A Conformational Distinction between Dihydropyridine Calcium Agonists and Antagonists

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Theoretical calculations of conformational energies of dihydropyridine calcium agonists and antagonists show that there is a conformation which can be adopted by agonists which is not available to antagonists, and is achievable with difficulty by a partial agonist; on the basis of these differences a model for the receptor can be hypothesised.

Despite the wide use and study of dihydropyridine calcium antagonists, and more recently agonists, a major problem has remained unsolved: how can very similar molecules produce diametrically opposed pharmacological effects? Here we provide an explanation based on quantum chemical calculations of conformational preference. Agonists can adopt a conformation not available to antagonists. It leads to a model of the receptor capable of allowing very similar molecules to be either agonists or antagonists. Even an enantiomeric form of a single molecule may be an agonist while its mirror image is an antagonist.

Nifedipine and the related dihydropyridine (DHP) calcium antagonists (Figure 1) are well established drugs in the treatment of cardiovascular disorders.[1,2] The very similar Bay K 8644 and CGP 28 392, also shown in Figure 1, are agonists.[3,4] Despite a number of attempts,[5] no clear distinctions in terms of structure have emerged. The antagonists suppress cardiac and smooth muscle contractility by modifying calcium channel activity and have a distinct binding site which correlates well with activity.[6] Both antagonists such as nitrendipine and agonists such as Bay K 8644 bind to the same high affinity site and can replace each other competitively.[7] The two types of compound also show very similar structure–activity relationships and have very similar conformational features as judged by *X*-ray crystallography.[5] Most strikingly it has recently been shown by Hof *et al.*[8] that even stereoisomers of a single molecule can have the *R* form acting as an antagonist while the *S* enantiomer is an agonist. This provides a hint that conformation could be the origin of the distinction since conformers may be substantially different for only minor chemical changes in a molecule.

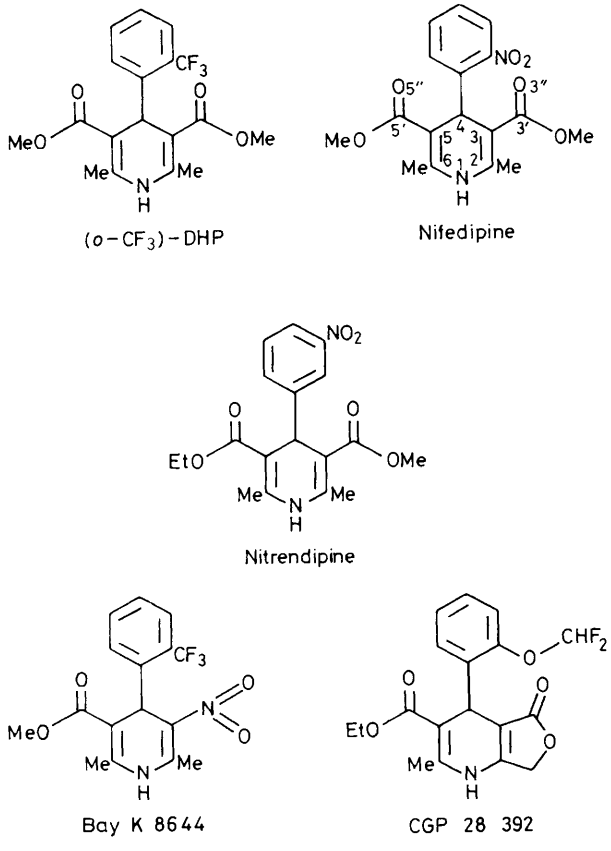

Figure 1. Structures of various dihydropyridine analogues. The numbering scheme employed is shown on the structure for nifedipine.

The importance of conformation in this area has been highlighted for dihydropyridines by the synthesis of rigid molecules which show that biological activity decreases when the 4-phenyl ring deviates from a perpendicular orientation bisecting the DHP ring.[9] Calculations on conformation have been undertaken for the compounds of Figure 1 using the molecular orbital program MOPAC.[10] The geometries were fully optimised with MNDO parameters[11] except for the orientations of the nitro groups in nitrendipine and Bay K 8644 which were kept planar to the phenyl or DHP ring as is known to be appropriate.[12] The actual conformational calculations employed a variation of parameterization of the MNDO method following recent suggestions of Dewar *et al.*[11]

The important conformational feature turns out to be the orientation of the carboxy or nitro side chains which are capable of hydrogen bonding. The range of conformations which encompass 99, 95, and 70% of the molecules at 37 °C are calculated using a statistical mechanical procedure on the computed potential surface[13] and are displayed in Figure 2 and Table 1.

The calculations suggest that in antagonists both carboxy groups are preferentially oriented in a plane which intersects the plane of the DHP ring with an angle of between 30 and 60°.

Table 1. The range of most probable conformations of carboxy or nitro side chains of dihydropyridine derivatives, φ_1 is the dihedral angle O-3'' C-3' C-3 C-2 and φ_2 is the dihedral angle O-5'' C-5' C-5 C-6 (for numbering see Figure 1).

Compound	Type of activity	Ranges of torsion angles which encompass 70% of the population of molecules at 37 °C φ_1	φ_2
(*o*-CF_3)-DHP	Antagonist	226—314°	43—134° 240—248°
Nifedipine	Antagonist	304—338°	25—52°
Nitrendipine	Mixed	307—362°	5—47°
Bay K 8644	Agonist	−29—25° 156—203°	49—110°
CGP 28 392	Agonist	179°	75—86° 109—182° 194—221°

By contrast in agonists the nitro group of Bay K 8644 is oriented in the plane of the DHP ring as is the carbonyl group of CGP 28 392 where it is also constrained in the lactone *trans* to the double bond.

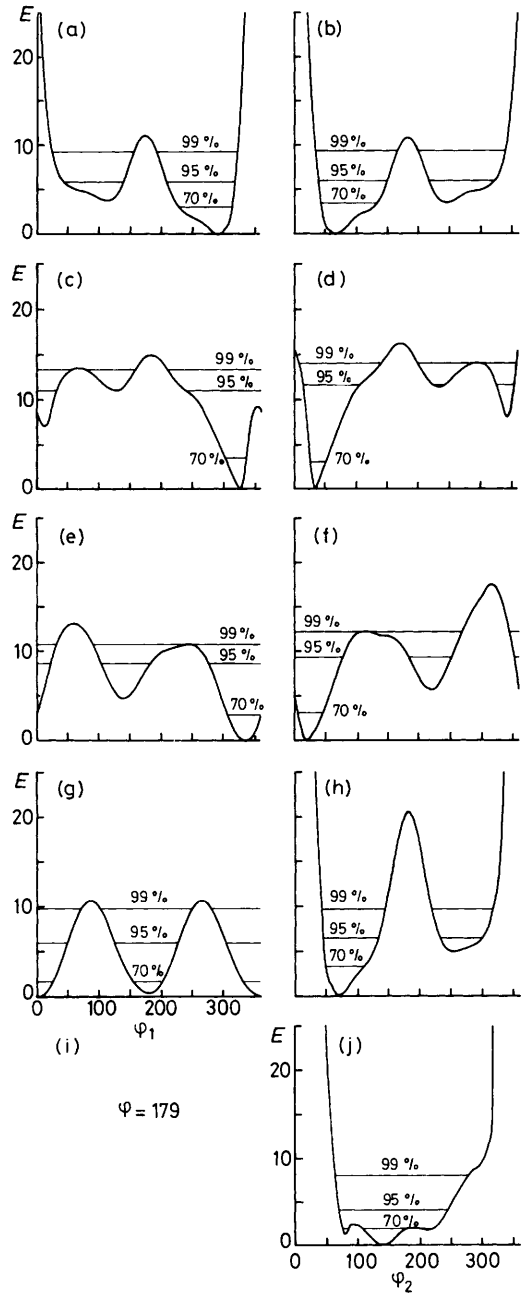

Figure 2. Conformational energy in kJ mol^{-1} as a function of rotating the side chain angle φ in the dihydropyridine analogues. The horizontal lines indicate ranges of populations of 70, 95, and 99% of molecues at 37 °C, φ_1 is the dihedral angle O-3'' C-3' C-3 C-2 and φ_2 is the dihedral angle O-5'' C-5' C-5 C-6.

(a) Rotation of the 3*R* side-chain of (*o*-CF_3)-DHP; (b) rotation of the 5*R* side-chain of (*o*-CF_3)-DHP; (c) rotation of the 3*R* side-chain of nifedipine; (d) rotation of the 5*R* side-chain of nifedipine; (e) rotation of the 3*R* side-chain of nitrendipine; (f) rotation of the 5*R* side-chain of nitrendipine; (g) rotation of the 3*R* side-chain of Bay K 8644; (h) rotation of the 5*R* side-chain of Bay K 8644; (i) indicates that the carbonyl group of CGP 28 392 is locked with $\varphi_1 = 179°$; (j) rotation of the 5*R* group of CGP 28 392. The calculations are presented for only one enantiomer but the results for the other isomer are mirror images of these diagrams.

On the basis of these differences a discriminating model for the receptor may be constructed (Figure 3). In this model the molecules are bound to the receptor at at least three positions. (a) The aromatic ring binds to a flat rigid part of the receptor. Evidence for this is the essential nature of a 4-aryl substituent of the DHP ring.[2] Deviation of the aromatic ring from the plane bisecting the DHP ring results in loss of activity.[9] (b) The N–H group of the DHP ring is a hydrogen-bond donor. Oxidation or substitution of this group results in the loss of activity.[2] (c) There is a common hydrogen-bonding site for the carboxy group of the ester in calcium antagonists; the carbonyl of the lactone and the oxygen of the nitro groups in agonists. However, owing to the different conformational preferences they induce different conformations in the receptor, resulting in distinct types of activity.

Hess *et al.*[14] have shown by measuring the calcium channel currents in single cardiac cells that there are three modes of gating behaviour even in the absence of drugs. Mode 1 has current records with brief openings; mode 0, or null mode, has no opening due to channels being unavailable, and mode 2 corresponds to long-lasting opening and very brief closing which is rarely seen. The dihydropyridine agonist Bay K 8644 enhances Ca^{2+} channel current by promoting mode 2, while the antagonist nimodipine inhibits the current by favouring[14] mode 0.

The different conformations suggested by the calculations may bind to the channels to promote different modes by stabilizing distinct conformations of the receptor appropriate in one case for long-lasting opening and in the other for permanent closing.

Although nitrendipine is predominantly an antagonist of calcium, its net effect in inhibiting the current has both antagonist and agonist components.[14] The conformational calculations can also lead to an understanding of this partial agonist behaviour since, as shown in Figure 2, although the nitrendipine carboxy group is predominantly oriented in a plane at 30° to the DHP ring (antagonist conformation), unlike nifedipine and the (*o*-CF_3)-DHP derivative, its carboxy group can be oriented in the DHP plane in a *trans* position within a 95% population limit (agonist behaviour).

Thus the conformational calculations when displayed as population diagrams lead to a distinction between agonists and antagonists of calcium on conformational grounds. They also permit the prediction of partial agonist behaviour. Both extreme classes may bind to the same receptor but induce different conformations of the macromolecule and owing to the unsymmetrical nature of the binding site even different stereosiomers of the same molecule could induce the different

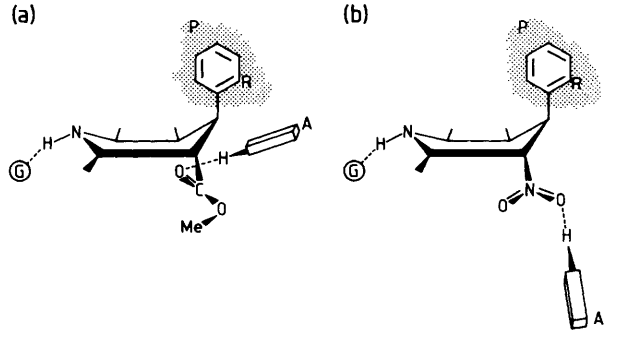

Figure 3. A model of the dihydropyridine receptor on the calcium channel. P indicates a planar portion of the receptor; G is a hydrogen bond receptor and A is a mobile hydrogen bond donor. (a) Receptor conformation which prefers binding antagonists. (b) Receptor conformation which prefers binding agonists.

conformations which lead to long-lasting opening or permanent closure of the channel.

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