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Electrostatic Potential Images of Drugs Targetting Dopamine Receptors

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The electrostatic potentials of five drugs targetting dopamine receptors were calculated on the molecular surface, or the solvent-accessible surface, using Cartesian coordinates and Mulliken net atomic charges obtained by the use of semi-empirical molecular orbital method, modified neglect of diatomic overlap. All of these electrostatic potential images, which were represented by color-coded graphics, showed the interesting feature that a positive potential region exists on one side of the molecular surface. This may reflect the specific orientation of the drug molecules for binding to dopamine receptors, which presumably show electrostatic and topographic complementarity.

Keywords——electrostatic potential; dopamine receptor; molecular surface; Mulliken net atomic charge; molecular orbital calculation; positive potential region

The electrostatic potential map of drugs at the molecular surface or the solvent-accessible surface[1] can provide useful information about the orientation of drugs to their receptor, and also about the nature of the binding site in the receptor on the basis of electrostatic and topographic complementarity in receptor-drug interactions.

We calculated the electrostatic potentials at the molecular surface of five drugs targetting the receptors for the central neurotransmitter, dopamine, (including D_1 and D_2 receptors[2]). These drugs, shown in Fig. 2, are phenylalkylamines and have a semi-rigid partial structure, so it is unlikely that large differences exist between the free and receptor-bound structures.

The results of these calculations were displayed with a color-graphics facility. Color-coded computer graphics representation of molecular surfaces[3] and the electrostatic potential surfaces[4] has been done at the University of California (San Francisco) Computer Graphics Laboratory, and we applied this representation using a micro-computer (NEC PC-9801) with the display program ESPFACE (written in N88-BASIC).

Methods

At van der Waals distances and beyond, the simple classical formula reproduces the quantum mechanically calculated electrostatic potential quite well.[5-7] The classical formula for the electrostatic potential at a point x, $V(x)$, for a system of charges q_i at points r_i in a vacuum is given by;

$$V(x)=\sum_i q_i/|r_i-x|$$

We used Mulliken net atomic charges obtained by a semi-empirical molecular orbital method, MNDO (modified neglect of diatomic overlap)[8] to represent q_i.

The coordinates of dopamine were optimized by MNDO and those of apomorphine and isobutaclamol were optimized by a molecular mechanics program MMI.[9] The coordinates of all atoms of octoclothepin and non-hydrogen atoms of haloperidol were obtained from an X-ray crystallographic data base, XDC, and hydrogen atoms of haloperidol were optimized by MNDO. The above calculations were performed on a HITAC M280H computer at the Computer Center of the University of Tokyo.

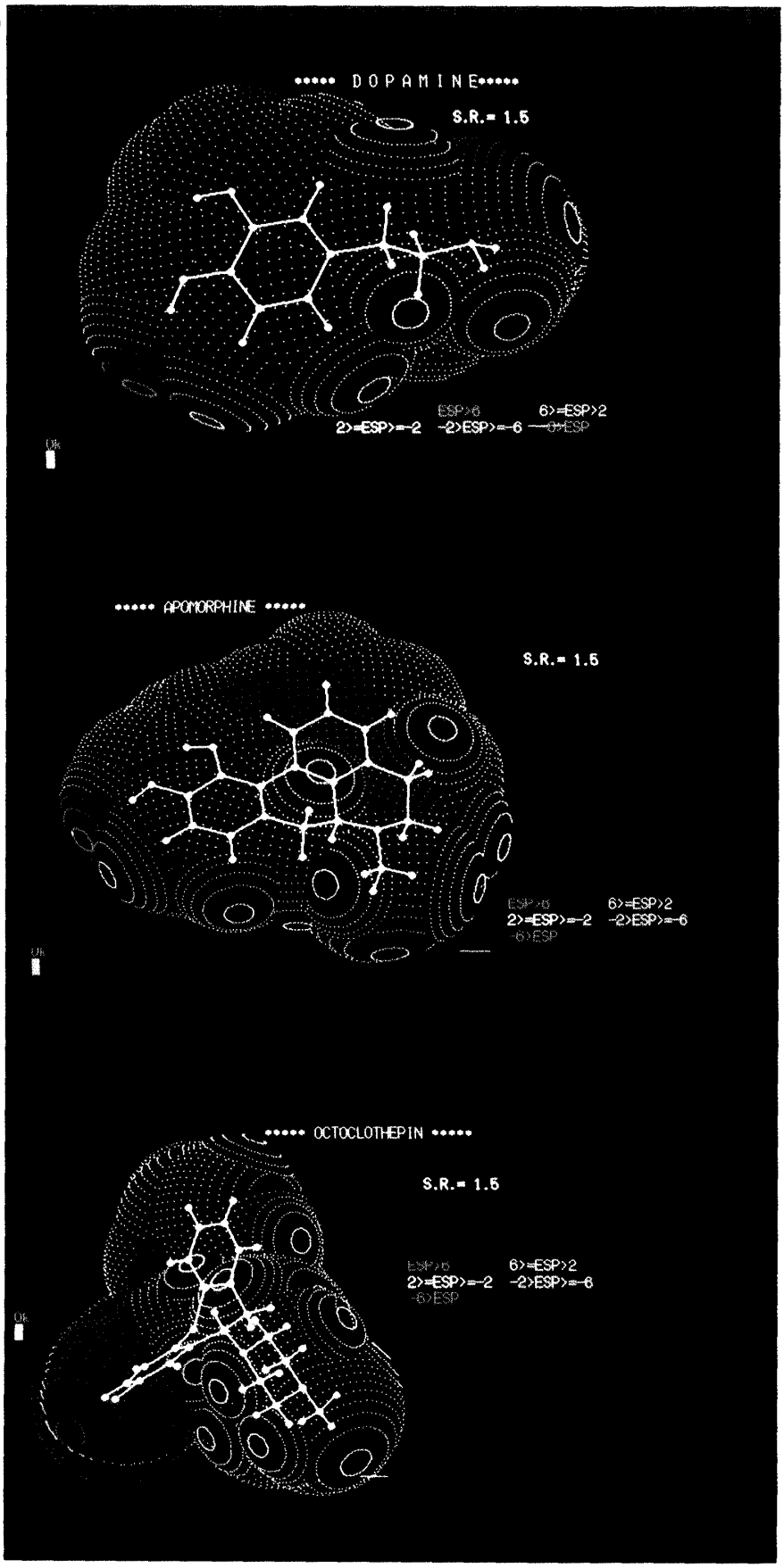

Fig. 1

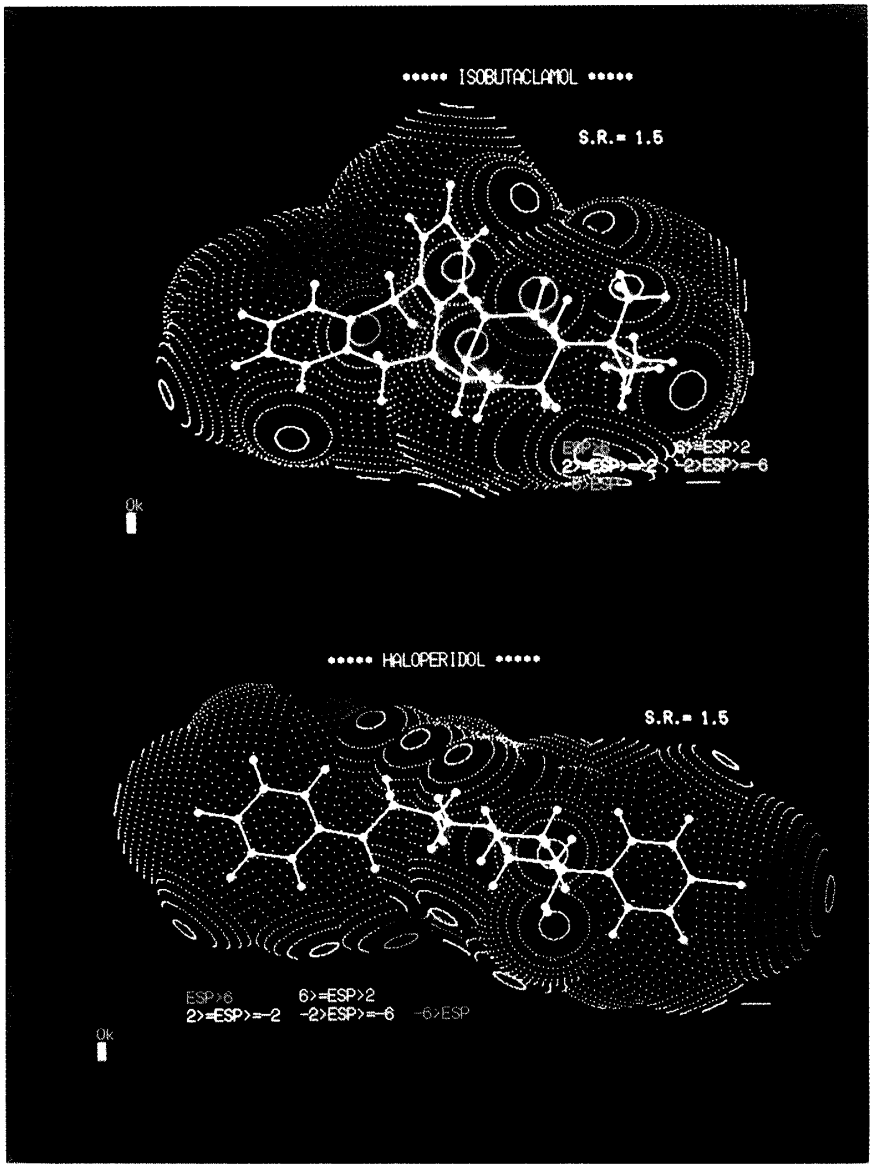

Fig. 1. Electrostatic Potential (ESP) Surfaces of Five Drugs Targetting Dopamine Receptors

(a), dopamine; (b), apomorphine; (c), octoclothepin; (d), isobutaclamol; (e), haloperidol.
Red dot, $6 < ESP$ (kcal/mol).
Pink dot, $2 < ESP \leqq 6$ (kcal/mol).
Yellow dot, $-2 \leqq ESP \leqq 2$ (kcal/mol).
Light blue dot, $-6 \leqq ESP < -2$ (kcal/mol).
Blue dot, $ESP < -6$ (kcal/mol).

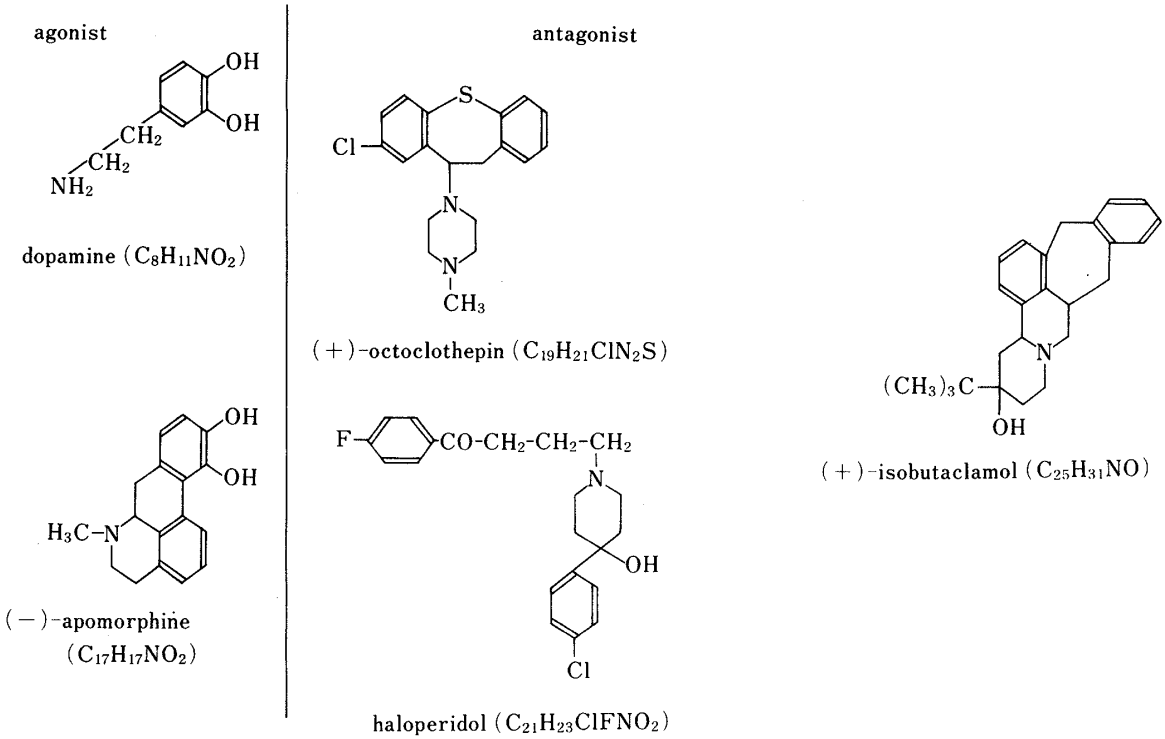

Fig. 2. Agonists and Antagonists of Dopamine Receptors

TABLE I. van der Waals Radii (Å)

C	1.7	F	1.4
H	1.1	Cl	1.8
N	1.5	Br	1.9
O	1.4	I	2.1
S	1.8	Solvent	1.5

We used 1.5 Å as the radius of the solvent sphere. The van der Waals radii of atoms used in the calculations are listed in Table I.[10] The electrostatic potentials were calculated with the PC-9801 computer at the molecular surface, *i.e.* the surface 1.5 Å distant from a given van der Waals sphere. The surface was colored according to the level of the electrostatic potential and displayed on the cathode-ray tube.

Results and Discussion

The electrostatic potential surfaces of five drugs targetting the dopamine receptors are shown in Fig. 1 (a, dopamine; b, apomorphine; c, octoclothepin; d, isobutaclamol; e, haloperidol). A red-colored dot in Fig. 1 represents a point where the electrostatic potential (ESP) is greater than +6 kcal/mol ($6 < ESP$). Pink, yellow, light blue and blue dots indicate $2 < ESP \leqq 6$, $-2 \leqq ESP \leqq 2$, $-6 \leqq ESP < -2$ and $ESP < -6$, respectively.

All of the electrostatic potential images in Fig. 1 show the interesting feature that the molecular surfaces have a positive potential region (red or pink dots) on one side of the molecule. With regard to dopamine (a) and apomorphine (b), the absolute small potential region (yellow dots) exists perpendicularly to the catechol ring plane, on one side of which there is the positive potential region (red or pink dots; the lower part of the molecule) while on the other side there is the lone pair of the nitrogen atom. For octoclothepin (c), the absolute

small potential region (yellow dots) is perpendicular to the benzene ring (chlorine non bonding) plane and the positive potential region (pink dots) is on the right side of the molecule. For isobutaclamol (d), the upper right part of the potential surface and the direction of the lone pair of a nitrogen atom resemble those of octoclothepin, although the positive potential level of isobutaclamol is lower than that of octoclothepin. For haloperidol (e), the absolute small potential region (yellow dots) is perpendicular to the fluorobenzene ring plane and the positive potential region (red or pink dots) is on the upper side of the molecule. Whether as agonists (dopamine and apomorphine) or antagonists (octoclothepin, isobutaclamol and haloperidol), these drugs which bind with the dopamine receptor have a positive potential region on the molecular surface of the benzene ring moiety and the lone pair of the nitrogen atom is located on the opposite side to that region, although there are subtle differences in the directions of the nitrogen lone pair of these drugs.

The above common feature of the molecular potential surface suggests that the dopamine receptor has a negatively charged pocket accommodating half of the benzene ring and a site hydrogen-bonding to the nitrogen atom on the opposite side of that pocket. Of course, it is necessary to examine the molecular potential surfaces of more drugs targetting dopamine and other receptors in order to confirm this conclusion.

Micro-computers are now widely available, and the use of color-coded graphics representation is a powerful method for visualizing the nature of the molecules. This method has great potential in the longer term as a guide for drug design.

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