Electrostatic Medium Effects and Formal Quantum Structure–Activity Relationships in Apomorphines Interacting with D_1 and D_2 Dopamine Receptors

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ABSTRACT

The binding of apomorphines (AM) to D_1 and D_2 dopamine receptors is analyzed through a formal quantum structure–activity relationship method. The calculations were carried out at the CNDO/2 level of the molecular orbital theory with a continuum representation of environmental effects. The results show that the D_1 receptor affinity variation is related to the variation of the electron-donating capacity of a C atom of the hydroxylic region of apomorphines in a low-polarity medium. The N-chain probably interacts with a hydrophobic region of the receptor. It is also concluded that the poor results for the D_2 binding affinity are explained by errors in the experimental measurements. Finally, it is proposed that future structure–activity relationship studies must be carried out for media of different polarities.

Introduction

Dopamine is an important neurotransmitter in the central nervous system. The search for an explanation of its physiological effects has led to the discovery of a variety of receptors [1, 2]. Their anatomical location and agonists and antagonists acting upon them are well known. Dopaminergic mechanisms are involved in a wide array of biological processes, such as appetite control, arousal, dementia, depression, extrapyramidal disorders, learning and memory, reward, schizophrenia, and sleep. Dopaminergic systems can be pharmacologically modulated by altering dopamine synthesis, metabolism, and uptake or by receptor stimulation or blockade.

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Apomorphines (AMs) are hemisynthetic substances derived from morphine and the N-substituted derivatives of normorphine by rearrangement, which formally incorporate a dopamine moiety in a rigid conformation in their structure (Fig. 1). They can interact with D_1 and D_2 dopaminergic receptors [3]. AMs have been employed to induce vomiting in acute poisoning and to treat Parkinson's disease and schizophrenia [4–7].

The importance of the dopaminergic system, the absence of studies relating the electronic structure of AM with their D_1 and D_2 receptor affinities [8–10], and the need of information regarding their binding mechanism to allow the rational design of new derivatives prompted us to choose a group of AMs for a quantum chemical structure–activity relationship (SAR) study (see Fig. 1 and Table I).

A second and very important reason for this choice is the following: Yigong et al. reported receptor affinities of some AMs for D_1 and D_2 receptors located in the corpus striatum of rat brain [3]. The labeled ligands employed were [^{3}-H]-SCH-23390 for D_1 receptors and [^{3}-H]-spiperone for D_2 receptors. Nevertheless, rat basal ganglia (especially the *globus pallidus* and the *pars reticulata* of the substantia nigra) also contains 5-HT_{1B} serotonergic receptors [11]. Also, some parts of the rat basal ganglia contain 5-HT_{2A} receptors [12]. It is well known that spiperone has an affinity for these two subtypes of serotonergic receptors [11]. As the serotonergic receptors were not selectively blocked when Yigong et al. measured the D_2 binding affinities [3], some of the apparent spiperone binding could be due to 5-HT receptors. If so, then the reported D_2 receptor affinities are unrealistic and the whole set of these affinities lacks internal coherence. **If all this line of reasoning is correct, we must obtain statistically poor SAR equations for the D_2 binding affinities. As this is not the case for the reported D_1 binding affinities, we must obtain statistically good SAR equations for them.** An additional source of error for the D_2 binding affinities might be the hypothetical binding of AMs to sigma receptors, given that the dopaminergic agent haloperidol binds to them with high affinity [12].

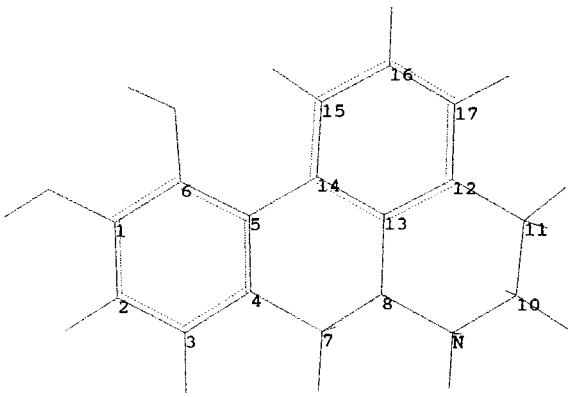

FIGURE 1. AMs showing the atom numbering for the common skeleton.

TABLE I
Experimental and calculated affinities for AMs interacting the D_1 dopamine receptor.

Molecule	*R*	log exp. *K* [a]	log calculated *K* [b]
1	—H	2.59	2.62
2	—Me	2.38	2.34
3	—Et	2.09	2.27
4	—*n*-Pr	2.53	2.36
5	—cyc-pr-Me	2.86	2.89
6	—CH_2 CH=CH_2	2.79	2.77

[a] [3]
[b] Equation (3).

Methods, Models, and Calculations

The methodology to obtain the SAR equations was proposed by one of us several years ago. As the method has been discussed thoroughly elsewhere, we shall present only a general sketch. Briefly, for a thermodynamic equilibrium state and 1 : 1 stoichiometry, the equilibrium constant K can be expressed as [13–15]

$$\log K = a + b \log M_D + c \log \sigma_D + d \log(I_1 I_2 I_3)_D + e\Delta E, \qquad (1)$$

where a, b, c, d, and e are constants, D refers to the drug molecule, σ is the symmetry number, M is the drug's molecular mass, $I_1 I_2 I_3$ is the product of the three moments of inertia about the three principal axes of rotation, and ΔE is the drug–receptor interaction energy.

The interaction energy is evaluated through the Klopman–Peradejordi–Gómez (KPG) approach as [14]

$$\Delta E = W + \sum_i \left[E_i Q_i + F_i S_i^E + G_i S_i^N \right] + \sum_i \sum_m \left[H_i(m) D_i(m) + J_i(m) S_i^E(m) \right] + \sum_i \sum_{ni} \left[R_i(m') D_i(m') + T_i(m') S_i^N(m') \right], \quad (2)$$

where W, E, F, G, H, J, R, and T are constants and Q_i, S_i^E and S_i^N are, respectively, the net charge, electrophilic superdelocalizability, and nucleophilic superdelocalizability of atom i. The index $m(m')$ refers to the contribution to the above properties of occupied (virtual) molecular orbital $m(m')$. Equation (2) was derived assuming that the only important component of ΔE is the change in electronic energy. As the physical meaning of these indices has been discussed elsewhere [13–15], we shall comment only on those appearing in the results.

Only drug-related terms appear in Eqs. (1) and (2). This is so because in the model employed to derive them it is assumed that the family of drugs interacts with the same partner (receptor, enzyme, etc.) in the same conformation and environment. Then, the electronic terms of the common partner are constants that do not appear explicitly. Inserting Eq. (2) into Eq. (1), we obtain the equation expressing the relationship between biological activity and reactivity parameters of the drug molecules only. When employed within an *in vacuo* CNDO/2 level of parametrization, it produced excellent results for phenylalkylamines [15], indolealkylamines [16–18], opiates [19], and carbamate insecticides [20], showing predictive capabilities [17, 21].

Because in this method the quantum chemical reactivity indices can be calculated at any desired level (semiempirical or ab initio) [13, 14], their physical interpretation is independent of the methodology used to get numerical values. Any method giving good results in calculating reactivity indices whose variation (and not their absolute values) explains the variation of the affinity within a given drug family is acceptable.

Affinity constants were measured using very well defined experimental conditions in which the polarity of the binding site area is an unknown but constant number. To find the equation best reflecting experimental results, we need to analyze SAR equations obtained for reactivity indices arising from calculations with different medium polarities. For this purpose, we include electrostatic environmental effects through an extended version of the generalized Born formula, which also considers steric hindrance effects upon desolvation of the atomic centers of the molecular system. For more details about the theory, we refer the reader to the literature ([22, 23] and references therein). This representation of environmental effects gave good results at the CNDO/2 level when applied to ion-pair formation [23] and receptor [24] and catecholamine storage [25] modeling.

The selected molecules are shown in Table I. The IC_{50} values were transformed to equilibrium constants, $\log K_i$ [26]. We must stress here that the number of selected molecules is formally restricted by this transformation: No other reported IC_{50} values can be incorporated into this set.

Numerical values for the electronic reactivity indices were obtained from a molecular wave function calculated within molecular orbital theory at the CNDO/2 level, using standard geometrical parameters. To test if geometry optimization significantly modifies the reactivity indices, we performed a geometry optimization using AM1 methodology for norapomorphine (molecule 1 in Table I). No significant changes of the reactivity indices were observed. Another point to consider is the solvation or not of some parts of the molecules. We assumed that the molecules enter the receptor desolvated. Finally, we have taken care that the numerical values of the nucleophilic superdelocalizabilities behave well in the sense that their values are always positive [27].

The statistical fitting of Eq. (1) was performed by means of a stepwise regression technique with $\log K_i$ as the dependent variable. The reactivity indices of a common skeleton composed of atoms 1–17 of Figure 1 were used as independent variables. The following 12 situations were analyzed:

- **A.** Interaction of AMs with D_1 receptors.
- **A1.** AMs in their basic form and in the presence or absence of a polarizable medium. In the last case, weakly ($\varepsilon = 5$) and highly ($\varepsilon = 80$) polarizable media were considered.
- **A2.** AMs in their protonated form for the case $\varepsilon = 1$, 5 and 80.

B. Interaction of AMs with D_2 receptors.

B1. AMs in their basic form for the case $\varepsilon = 1$, 5, and 80.

B2. AMs in their protonated form for the case $\varepsilon = 1$, 5 and 80.

Results and Discussion

More than 200 SAR equations were analyzed, and the results can be summarized as follows: For the cases A1, B1, and B2, no statistically significant equations were obtained. For the basic form of AMs (cases A1 and B1), this is to be expected because these molecules are protonated in the biophase.

The case of protonated AMs interacting with D_2 receptors is more puzzling and deserves an analysis. At the level of the theory, these poor results could be explained by that our method cannot deal with these experimental results, by that CNDO/2 calculations of reactivity indices (*in vacuo* and in the presence of polarizable media) are not reliable, or by both. These possibilities are ruled out because

1. It has been shown, both theoretically and practically, that the method employed here has produced the best equations known for very different sets of biologically active molecules which had been studied by other methods [15–21];
2. The use of this method, coupled to CNDO/2 reactivity indices, has proved to be predictive for a molecule that resisted other SAR studies [4, 17, 18, 28]; and
3. We obtained a statistically good equation for D_1 receptor affinities (see below).

All this leads to the conclusion that the poor results are to be explained at the experiment level. Therefore, we suggest that the D_2 binding affinities reported by Yigong et al. are not such. This means that they did not block one or more non-D_2 receptors with which the radioligand and/or the apomorphines also interacted during the experimental measurements.

The best statistically acceptable result was the one relating D_1 dopamine receptor affinity to reactivity indices of protonated molecules for the case of a low-polarity medium ($\varepsilon = 5$). The corresponding equation is

$$\log K_i = 90.8623 + 65.4487 S_5^E(H-1) \quad (3)$$
$$n = 6 \qquad \mathrm{SD} = 0.14 \qquad R = 0.88,$$

where $S_5^E(H-1)$ is the contribution of atom 5 to the electrophilic superdelocalizability of the second HOMO. The F-test result is $F(1,3) = 17.58$ ($P < .0025$) and the Student's t test gave $t[S_5^E(H-1)] = 4.19$ ($P < .005$). The values of the F-test and Student's t test results for Eq. (3) show that it is statistically significant (note the P value associated to F). The K values predicted by Eq. (3) are shown in Table I.

Our results show that the D_1 receptor affinity variation is related to the variation of a definite set of molecular reactivity indices. This implies a common interaction mechanism between all the drugs analyzed and D_1 receptors.

We may see from Eq. (3) that a high affinity is associated with a high $S_5^E(H-1)$ value. This suggests that atom 5 participates in charge transfer toward the receptor through its contribution to the electrophilic superdelocalizability of the second HOMO. The importance of the occupied molecular orbitals located just below the HOMO has been known for a long time [29–31]. This result agrees with suggestions that in apomorphines the critical region for their interaction with dopamine receptors resides in the hydroxylated ring [32]. We may ask why the contribution of atom 5 to the electrophilic superdelocalizability of the HOMO does not appear in Eq. (5). This question arises because if atom 5 is donating charge through the (HOMO-1) it is to be expected that it should also donate charge from the HOMO itself. In Figures 2 and 3,

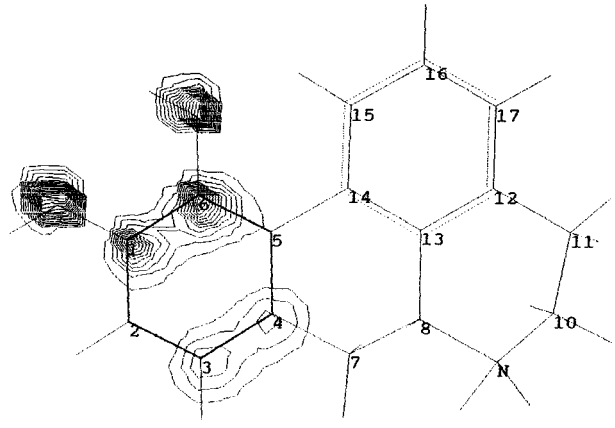

FIGURE 2. Electronic density distribution map for the HOMO molecular orbital of norapomorphine. The map is located 0.5 Å above the plane containing atoms 1–6.

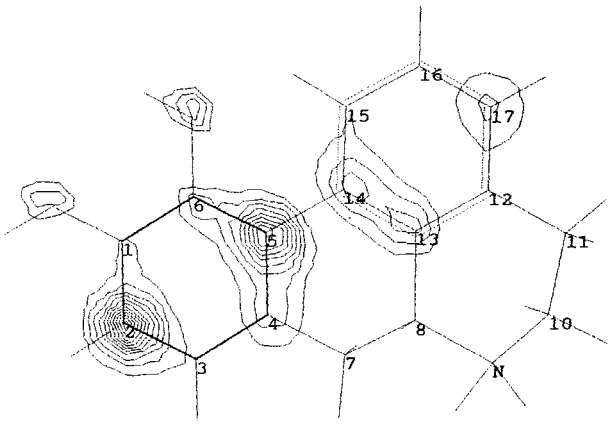

FIGURE 3. Electronic density distribution map for the HOMO-1 molecular orbital of norapomorphine. The map is located 0.5 Å above the plane containing atoms 1 –6.

we present, respectively, the electronic density distribution for the HOMO and (HOMO-1) molecular orbitals of norapomorphine (molecule 1). Figure 2 shows that the HOMO is of π character and located mainly on atoms 1 and 6. Figure 3 shows that the (HOMO-1) is also of π character but centered mainly on atoms 2 and 5. The absence of a significant electronic density of the HOMO at the level of atom 5 perfectly explains the appearance of S_5^E(HOMO-1) in Eq. (3). It is highly probable that the HOMO itself also participates in the formation of the AM–receptor complex, its contribution appearing as constant in Eq. (3). This result stresses the importance of the occupied molecular orbitals other than the HOMO in biological processes. The inclusion of an electrophilic superdelocalizability (ES) instead of an electronic density in the SAR equation gives strength to the above reasoning: Remembering that an orbital ES is simply the charge density divided by the orbital energy, we may say that ES reflects the ''distances'' from the (HOMO-1) electron density to the zero energy in the set of molecules. Then, this index is particularly well suited for comparisons within a set of molecules.

On the other hand, the examination of experimental K values shows that N-substitution affects them, but nevertheless, no related reactivity indices (of the N atom) appear in Eq. (3). Probable explanations are

(a) As affinity increases when the polarity of the substituent decreases from R = Et to R = cyPrMe, it is possible that the receptor contains a hydrophobic region that interacts with the N-substituent to favor complex formation with less polar substituents. This suggestion is consistent with the data showing that, at physiological pH, these molecules exist to a very large extent in protonated forms and also with the fact that the best equation corresponds to a low polarity medium.

(b) An electronic influence of the N-substituent exists on the N atom, but it does not appear in the results because the variation of the corresponding explanatory variable is not enough significant to be included in the regression equation.

Another conclusion of our work is that the continuum representation of electrostatic environmental effects at the CNDO/2 level is able to provide results that are in agreement with the known experimental data. As the results reported here correspond to a low-polarity medium, it would be highly desirable that future SAR reports explore media of different polarity and not present only *in vacuo* results. The only exception to this could be when the statistical indices associated to the SAR are very good (i.e., $R > 0.95$ and $s < 0.18$). We may add that, recently, it was shown again that for the case of kynurenic acid derivatives acting at the Gly/NMDA receptor site the best SAR equations were for the case of a polarizable medium [33].

If the results and conclusions reported here are correct, then quantum pharmacology has conclusively reached the status of a solid branch of applied quantum mechanics and relatively old semiempirical methods, considered obsolete by some authors, are still a valid tool. The discussion is open.

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References

1. G. J. LaHoste and J. F. Karshall, Ann. N.Y. Acad. Sci. **702**, 183 (1993).
2. P. Sokoloff, B. Giros, M. P. Martres, M. L. Bouthenet, and J. C. Schwartz, Nature **347**, 146 (1990).

3. G. Yigong, J. R. Vishnu, A. Campbell, N. S. Kula, J. R. Baldessarini, and J. L. Neumeyer, J. Med. Chem. **33**, 39 (1990).
4. F. J. de Castro, R. W. Jaeger, A. Peters, V. T. Rolfe, C. Lorenz, and R. Lauritsen, Clin. Toxicol. **12**, 65 (1978).
5. J. Braham, I. Sarova-Pinhar, and Y. Goldhammer, Br. Med. J. **3**, 768 (1979).
6. S. Lal, C. E. de la Vega, T. L. Sourkes, and H. G. Friesen, Lancet **2**, 661 (1972).
7. S. Lal and N. P. V. Nair, in *Psychoneuroendocrine Dysfunction*, N. S. Shah and A. G. Donald, Eds. (Plenum, New York, 1984), pp. 485–501.
8. P. S. Gupta, Chem. Rev. **89**, 1765 (1989).
9. M. P. Seiler, R. Markstein, M. D. Walkinshaw, and J. J. Boelsterli, Mol. Pharmacol. **35**, 643 (1989).
10. B. Testa, N. El Tayar, P. A. Carrupt. H. Van de Watelberg, G. J. Kilpatrick, P. Jenner, and C. D. Marden, J. Pharm. Pharmacol. **39**, 767 (1987).
11. D. Hoyer, D. E. Clarke, J. R. Fozard, P. R. Hartig, G. R. Martin, E. J. Mylecharana, P. R. Saxena, and P. A. Humphrey, Pharmacol. Rev. **46**, 157 (1994).
12. J. M. Walker, W. D. Bowen, F. O. Walker, R. T. Matsumoto, B. de Costa, and K. C. Rice, Pharmacol. Rev. **42**, 355 (1990).
13. J. S. Gómez-Jeria, Int. J. Quantum Chem. **23**, 1969 (1983).
14. J. S. Gómez-Jeria, in *Molecules in Physics, Chemistry and Biology*, J. Maruani, Ed. (Kluwer, Dordrecht, 1989), Vol. 4, pp. 231–251.
15. J. S. Gómez-Jeria and D. Morales-Lagos, in *QSAR in Design of Bioactive Compounds*, M. Kuchar, Ed. (J. R. Prous, Barcelona, 1984), pp. 145–173.
16. J. S. Gómez-Jeria and D. Morales-Lagos, J. Phar. Sci. **73**, 1725 (1984).
17. J. S. Gómez-Jeria,D. Morales-Lagos, B. K. Cassels, and J. C. Saavedra-Aguilar, Quantum Struct.-Act. Relat. **5**, 153 (1986).
18. J. S. Gómez-Jeria, J. I. Rodriguez-Gatica, D. Morales-Lagos, and J. C. Saavedra-Aguilar, Int. J. Quantum Chem. **28**, 421 (1986).
19. J. S. Gómez-Jeria and P. Sotomayor, J. Mol. Struct. (Theochem) **166**, 493 (1988).
20. J. S. Gómez-Jeria, C. Donoso-Espinoza, and M. Ojeda-Vergara, J. Mol. Eng. **5**, 391 (1996).
21. J. S. Gómez-Jeria, B. K. Cassels, and J. C. Saavedra-Aguilar, Eur. J. Med. Chem. **22**, 433 (1987).
22. R. Contreras and J. S. Gómez-Jeria, J. Phys. Chem. **88**, 1905 (1984).
23. J. S. Gómez-Jeria and R. Contreras, Int. J. Quantum Chem. **30**, 581 (1986).
24. J. S. Gómez-Jeria, J. Parra-Mouchet, and D. Morales-Lagos, J. Mol. Struct. (Theochem) **236**, 201 (1991).
25. J. S. Gómez-Jeria, J. Parra-Mouchet, and D. Morales-Lagos, Int. J. Quantum Chem. **40**, 299 (1991).
26. J. S. Gómez-Jeria, Il Farmaco, **40**, 299 (1985).
27. J. S. Gómez-Jeria, J. Pharm. Sci. **71**, 1423 (1982).
28. B. W. Clare, J. Med. Chem. **33**, 687 (1990).
29. K. Fukui, T. Yonezawa, C. Nagata, and N. Shingu, J. Chem. Phys. **22**, 1433 (1954).
30. K. Fukui, T. Yonezawa, and C. Nagata, Bull. Chem. Soc. Jpn. **27**, 423 (1954).
31. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions* (Wiley, London, 1976).
32. D. T. Manallack and P. M. Beart, J. Pharm. Pharmacol. **40**, 422 (1988).
33. L. Lagos-Arancibia, Thesis (Faculty of Chemical and Pharmaceutical Sciences, University of Chile, 1995).