Communications to the Editor

A Stereochemical Explanation of the Dopamine Agonist and Antagonist Activity of Stereoisomeric Pairs

Sir:

The structural features of dopamine (DA) agonists and antagonists have until recently been clearly distinguished.[1,2] This changed, however, with the observation that (3*R*)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP) (Figure 1a) is a DA agonist whereas the 3*S* antipode (Figure 1b) blocks postsynaptic DA receptors.[3,4] Similarly, while (6a*R*)-apomorphine and (6a*R*)-*N*-*n*-propylnorapomorphine (NPA) (Figure 1a) are well-known DA agonists, the 6a*S* antipodes have been reported to be DA antagonists in behavioral and biochemical indices of receptor activity.[5-9] Very recently, the 1*S*,2*R* antipode of *cis*-1-methyl-5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-MDAT) (Figure 1b) was found to be a postsynaptic DA antagonist while, once again, the 1*R*,2*S* antipode (Figure 1a) is a DA agonist.[10] It has also been suggested that since the (3*S*)-PPP and (6a*S*)-NPA DA antagonists appear to have selective actions in limbic regions of the brain, they deserve consideration as possible selective antipsychotic agents that may lack the extrapyramidal neurological toxicity of other DA antagonists.[7,11] The present analysis was undertaken to seek a molecular basis for the enantiomeric selectivity of the above compounds. These structures have in common a *m*-hydroxyphenyl (analogous to the *m*-hydroxyl function of DA) separated by two carbon atoms from an ammonium group (for the protonated molecule) so that the three-dimensional pharmacophores may be similar. A number of models have been proposed to account for the activity and inactivity of compounds at DA receptors.[1,12-19] However, none address the postsynaptic DA agonist–antagonist enantioselectivity of the above compounds. Moreover, these models lack predictive power for the dopaminergic activities of the 3-PPP antipodes since the asymmetric centers of previously examined compounds, such as the aporphines, have generally been located on the carbon that is α to the nitrogen, whereas in 3-PPP it is located β to the nitrogen.

Methods

A complication that must be considered is that the molecules under consideration have considerable internal flexibility. For 3-PPP, rotation is possible about the bond between the phenyl and piperidine rings while the N-substituents can rotate in 5-OH-MDAT. While NPA is more rigid than the other two compounds, different puckerings of the saturated rings are possible. Other possible conformers have been considered as well. The conformational flexibility of 3-PPP and 5-OH-MDAT have been characterized with the empirical MM2 (Molecular Mechanics II) computer program[20] while the MMP2[21] version was required for NPA since it contains delocalized electron systems separated by a bond with single bond character. These programs have been shown to yield quantitatively reliable results in calculating energies and geometries of hydrocarbons and amines.[22,23] Our previous experience with the MM2 program also indicates that it produces conformational and geometrical results that are consistent with those of X-ray crystallography and nuclear magnetic resonance spectroscopy.[24-31] The calculations were performed in two different ways. In the first, the energies of various possible conformers were minimized with respect to all internal coordinates which allows the determination of their relative stabilities. In the second

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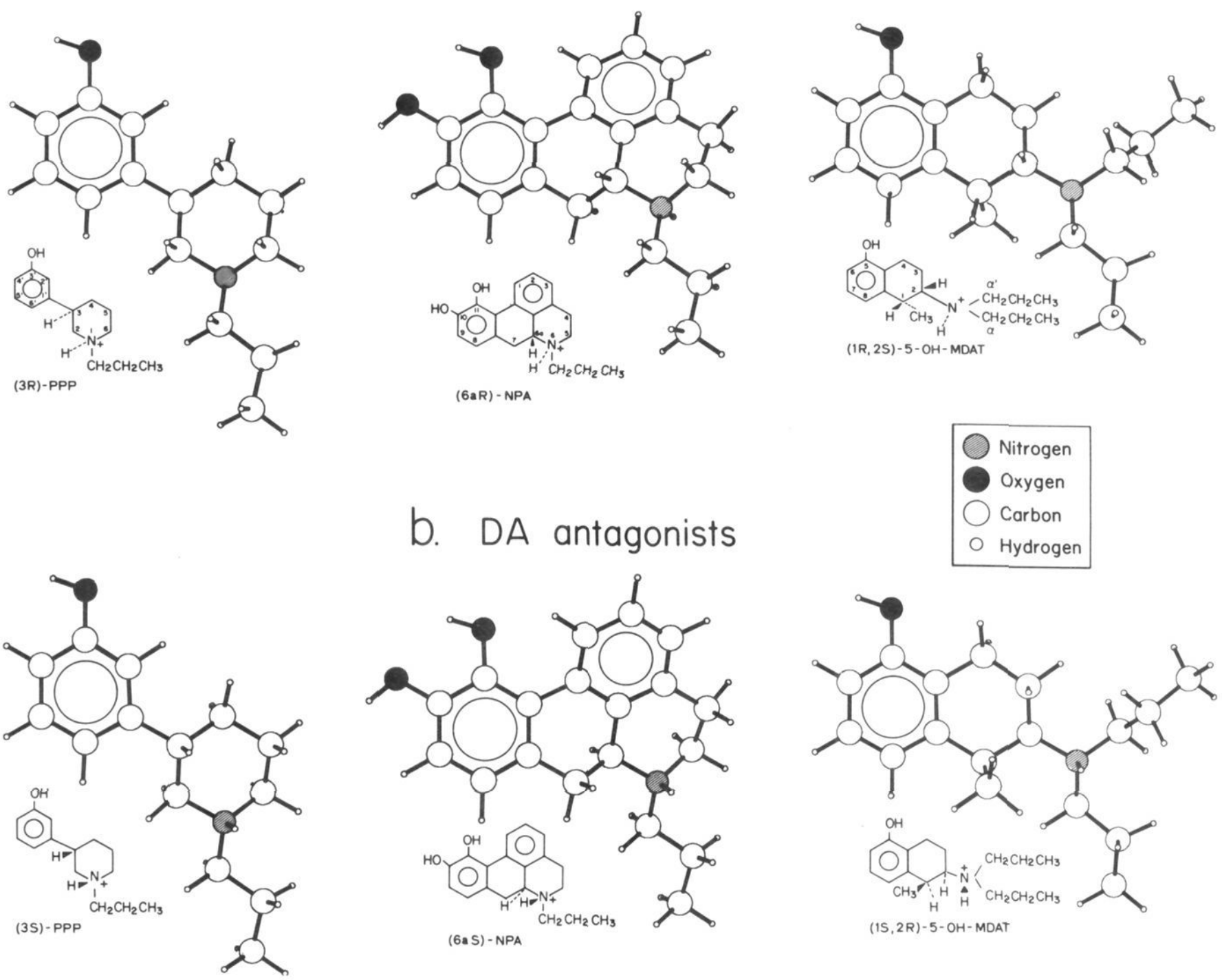

Figure 1. (a) Dopamine agonists. The conformation for (3*R*)-PPP (τ(C2′–C1′–C3–C2) = 150°) that best superimposes onto other DA agonists. Energy-minimized structure for (6a*R*)-NPA. Preferred conformation for (1*R*,2*S*)-5-OH-MDAT with τ(C3–C2–N1–C_α) = 180° and an arbitrary conformation of the *N*-propyl groups. (b) Enantiomers reported to be postsynaptic DA antagonists. The conformation for (3*S*)-PPP (τ(C2′–C1′–C3–C2) = 210°) that best superimposes onto the other DA antagonists. Energy-minimized structure for (6a*S*)-NPA. Preferred conformation for (1*S*,2*R*)-5-OH-MDAT with τ(C3–C2–N1–C_α) = 180° and an arbitrary conformation of the *N*-propyl groups.

procedure, the variable dihedral angle was constrained with 10° increments and the energy was minimized with respect to the remaining internal coordinates. This procedure allows the determination of the barriers to rotation for that dihedral angle. All calculations were for the protonated molecules. A correction to the MM2 program for constrained minimizations was used.[32]

Results and Discussion

For 3-PPP, three pairs of stable energy minima for phenyl rotation were found with the favored *N*-propyl equatorial conformation. Each pair consisted of a conformer and its 180° rotamer that had the same computed intramolecular energy. The lowest energy pair have the phenyl ring approximately eclipsing the hydrogen in the 3-position of the piperidine ring whereas in the other two pairs, with energies 0.6–0.7 kcal/mol higher, the phenyl ring approximately eclipses one edge of the piperidine ring. The flexibility of the compound is illustrated in the computed barrier to rotation of the phenyl ring with a maximum barrier of 3 kcal/mol (Figure 2). These results suggest that, in interacting with DA receptors, the phenyl ring in 3-PPP should be able to orient to the requirements of the receptors. Similar results have been reported pre-

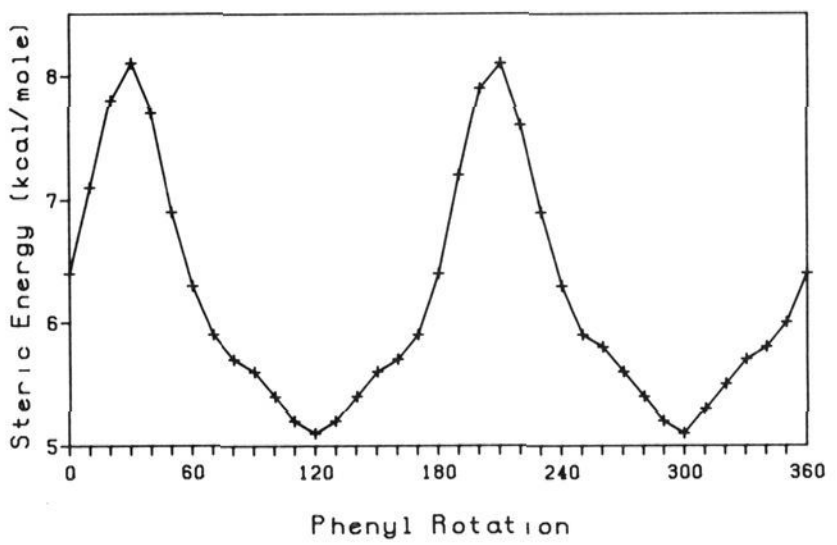

Figure 2. Barrier to rotation about the phenyl–piperidine bond in (3*S*)-PPP as measured from τ(C2′–C1′–C3–C2).

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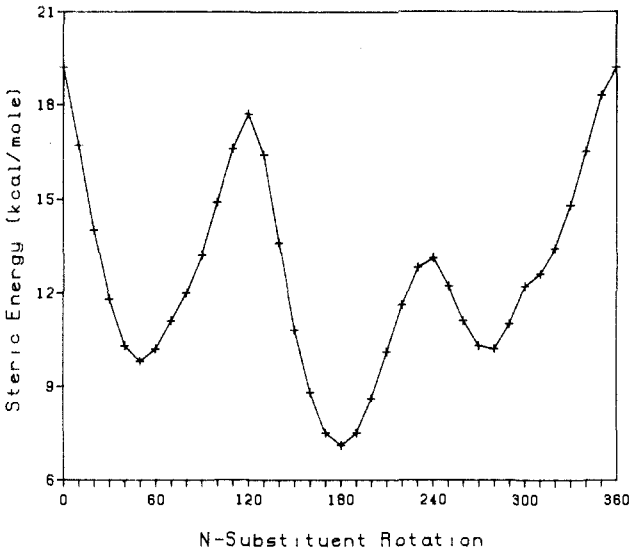

Figure 3. Barrier to rotation about N1–C2 bond in (1*S*,2*R*)-5-OH-MDAT (for the *N*,*N*-dimethyl analogue) as measured from τ(C3–C2–N1–C_α).

viously for 3-PPP.[18] *N*-Propyl axial conformers were consistently less favorable than *N*-propyl equatorial ones by ca. 2.3 kcal/mol.

For 5-OH-MDAT, the reported calculations are for the compound with *N*-methyl rather than *N*-propyl groups since the latter have a great deal of flexibility with a large number of possible conformations. It was also not possible to rotate about the N–C2 bond with a fixed conformation of the *N*-propyl groups due to the sterically crowded nature of that part of the molecule. For the *N*,*N*-dimethyl compound, three stable energy minima were found corresponding to gauche and trans conformations of the *N*-methyl groups. The conformer with the lowest energy (Figure 1) was favored by 2.7 and 3.0 kcal/mol over the other two. This can also be seen in the computed barrier to rotation of the *N*-methyl groups for the 1*S*,2*R* antipode (Figure 3). The unfavorability of the two higher energy conformers is due solely to steric interactions between the *N*-methyl groups and the *cis*-1-methyl group since, in the compound without the latter, the three conformers have energies within 0.4 kcal/mol (unpublished results). Substitution of *N*-methyl for the *N*-propyl groups will have only a minor effect on the preferred conformation about the N–C2 bond since the unfavorability of the two higher energy conformers is clearly due to steric interactions between the *cis*-1-methyl group and the N-substituent. The lowest energy conformation in which the ammonium group is axial rather than equatorial was 3.7 kcal/mol higher in energy than the global minimum.

The preferred three-dimensional structures of the antipodes of NPA (Figure 1) were determined by minimization with respect to all internal coordinates. Other conformations of the saturated rings were also considered but proved to be significantly less favorable. The conformation shown in Figure 1 in which the puckering of the piperidine is such that the N–H points in the opposite direction (keeping the *N*-propyl in the equatorial conformation) had an energy that was 2.3 kcal/mol higher. One surprising result was that the conformer in which the *N*-propyl group is in an axial position is only 0.3 kcal/mol higher in energy than the one in which it is equatorial (Figure 1). This unexpectedly small difference appears to be due to two factors. First, there are close steric contacts between an equatorial N-substituent and one of the hydrogens at C7. Secondly, there are more favorable attractive interactions between an axial N-substituent and the rest of the molecule. Despite this relative favorability, the axial N-substituent conformer does not appear to be significant for this analysis since there are no corresponding conformers in the other two compounds. The computed low-energy conformation of the aporphine structure is quite similar to that observed by X-ray crystallography for apomorphine.[33,34]

Given the reported postsynaptic DA antagonism of (3*S*)-PPP, (6a*S*)-NPA, and (1*S*,2*R*)-5-OH-MDAT, it was of interest to superimpose their structures. Of the two phenyl hydroxyls characteristic of many catechol DA agonists, the *m*-hydroxyl is pharmacologically more crucial than the *p*-hydroxyl in DA agonistic aminotetralins, aporphines, and 3-PPPs.[15,35–39] Our previous[40] and unpublished data on the 11-monohydroxyaporphine analogues indicate again that the *m*-hydroxyl appears to be crucial for agonist and antagonist activity. Therefore, in superimposing these structures it seems appropriate to superimpose the meta phenyl hydroxyls preferentially. The *N*-alkyl groups should also be superimposed since they appear to play an important role in affinity and activity at DA receptor sites.[15,37,40–43] Finally, it has been suggested that the orientation of the ammonium hydrogen (or lone-pair electrons) should be considered.[2,14,18–19,44] With use of these criteria for the putative DA antagonists, the preferred conformer of (6a*S*)-NPA superimposes quite well with preferred conformer of (1*S*,2*R*)-5-OH-MDAT (Figure 1b). However, none of the six stable conformers of the antagonist (3*S*)-PPP proved a good fit to the other two antagonist antipodes. However, by rotating the phenyl ring of (3*S*)-PPP by 50° from one of the preferred conformers (Figure 1b), all three compounds have similar three-dimensional orientations of the phenyl *m*-hydroxyl, the N-substituents, and the ammonium hydrogen. This simultaneous superposition of these three structural elements could not be done with the DA agonist (3*R*)-PPP. A similar juxtaposition occurs for the three DA agonists shown in Figure 1a. It should be noted that the "planar" form of 3-PPP is unfavorable by 3 kcal/mol (Figure 2). If the geometries of NPA and 5-OH-MDAT are assumed to be optimal for interacting with DA receptors, the energy penalty for 3-PPP could account for the relative weakness of its isomers on DA agonist and antagonist assays[19,39] though other explanations are also possible.

It appears that the agonism–antagonism of enantiomeric pairs may not be unique to dopaminergic compounds but

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may occur in other drug–receptor systems. For example, opioid phenylmorphans and 3-phenyl- and 4-phenylpiperidines also form such pairs.[27,45-47] A possible molecular explanation for the opposite activity of enantiomers may be the delocalization of charge that occurs when amines are protonated.[48] That is, rather than being concentrated on the ammonium hydrogen, the positive charge is spread over the adjacent C–N bonds so that the "back" of the N–H bond also contains significant positive charge. Thus, (6a*S*)-NPA may be able to bind to the same receptor site as (6a*R*)-NPA since the overall shapes of these molecules are similar and there is sufficient charge at the back of the N–H bond to allow binding to a complementary electrostatic site in the receptor. Antagonists may bind to the same receptor site as agonists, but it appears that agonist activity requires the proper N–H orientation.

To summarize, two ((6a*S*)-NPA and (1*S*,2*R*)-5-OH-MDAT) of the three postsynaptic DA antagonists can be closely superimposed with the juxtaposition of the phenyl *m*-hydroxyl, the N-substituent, and the direction of the N–H bond. The third antagonist, (3*S*)-PPP, can also assume this conformation with only a moderate energy penalty possibly accounting for its relatively low potency. A similar juxtaposition occurs for the three DA agonists. These observations point out the importance of the orientation of the ammonium hydrogen (or lone-pair electrons) in determining agonist and antagonist activity at DA receptors. This view is consistent with a previous proposal[17] that the 6a-hydrogen at the chiral center of aporphines is responsible for the enantiomeric selectivity of such aporphines since the chiral center also determines the orientation of the ammonium hydrogen.

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Registry No. (3*R*)-PPP, 85976-54-1; (3*S*)-PPP, 85966-89-8; 3-PPP, 75240-91-4; (6a*S*)-NPA, 79703-31-4; NPA, 18426-20-5; (1*R*,2*S*)-5-OH-MDAT, 96148-66-2; (1*S*,2*R*)-5-OH-MDAT, 96148-67-3; 5-OH-MDAT, 90295-44-6.

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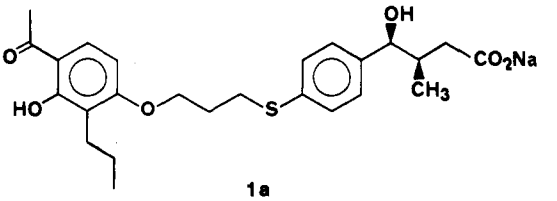
Design and Synthesis of Sodium ($\beta R^*,\gamma S^*$)-4-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-γ-hydroxy-β-methylbenzenebutanoate: A Novel, Selective, and Orally Active Receptor Antagonist of Leukotriene D_4

Sir:

The leukotrienes C_4, D_4, and E_4 are peptido–lipid conjugates derived from the 5-lipoxygenase pathway of arachidonic acid metabolism that collectively account for the biological activity known as slow-reacting substance of anaphylaxis (SRS-A).[1-5] These products have been ascribed an important role in the etiology of human asthma on the basis of their demonstrated release upon antigenic stimulation from human and animal lung tissue,[6,7] their potent and long-lasting contractile effects on airway smooth muscle[8,9] and their abilities to promote mucus production,[10] decrease mucocillary clearance[11] and modulate vascular permeability.[12,13] From these observations has evolved the hypothesis that a potent and specific leukotriene antagonist should offer an effective new treatment for asthma. This hypothesis remains to be tested in clinical trials, when a suitably safe and potent drug is available.[14]

In this paper we describe the research that has led to the discovery of sodium ($\beta R^*,\gamma S^*$)-4-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-γ-hydroxy-β-methylbenzenebutanoate (L-649,923) (**1a**), a potent and orally active antagonist of LTD_4 that has the potential to help define the role of leukotriene D_4 in human disease.



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