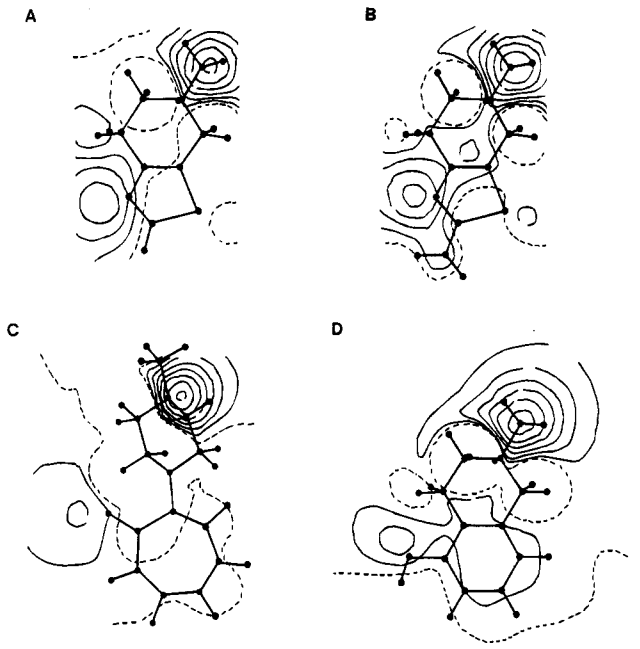

Figure 1. The molecular electrostatic potential (MEP) pattern of **1c** (A), **1b** (B), **2b** (C), and **3** (D). The contours drawn represent isopotential values incremented by −0.01 hartrees from 0.00 hartrees (hatched lines). The *N*-alkyl substituents of **1b,c** and **3** were substituted by hydrogen atoms in the MEP calculations.

tion of the thiazole N σ-lone pair electron density. The position of the local minimum is situated closely to the thiazole N atom that could act as a proton acceptor in a hydrogen-bond interaction. The thiazole 2-NH_2 substituent in **1b** has negligible influence on the position of the local minimum as compared to that in **1c**; however, the minimum in **1b** is lower by 6 kcal/mol. In the MEP pattern above the tropone moiety in **2b**, the position of the local minimum is due to the σ-lone pairs of the carbonyl O atom in analogy to the hydroxy O atom of the phenol moiety in **3**. As both O atoms have a dominant contribution to the position of MEP minima, they can both act as proton-acceptor sites.

Calculation of the MEP maps for **1b,c** and **2b** complements those of the set of rigid DA congeners and partial ergoline analogues that were calculated previously.[5] It is easily verified that the characteristic feature of the MEP maps, the position of local minima with regard to the amine N atom and the aromatic ring, are fully correlated within such a diverse set of aromatic moieties. In particular, the MEP pattern above the thiazole moiety in **1c** is similar to that of the pyrazole in **5** (Figure 1d in ref 5). The minimum located at the pyridine type N atom of the pyrazole ring in **5** corresponds to the minimum at the N atom of the thiazole ring in **1c**.

MEP-Based Superimpositions. The superimpositions shown in Figure 2 were carried out by the matching of MEP minima generated in the surroundings of the aromatic moiety with regard to the coincident amine N atoms that project their lone pairs into the same direction.

The superimpositions of *S*-**1b** and *R*-**4** (Figure 2A) shows in addition to congruent chiral centers the correspondence between the thiazole N atom and the apomorphine 11-OH (*m*-OH) as well as the thiazole 2-NH_2 and the apomorphine 10-OH. The latter correspondence is particularly interesting since the apomorphine 10-OH substituent is not essential for DA receptor activity,[14] and the same might be true for the thiazole 2-NH_2 substituent according to quotations in ref 7. The spatial correspondence between the aporphine 11-OH (*m*-OH) and the thiazole N atom that have the major effect on the position of the MEP minima indicates that the thiazole N atom is the essential chemical group responsible for dopaminergic activity of 6-aminobenzothiazole derivatives and analogues. The correspondence between the phenole (or catechole) OH and the thiazole N atom was also suggested for β-adrenergic agonists isoproterenol and tazolol.[21]

The superimposition of *S*-**1b** and **2b** (Figure 2B) brings the carbonyl O atom in close proximity to the thiazole N atom. The correspondence between the σ-lone pair heteroatoms, the carbonyl O atom, and thiazole N atom, found for DA agonists, has been also demonstrated for serotonergic 5-HT_3 antagonists.[22]

The superimposition of *S*-**1b** and *R,R*-**5** (Figure 2C) shows congruent chiralities and a perfect fit of σ-lone pair heteroatoms, the thiazole, and pyrazole N atom, as well as a rather poor fit of the XH groups, the thiazole 2-NH_2 substituent, and the pyrazole NH group. The correspondence between the thiazole N atom and the pyrazole σ-lone pair N atom of the 2*H*-tautomer indicates that the 2*H*-tautomer had to be recognized by the DA receptor.

In the superimpositions presented above an optimal fit of the MEP minima as well as the lone pair heteroatoms was obtained on the scale of an average skeleton bond length. Because of the wide area of the low electrostatic potential generated above the aromatic ring, the interaction with the receptor site group has not to be very stringent with regard to the geometrical disposition of both moieties. It is believed that the receptor site is rather flexible as it can accommodate

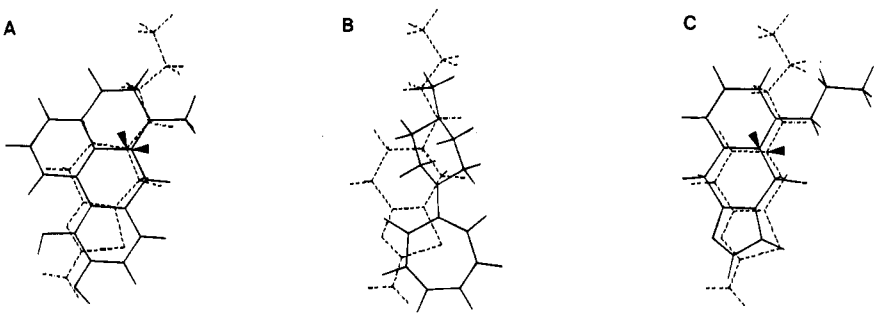

Figure 2. Superimposition of *S*-**1b** (hatched lines) onto *R*-**4** (A), **2b** (B), and *R,R*-**5** (C). CH bonds of the corresponding chiral centers project upward with reference to the plane of the paper as indicated by filled triangles.

ligands with markedly different geometric parameters. The distance between the amine N atom and the *m*-hydroxyl O atom in **3** is 6.5 Å; in 7-hydroxy-2-aminotetralin, which is also a potent DA agonist, it amounts to 7.5 Å.

Congruent superimpositions with regard to chirality and molecular volumes were obtained between agonists possessing different pharmacological profile—a nonselective D-1/D-2 agonist (**4**), a selective D-2 agonist (**5**), and a preferential autoreceptor agonist (**1b**). The MEP minima fitting had therefore to represent a general dopaminergic pharmacophore. Liljefors and Wikström pointed out that post- and presynaptic DA receptors are closely related. The structural basis for selectivity in DA (semi)rigid analogues between the pre- and postsynaptic sites is believed to be a delicate balance between the lipophilicity and steric demands of *N*-alkyl groups.[18] It is interesting to note that the MEP minima disposition presented in Figure 1 closely corresponds to the disposition of the two major binding sites of the so-called "extended rotamer-based dopamine receptor model" elaborated by Seiler and co-workers.[23] The model relies upon superimpositions of α- and β-rotameric conformations of the DA fragment embedded in several rigid structures and was proposed to be valid for D-1 as well as D-2 agonists. The structural basis for D-1 selectivity in 1-phenylbenzazepines, 3′,4′-dihydroxynomifensine and benzergolines probably lies in additional lipophilic interaction of the phenyl ring.[24] Pettersson and coworkers have concluded on the basis of MEP calculations of 1-phenylbenzazepines that the 8-OH substituent had to interact as a hydrogen-bond acceptor in order to obtain a favorable contribution of the important 1-phenyl substituent.[25] It seems therefore that the electron lone pair interaction of the OH substituent also pertains to the D-1 receptor site ligands. Alkorta and Villar have performed three-dimensional MEP calculations on several D-1 selective, D-2 selective, and D-1/D-2 nonselective DA receptor agonists. They have demonstrated that all three groups of compounds had some MEP features in common which should be viewed as primary requirements for binding and that the MEP only can hardly account for the differences in D-1/D-2 selectivity.[26] However, MEP minima-based matchings can be used as a discriminative factor in hydroxy-substituted 2-aminotetralins for interaction with DA and 5-HT receptors. We demonstrated by quantitative estimation of the MEP similarity that **3** has a higher degree of similarity to 7-hydroxy-2-aminotetralin than to an 8-hydroxy analogue, a 5-HT1A agonist.[27] With MEP-based superimpositions we were able to discriminate between the inactive 2-azaergoline and ergoline because the superimposition of 2-azaergoline was not sterically compatible with potent DA agonists.[5]

In conclusion, matching of the MEP minima of **1b,c** and **2b** with those of rigid DA congeners and partial ergoline analogues calculated previously additionally corroborates the proposition that they represent an element of dopaminergic pharmacophore. Recognition and binding of the aromatic moiety of DA agonists has to be effected by the π- or lone pair electron density interaction, possibly with a proton-donor group located at the receptor site or by stacking with a heterocyclic ring.[28] In view of the potent activity of agonists that are devoid of the proton-donor group, the interaction of the aromatic or heterocyclic XH group or substituent as a hydrogen bond proton donor seems not to be essential for binding and activating the DA receptor. The model suggesting the π- or lone pair electron density interaction easily accommodates structures of different chemical classes and is consistent with respect to chirality. This is an important issue not only for the definition of the dopaminergic pharmacophore but also for the novel DA agonists design.

Methods

Molecular models were constructed by the Insight program package. The conformations of the models correspond to the X-ray crystallographic data.[2b,8a,15,16] Molecular geometries were calculated by the Discover molecular mechanics method using steepest descent and VA09A algorithm.[29] The minimization was carried out until the rms of gradients was less than 0.0001 kcal/(mol Å). Ab initio molecular orbital calculations were carried out by the program package Gaussian 88.[30] Wave functions for molecular electrostatic potential were calculated at the Hartree-Fock level with the STO-3G basis set. The electrostatic potential was calculated in a plane 1.6 Å below the plane of the aromatic ring in the direction of the amine N atom electron lone pair. The points in which the potential was calculated form an orthogonal grid with a step of 0.5 Å. Molecular superimpositions were constructed by keeping the amine N atoms coincident and the aromatic rings coplanar and matching the electrostatic potential minima of the aromatic rings.

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