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QUANTUM CHEMICAL STUDY OF ELECTRONIC STRUCTURE AND RECEPTOR BINDING IN OPIATES.

J.S.GOMEZ-JERIA and P.SOTOMAYOR

Department of Chemistry, Faculty of Sciences, University of Chile, P.O.Box 653, Santiago (Chile).

SUMMARY

A Quantitative Structure-Activity Relationship study for a group of opiates interacting with the mu receptor was carried out. The study consisted in searching a relationship between the drug-receptor equilibrium constant and steric/electronic structure factors. Several equations were obtained and analyzed. It is possible to conclude from this study that if all the experimental values correspond only to the interaction with the mu receptor, then the hypothesis of a common skeleton interacting with the mu receptor cannot be supported.

INTRODUCTION

In vivo and in vitro experiments have shown the necessity to postulate the existence of several opiate receptors (ref.1 and 2). The receptors have been termed mu, delta and kappa. Also, the existence of additional opiate receptors has been proposed (ref.3 and 4). The mu receptor, subject of this study, has been associated with analgesia, bradycardia, miosis, respiratory deceleration and indifference. Its prototypic agonist is morphine.

In the pharmacodynamic phase of drug action, the drug-receptor (DR) interaction in the target tissue is the first step. In the case of opiates, a large amount of experimental drug-receptor(s) equilibrium constants is available in the form of K or IC_{50} values.

Given the great importance of opiates in Medicine, we have undertaken a Quantitative Structure-Activity Relationship (QSAR) study in order to get a deeper insight into the mechanism by which these molecules interact with the mu receptor. In this paper, we present results concerning the analysis of the hypothesis stating that all the opiates have a common set of atoms that interact with the receptor. This set is called the common skeleton.

METHODS, MODELS AND CALCULATIONS.

For a 1:1 stoichiometry in the formation of the drug-receptor complex, it has been shown that the equilibrium constant, K, can be written as (ref. 5 and 6):

$$\log K = a + \sum_s \sum_{k \epsilon s} b_{k,s} m_{k,s} R^2_{k,s} + \sum_p \{ e_p Q_p + f^E_p + g_p S^N_p \} +$$

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$$+\sum_{p}\sum_{m=z}^{occ}\{h_p(m)D_p(m)+j_p(m)S_p^E(m)\}+\sum_{p}\sum_{m'=v}\{r_p(m')D_p(m')+t_pS_p^N(m')\} \qquad (1)$$

where a,b,e,f,g,h,j,r and t are constants, $S_p^E(m)$, $S_p^N(m')$ and $D_p(m)$ are, respectively, the Orbital Electrophilic Superdelocalizability (ESD) of Molecular Orbital (MO) m at atom p, the Orbital Nucleophilic Superdelocalizability (NSD) of MO m' at atom p, and the Orbital Electron Density (ED) of MO m at atom p. S_p^E, S_p^N and Q_p are, respectively, the atomic total ESD, the atomic total NSD and the net charge of atom p. The summation on m includes a group of MO's close to the HOMO (Highest Occupied Molecular Orbital) and the HOMO itself. The summation on m' includes the LEMO (Lowest Empty Molecular Orbital) and a group of low-lying virtual MO's. Finally, m_k and R_k are, respectively, the mass of atom k and its distance to a given coordinate system (ref.7). The summation on s is over the different substituents and the summation on k is over the atoms belonging to the s-th substituent. This term allows the separate analysis of the geometrical features of the substituents which may be important in the DR interaction.

Eq.(1) corresponds to a model-based equation that must have solution if the model describes correctly the physical situation (ref.8). The application of this method to a QSAR study on tryptamines has given excellent results (ref.9).

The relevant factors of Eq.1 for the case analyzed here are obtained by using Multiple Regression Analysis with K as the dependent variable. The chosen compounds for this study are displayed in Table I. The experimental values were taken from the literature (ref. 10-13), and since they are in the form of IC_{50} values, we transformed them to more reliable numbers (ref.14). Here, we have assumed that all the IC_{50} values were measured in the same experimental conditions (ref.10), and that the radioligand and the opiates analyzed here bind only to the mu receptor.

The quantum-chemical reactivity indices of Eq.(1) were calculated with the Molecular Orbital Theory at the CNDO/2 level, in spite of the fact that some problems may appear in the calculation of the NSD's (ref.15). To estimate the the steric factor, we employed different coordinate systems that are discussed in the next section.

RESULTS AND DISCUSSION

To test the common skeleton hypothesis, we included in the Multiple Regression Analysis only the parameters associated to the atoms marked 1 to 12 in Fig.1. Also, we employed the following different groups of molecules: I (all the molecules), II(molecules 1-9), III(molecules 13-19), IV(molecules 20-28), V(molecules 1-9,13-19), VI(molecules 10-19), VII(molecules 1-12), VIII(mo-

lecules 1-19), IX(molecules 10-12,20-28), X(molecules 1-9,20-28), and XI(molecules 13-19,20-28).

Groups I, IV to VI and VIII to XI produced regression equations having standard deviation (SD) values higher than 0.34, therefore we shall not discuss these results but, for comparison purposes we present in Table 1 the calculated IC_{50} values for Group I (all the other results are available on request).

For the other molecular groups, the best equations we found, considering all aspects of statistical analysis, are:

For Group II (Benzomorphanes):

$$\log (0.294\ IC_{50}-0.0147)= -91.31+347.99D_4(HOMO-1)+0.16\ S^N_{12} + 0.28\ T_8(2) \qquad (2)$$

with R=0.90 (96%), SD=0.11 and F(3,5)=38.67 ($p<0.0005$). The Student t test values are: $D_4(HOMO-1)=3.59$ ($p<0.005$), $S^N_{12}= 7.65$ ($p<0.0005$) and $T_8(2)=4.36$ ($p<0.005$).

For Group III (Morphines):

$$\log(0.294\ IC_{50}-0.0147)= 3.88 -91.52\ Q_4 -1197.84\ D_7(LEMO) + 0.02\ T_2(4) \qquad (3)$$

with R=0.99 (98%), SD=0.21 and F(3,3)= 85.34 ($p<0.0005$). The Student t test values are: $Q_4= -8.63$ ($p<0.0005$), $D_7(LEMO)= -5.25$ ($p<0.0005$) and $T_2(4)= 10.63$ ($p<0.0005$).

For Group VII (Benzomorphanes plus Morphinanes):

$$\log(0.294\ IC_{50}-0.0147)= -17.44 + 864.87\ D_3(LEMO) + 0.15\ S^N_7 - 4.88\ D_{10}(LEMO) +$$

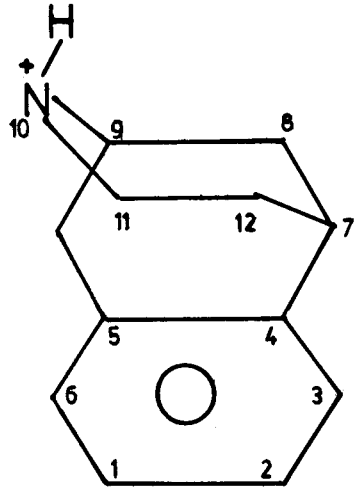

Figure 1. Common skeleton for the opiates showing the atom numbering.

TABLE 1.
Experimental and theoretical IC_{50}[a].

	Molecule	Exp. IC_{50}	A[b]	B[c]	C[d]	D[e]
1.	Normetazocine	50.0	12.2	35.1	----	53.9
2.	N-methyl-NMZ	9.0	5.5	5.7	----	6.7
3.	N-ethyl-NMZ	20.0	3.9	13.2	----	19.1
4.	N-propyl-NMZ	5.0	4.0	5.6	----	10.7
5.	N-butyl-NMZ	8.0	5.4	5.1	----	11.5
6.	N-amyl-NMZ	10.0	8.4	6.2	----	11.7
7.	N-hexyl-NMZ	10.0	15.1	8.2	----	12.0
8.	N-CNE-NMZ	3.0	11.6	2.6	----	4.0
9.	6-methyl-8-OH-BM	40.0	26.2	35.6	----	50.3
10.	3-OH-N-methyl-MO	0.7	0.4	----	----	1.4
11.	3-OH-N-CNE-MO	1.5	2.4	----	----	1.3
12.	3-OH-N-CNM-MO	7.0	0.8	----	----	3.4
13.	Morphine	3.0	1.7	----	3.5	----
14.	3-deoxymorphine	100.0	73.6	----	101.1	----
15.	Codeine	800.0	150.7	----	487.3	----
16.	N-CNE-norcodeine	700.0	423.5	----	1087.3	----
17.	N-CNE-NM	20.0	4.3	----	12.6	----
18.	N-allyl-NM	1.5	1.5	----	2.0	----
19.	6-deoxy-DHM	0.6	0.7	----	0.4	----
20.	3-deoxy-DHME	20.0	20.4	----	----	----
21.	DHME	1.0	2.1	----	----	----
22.	Oxymorphone	0.25	1.1	----	----	----
23.	N-CNE-noroxymorphone	60.0	3.4	----	----	----
24.	3-deoxy-DHM	90.0	49.2	----	----	----
25.	3,6-dideoxy-DHM	10.0	27.1	----	----	----
26.	3-deoxy-DHNM	60.0	96.6	----	----	----
27.	N-allyl-3-deoxy-DHM	100.0	50.4	----	----	----
28.	DHM	3.0	1.9	----	----	----

a. Abbreviations : NMZ=normetazocine, DHM=dihydromorphine, DHME=dihydromorphinone, DHNM=dihydronormorphine, MO=morphinan, NM=normorphine, BM=benzonorphane, OH=hydroxy, CNM=cyanomethyl, CNE=cyanoethyl.

b. Calculated IC_{50} for group I., c. With Eqn.(2)., d. With eqn.(3)., e. With eqn.(4).

$$219.15\ Q_{11} \qquad (4)$$

with R=0.94 (88.4%), SD=0.22 and F(4,7)=16.8 ($p<0.0005$). The Student t test values are: D_3(LEMO)=2.79 ($p<0.01$), S_7^N= 2.80 ($p<0.01$), D_{10}(LEMO)= -2.09 ($p\sim 0.025$) and Q_{11}= 5.33 ($p<0.0005$).

Inspection of Eq.(2) suggests the following tentative hypothesis:

1. There is a negative center in the mu receptor to interact with atom 12.

2. Considering that $T_8(2)$ is calculated in the molecular center of mass, we think that the appearance of this term is hindering a more subtle effect like the influence of the methyl group located at C-7 that was not included in the statistical analysis.

3. The appearance of D_4(HOMO-1) suggests the existence of a positive or electron-deficient center in the receptor.

Equation 3 also suggests that the receptor has a negative center located near C-12 or C-7 and an electron-deficient center close to C-4. The appearance of T_2 indicates that the steric effect of the C-2 substituent influences the IC_{50} value by affecting the number of molecules reaching the correct position to interact with the receptor.

Equation 4 has only one relevant reactivity index: Q_{11} which also plays in favour of the existence of a negative center in the receptor. Given the low values of the Student test for the other reactivity indices, no more reasonable conclusions can be reached.

The following general conclusions can be drawn from this work:

1. The electron-deficient center near C-4 may be identified as a part of the aromatic binding site in the opiate receptor model of Gero (ref. 16).

2. Even though the benzomorphanes exhibit different pharmacological characteristics, equation 2 seems to well describe their interaction with the mu receptor.

3. Since an unique equation for the whole group of molecules was not obtained, the hypothesis of a common skeleton interacting with the mu receptor cannot be supported.

It seems necessary to carry out the following extensions of this work:

1. A separate statistical analysis of both agonists and antagonists.

2. To employ the Kolb model (ref. 17) to analyze the possibility of different conformations of the N-substituent.

3. To include in the statistical analysis the possibility that other parts than the common skeleton interact with the mu receptor (ref.16 and 17).

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