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ARTICLE

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Interaction between dihydropyridines and phospholipid bilayers: a molecular dynamics simulation

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Abstract Interaction of the calcium-channel antagonist dihydropyridines (DHPs), lacidipine and nifedipine, with a phospholipid bilayer was studied using 600 ps molecular dynamic simulations. We have constructed a double layer membrane model composed of 42 dimirystoyl-phosphatidylcholine molecules. The DHP molecules locate at about 7 Å from the centre of the membrane, inducing an asymmetry in the bilayer. While lacidipine did not induce significant local perturbations as judged by the gauche-trans isomerisation rate, nifedipine significantly decreased this rate, probably by producing a local rigidity of the membrane in the vicinity of the DHP.

Key words Molecular dynamics · Lipid bilayer · Dihydropyridine · Membrane · Molecular modelling

Introduction

Biological membranes are complex systems that can be schematised as a lipid bilayer matrix bearing integral or adsorbed proteins. They are involved in the formation and maintenance of ionic and metabolic gradients essential for most cellular functions. The membrane lipids, mainly phospholipids (PL), constitute a major hydrophobic barrier to transmembrane fluxes of charged solutes. Therefore, the translocation of ions and metabolites from one side of the membrane to the other is mediated by membrane proteins constituting ion channels, carriers and pumps. Most of these transport mechanisms can be regulated by external molecules, either binding directly to the aqueous-phase moiety of the protein, or to sites located in the hydrophobic part of the molecule. The properties of the aliphatic chains and the polar head groups of the PL determine the properties of biological membranes, such as thickness, surface charge and viscosity. Consequently, these molecules may play a role in the interaction between the membrane proteins and external modulating molecules.

The α_1 subunit of the L-type voltage-gated calcium channels is pharmacologically modulated by 1,4-dihydropyridine (DHP) Ca^{2+} antagonists and agonists (Beam 1984; Gambale and Dellacasagrande 1994), which have been used as antihypertensive and antiarhythmic drugs. It has been recently proposed that DHP binds to the putative pore-forming segments in the III and IV repeats of the calcium channel α_1 subunit (Grabner et al. 1996; Peterson et al. 1996). Most DHP molecules used in therapeutics have a marked lipophilic character, being absorbed into the cytoplasmic membrane lipid-bilayer (Herbette et al. 1986; Mason et al. 1989, 1990). DHP properties, such as steric bulkiness and hydrophobicity, that determine the concentration and mobility of the DHP in the lipid phase, will determine the pharmacokinetics of these molecules (Gaviraghi 1989; Herbette et al. 1993a). Consequently, a good knowledge of the lipid-DHP interaction properties will give further information needed for the design of more efficient therapeutic agents.

We have simulated the interaction between two DHPs, nifedipine and lacididipine, and a PL-bilayer constructed with dimiristoyl-phosphatidylcholine (DMPC), whose physico-chemical parameters are representative of natural membranes. The characterisation of the PL-DHP interaction can be used to evaluate the position of these molecules within the bilayer. These studies may give information useful to understand the DHP properties that could determine the pharmacokinetics of these drugs, as well as possible effects of these molecules on the membrane structure itself. We conclude that the DHPs do not produce a macroscopic modification of the lipid membrane structure, but only local effects in the vicinity of the molecules.

Methods

We have constructed a lipid bilayer containing 42 (21 molecules per monolayer) DMPC molecules (Fig. 1A) on the

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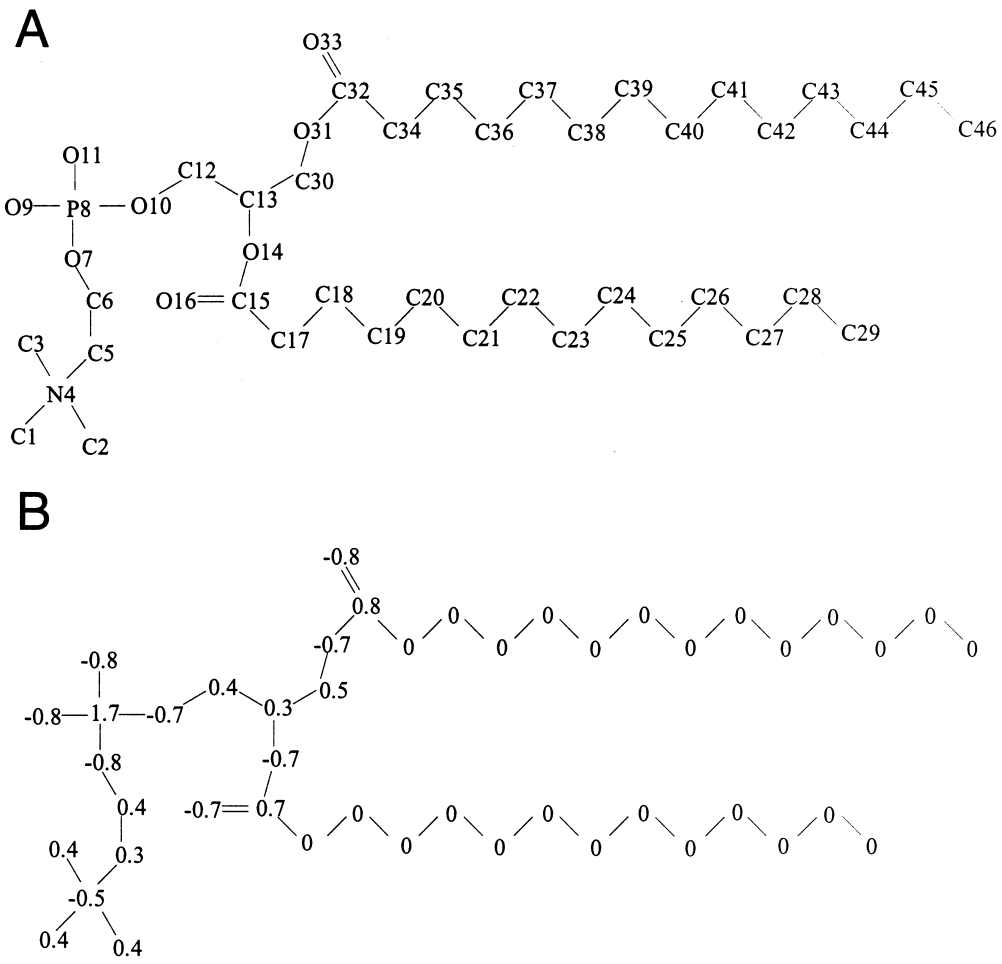
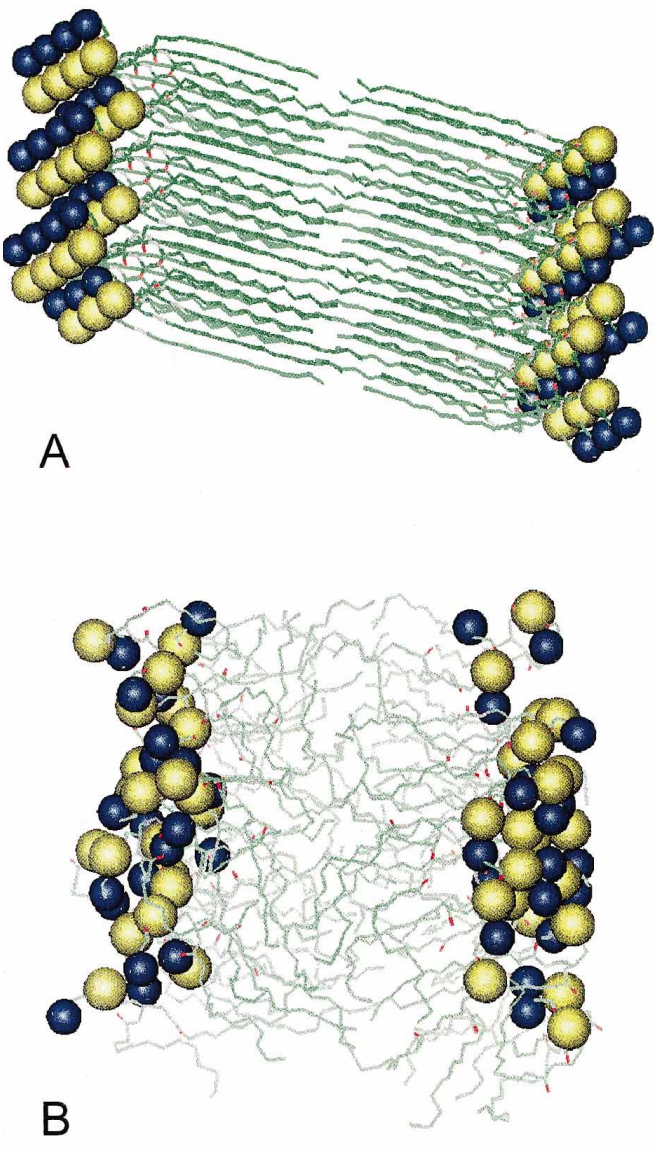


Fig. 1A, B DMPC molecule. (**A**) Atom numbering and (**B**) charge distribution of the molecule. The numbers on each atom correspond to the partial atomic charge in units of electronic charge

basis of crystallographic data (Hauser et al. 1981). The partial atomic-charges of the PL (Fig. 1B) were assigned according to Chiu et al. (1995), and were calculated using the algorithm Gaussian-92 (ab-initio calculus of molecular orbitals) and extracted from the SCF (Self Consistency Field) total electron density by Mulliken population analysis (Mulliken 1955). The initial conformation of the PL bilayer is shown in Fig. 2A. The structure was not solvated, to minimise the time required for calculations. This choice is justified by the assumption that, since DHPs are lipophilic molecules, their interactions with the PL hydrocarbon chains are presumably not significant affected by the absence of water molecules (Karplus and Petsko 1990).

The molecular dynamics simulation was done using CHARMM, a program developed for calculations of molecular energy, energy minimisation and free dynamics, using the extended atom model (Brooks et al. 1983). Hydrogen atoms are not explicity included in the calculation to reduce the degree of freedom and consequently to reduce the calculation times. A similar strategy has been previously used for simulation of PL molecules (Chiu et al. 1995; Robinson et al. 1994, 1995). A relative dielectric constant, non radius dependent, $\varepsilon_r = 2.2$, was used to reproduce the fully hydrated lipid bilayer environment. The nonbonded interactions (i.e. Van der Waals and electrostatic) were calculated at every time step. To improve the time efficiency a cut-off criterion was introduced. The interactions were weighted by a smoothing function (Brooks et al. 1983) between $C_{on} = 12$ Å and $C_{off} = 15$ Å. Beyond the C_{off} limit the long range interactions were not calculated, because the contribution of the non-bonded interaction to the total energy becomes negligible (Chiu et al. 1995).

Before molecular dynamic simulations, we minimised the energy of the lipid bilayer system. Subsequent simulation was done with a time step of 1 fs. With this time interval the potential energy changes between two successive steps are small enough to generate no significant calculation errors (Brooks et al. 1983; Karplus and Petsko 1990). The system was gradually heated to a temperature of 325 °K for 10 ps, to overcome the crystal to liquid-crystal transitions of DMPC bilayers (Ladbrooke and Chapman 1969), and then equilibrated for 40 ps. Then a completely free dynamic, with no periodic boundary conditions, was executed for 550 ps. In Fig. 2b the final configuration of this dynamic run is shown. In order to control the stability of the system during the simulation, we continuously monitored the average temperature that is related to the kinetic energy of the system, yielding a value of 324±5 °K (mean±s.d.). After this procedure, DHPs were inserted into a void of the lipid bilayer, in a position equivalent to



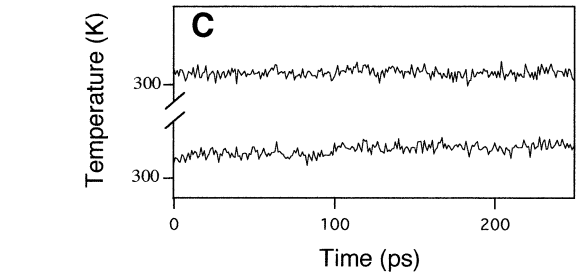


Fig. 2A–C Lipid bilayer constructed with DMPC. **A** Initial conformation of a lipid bilayer composed of 21 DMPC molecules per layer. Data were obtained from X-ray crystallography (Hauser et al. 1981). **B** Final conformation of the DMPC bilayer after 550 ps of molecular dynamics simulation. Note the increase in the degree of disorder of the system, produced by the crystal to liquid-crystal transition. Only polar heads are represented as balls; color coding: green for C, red for O, yellow for P, blue for N. Hydrogens are omitted for clarity. **C** The time course of the mean temperature of the system during the dynamic simulation is quite constant, reflecting the stability of the system

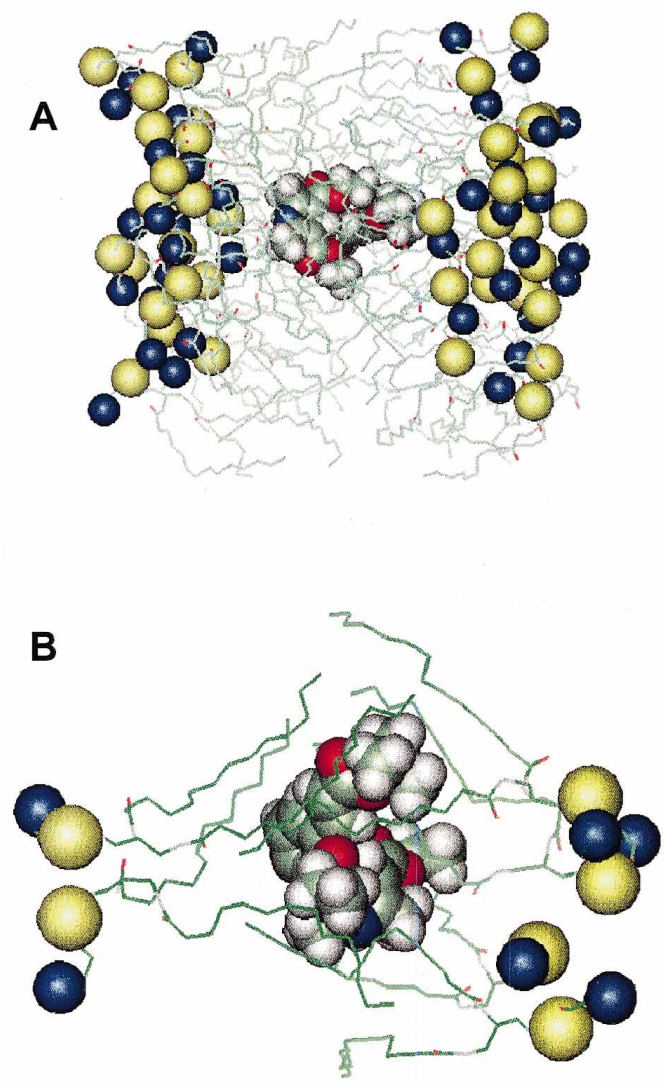


Fig. 6 A The configuration of the lipid bilayer containing nifedipine molecule after 350 ps of molecular dynamics simulation. **B** The nifedipine molecule is displayed together with the six closest PL. These PL molecules were used for the analysis of the isomerisation kinetics. DHP hydrogens are in *grey*

that estimated by X-ray diffraction (Bangalore et al. 1994; Herbette et al. 1993). The nifedipine crystallographic structure was obtained from CCDC (Cambridge, United Kingdom) and lacidipine crystallographic data was obtained from Glaxo-Wellcome Ricerche (Verona, Italy). An all-atom representation was adopted because the limited number of atoms in DHPs does not affect the calculation. The DHP partial charges were assigned using MOPAC (Stewart 1990), and are shown in Fig. 3. The energies of the nifedipine and lacidipine molecules were minimised before their insertion into the lipid bilayer. The energy of the whole system was minimised to reduce any unfavourable steric interaction. A dynamic run was executed in conditions identical to those of the control conditions (without DHP): 10 ps heating, followed by 100 ps equilibration, and 600 ps of free dynamics.

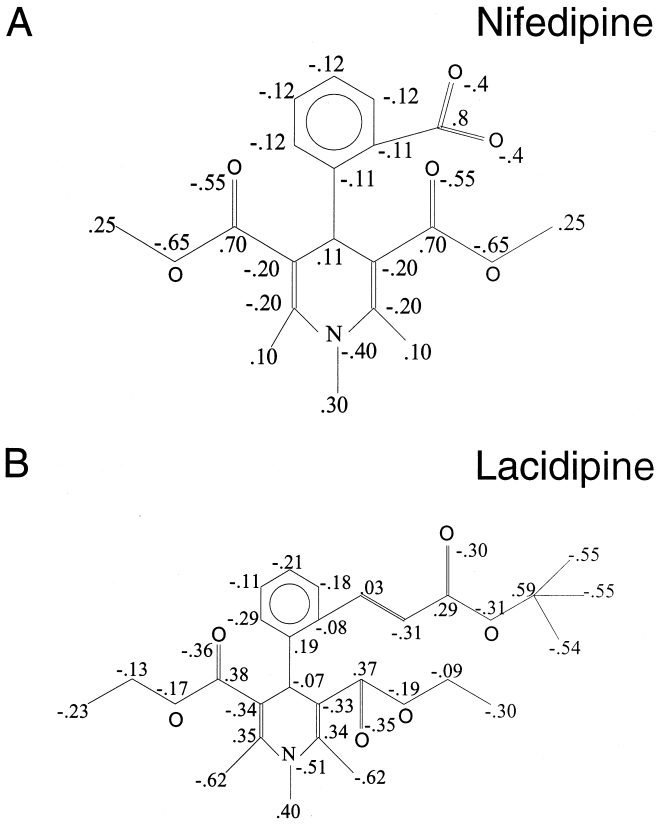


Fig. 3A, B Charge distribution calculated for the DHP molecules, (**A**) nifedipine and (**B**) lacidipine. For clarity some hydrogen atoms are not included

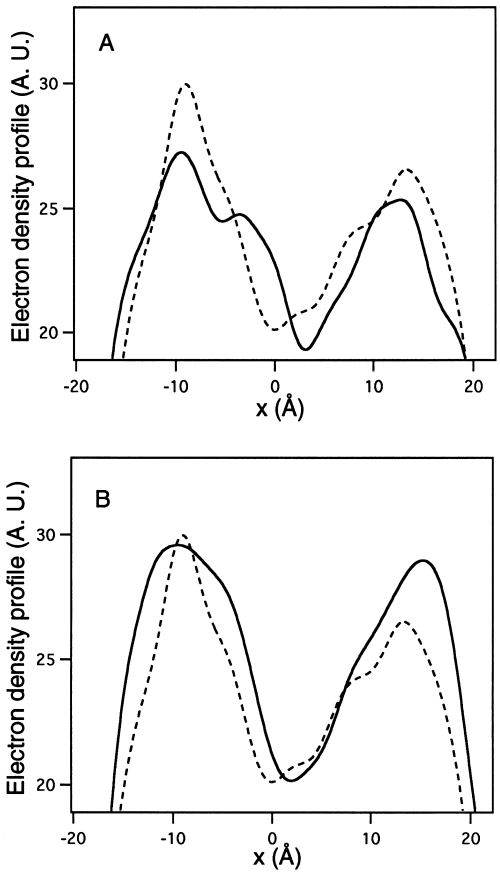


Fig. 4A, B Electronic density profile $\rho(x)$, in arbitrary units (A.U.), of the DMPC bilayer in the absence (*broken line*) and in the presence (*continuous line*) of DHPs (**A**) nifedipine and (**B**) lacidipine, calculated from the conformation of the system over the last 50 ps of the molecular dynamics simulation

All molecular modelling, including refinement of the structure, and molecular dynamics was done using the software package QUANTA (MSI, Burlington, MA) on a Risc-6000 computer (IBM 380). The analysis of data was done using QUANTA and some programs written in C. Statistical analysis and graphs were done with Sigma-Plot (Jandel Scientific, Erkrath, Germany) or Igor (Wavemetrics Inc, Lake Oswego, OR).

Results

During the execution of a dynamic molecular simulation, the temperature of the system is gradually increased from 0 °K to the final value, T_f. In the heating procedure, random velocities are assigned to each atom, according to a Gaussian distribution, with a mean value that depends on the temperature of the system. When T_f is reached, the whole system is allowed to redistribute the kinetic energy through the atom bonds, until the temperature and the structure of the system reach a steady-state (Brooks et al. 1983). This equilibration process is facilitated by a periodic adjustment of velocities appropriate to the temperature selected. At the end of the equilibration, velocities are no longer modified and the system is allowed to evolve spontaneously. If the equilibration of the system is performed properly, the temperature will not change appreciably any more, consistent with the finite number of atom in the system. As an example, in Fig. 2C the temperature of the system is plotted as a function of the conformation number (expressed in ps) during 550 ps of dynamic simulation of the DMPC bilayer, yielding a mean (±s.d.) value of 324±5 °K.

The position of the DHP molecules within the lipid bilayer and its whole organisation was evaluated from the electron density profile, $\rho(x)$. It was calculated by averaging the resulting $\rho(x)$ from the conformation obtained in 10 iterations (one every 5 ps) during the last 50 ps of each dynamic run. Each atom is weighted by its atomic number and the resulting function was smoothed. The resulting $\rho(x)$ of the simulated DMPC bilayers (broken lines in Fig. 4) has two high density peaks, coincident with the mean position of the polar head of PL, containing the high electron density phosphorus atoms, and decreases near the centre of the bilayer, as methyl groups at the end of the hy-

drocarbon chains occupy more space than methylene groups in the interior of the membrane. These observations are consistent with the $\rho(x)$ directly calculated by X-ray diffraction (Franks 1976; Levine and Wilkins 1971; Nagle and Wiener 1988). The position of the DHPs inside the lipid bilayer is revealed by a shoulder in the hydrocarbon chain region of $\rho(x)$, in agreement with the X-ray diffraction data (Herbette et al. 1993), located at 6.6 Å from the adjacent high electron density peak for nifedipine, and 5.8 Å for lacidipine (Fig. 4). The shoulder produced by lacidipine is more pronounced than that of nifedipine, in accord with the different electron density of the two DHPs. The DHPs produced a small displacement of the minimum of $\rho(x)$ by 2–3 Å towards the monolayer opposite to the DHP location (see Fig. 4B).

The average thickness of our DMPC model-bilayer measured as the phosphorous-phosphorous distance in the $\rho(x)$ was 30 ± 1 Å (mean ± s.d.). This value is slightly smaller than that experimentally measured by X-ray diffraction (Lewis and Engelman 1983), probably due to the inhomogeneity of the C14:0 experimental sample or to the presence of water molecules (ignored in our simulation), which may induce a decrease of the dipole attraction between the head groups of the two layers (Levine and Wilkins 1971). The incorporation of the DHPs into the model membrane does not significantly modify the bilayer thickness, yielding a value of 30 ± 1 Å in the presence of nifedipine and 32 ± 2 Å in the presence of lacidipine.

Eleven dihedral angles can be defined in each one of the two hydrocarbon tails (see Fig. 1). During the dynamics, each angle can assume values of 0° or ±120° corresponding respectively to trans, gauche$^+$ and gauche$^-$ conformations. In the crystallographic configuration most of the angles are in the trans conformation, because the fatty acid chains are completely extended in the gel phase (Hauser et al. 1981). Conversely, in the fluid phase many carbons turn their angles to the gauche conformation and the hydrocarbon tail presents kinks or turns. As has been derived from experimental data (Seelig and Seelig 1980) and molecular simulations (Stouch 1993) the dwell times in the trans and gauche configurations are about a few tens of ps (from 10 to 100 ps). The fraction of angles in the trans and gauche configurations gives information related to the disorder degree of the PL hydrocarbon chains. Two examples of the time course of this isomerisation are shown in Fig. 5 where C22–C25 and C26–C29 angles were monitored during 100 ps of dynamic simulation of the DMPC bilayer. In one case (C22–C25; upper panel), the angle stayed in the trans configuration for the entire simulation period, while in the second case (C26–C29; lower panel), a transition from trans to gauche$^+$ conformation, lasting about 25 ps is observed. To enhance possible differences due to the presence of DHPs we limited our analysis to the six closest PL surrounding the DHP molecule, as shown in Fig. 6.

The probability of an angle being in the trans or gauche conformation depends on its distance from the glycerol moiety (Stouch 1993), and consequently the frequency and the size of voids related to the percentage of trans angles,

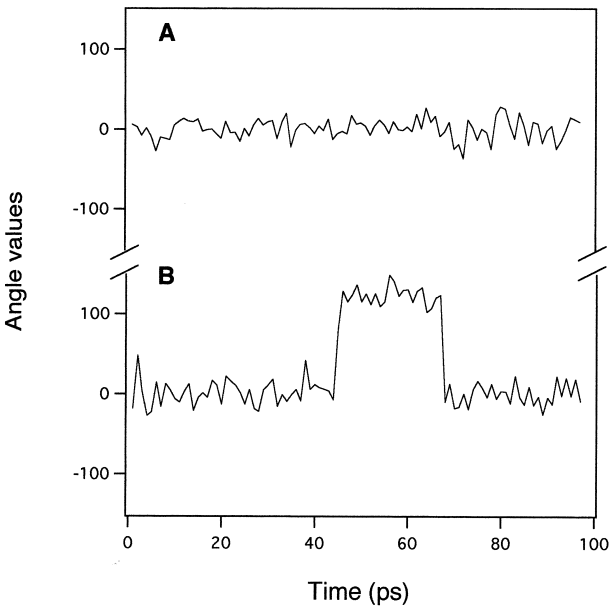


Fig. 5A, B Time course of dihedral angles formed by (**A**) C22–25 atoms and (**B**) C26–29 atoms of one PL molecule during a 100 ps simulation, in the presence of nifedipine. A trans-gauche-trans transition is observed in B

where the DHP molecule could localise, may change along the hydrocarbon chain (Dill and Flory 1980). Therefore, the membrane hydrocarbon phase was ideally divided into two parts: carbon atoms from C15 to C24 and from C32 to C41 were used to define 12 dihedral angles on the two lipid-hydrocarbon chains in proximity to the glycerol moiety, and carbon atoms from C22 to C29 and from C39 to C46 were used to define 10 dihedral angles near the centre of the membrane. Therefore, a total of 72 dihedral "glycerol" angles and 60 dihedral "methyl" angles were defined on the six PL molecules considered. We evaluated the fraction of trans conformations in the "glycerol" and in the "methyl" part of the molecules at each step during the dynamic simulation (550 ps for the lipid bilayer system and 600 ps for the lipid bilayer in the presence of DHPs). The fraction of trans conformations observed during a dynamic simulation of the model membrane, and in the presence of DHP, is presented in Table 1. The presence of each DHP changed up to a maximum of 2% the probability of an angle being in the trans or gauche configuration, and this change is not statistically significant.

The reversible isomerisation of a dihedral angle, i.e. that transition between the trans and gauche conformations, can be represent by first order kinetics (Kelly 1979):

$$\text{trans} \underset{\beta}{\overset{\alpha}{\leftrightarrow}} \text{gauche} \qquad (1)$$

where α and β are the rate constants for the transition between the two configurations. The two time constants, τ_t and τ_g, characterising the mean permanence time in the trans and gauche conformation are defined by the relations:

$$\tau_t = \frac{1}{\alpha}; \tau_g = \frac{1}{\beta} \qquad (2)$$

Table 1 Fraction of the trans conformations of the "glycerol" and "methyl" regions, evaluated during a dynamic simulation. Data correspond to simulations of the model DMPC bilayer, in the absence and in the presence of DHPs

	p_{trans} ("glycerol")	p_{trans} ("methyl")
Phospholipid	0.667±0.002	0.614±0.002
Phospholipid+nifedipine	0.660±0.002	0.612±0.002
Phospholipid+lacidipine	0.657±0.003	0.602±0.002

Table 2 Dwell times in the trans and gauche configurations, τ_t and τ_g, measured on the twelve terminal angles of the 6 PL near to the DHPs. Dwell time values were taken from the fitting of Fig. 7, ±s.e.m. The isomerisation rate, expressed as the number of transitions observed per unit time, was evaluated by counting the number of isomerisations for each angle during 550 ps of simulation

	Phospholipid	Phospholipid+ nifedipine	Phospholipid+ lacidipine
τ_t (ps)	24.4±1.0	31.8±0.7	26.7±0.8
τ_g (ps)	21.6±1.0	25.7±1.0	22.7±0.6
Isomerisation rate (ns^{-1})	46±4	37±3	42±2

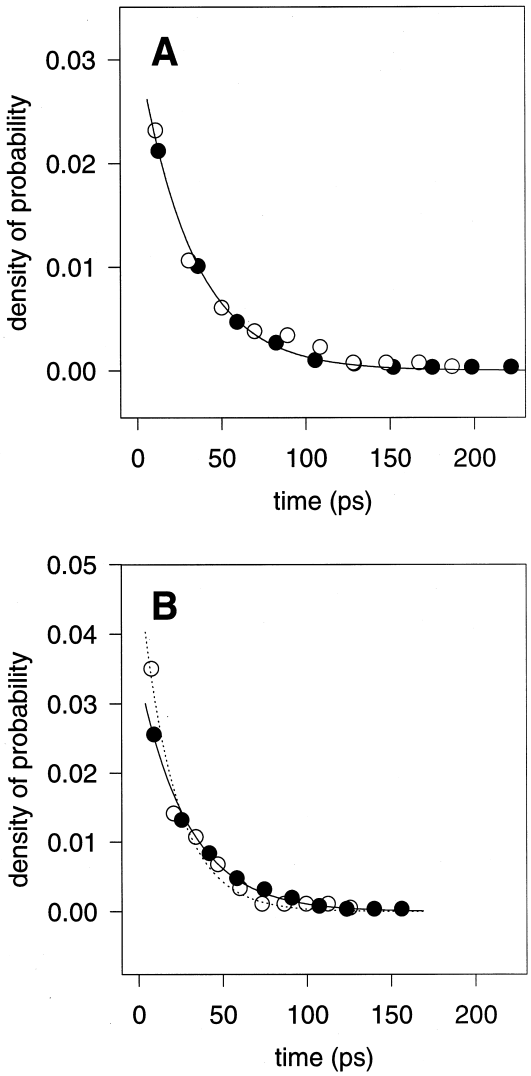


Fig. 7A, B Cumulative density probability distribution of the trans (**A**) and gauche (**B**) configurations of the angle defined by the last four carbon atoms of the six PL represented in Fig. 6. Empty circles represent the result of the analysis in the absence of DHP, and filled circles in the presence of nifedipine. *Continuous* and *dotted curves* represent the best fit of experimental data by a single exponential function (Eq. (3)). Results of the fit are described in Table 2

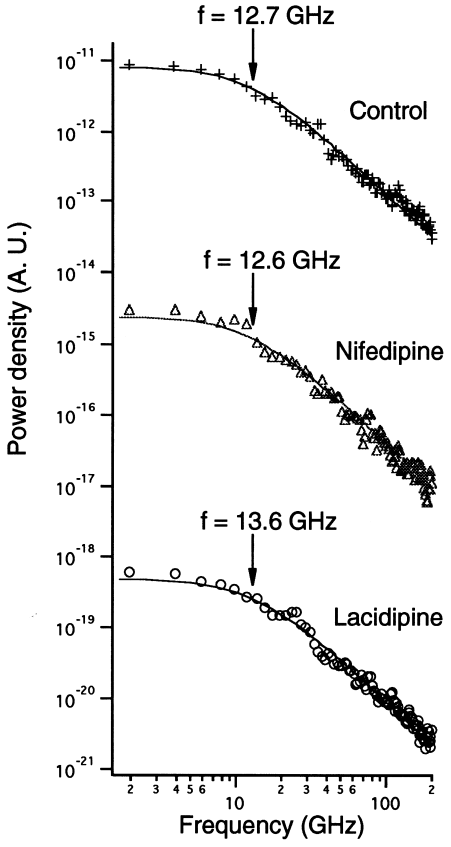


Fig. 8 The power spectral density (in arbitrary units, A.U.) of the time course of the trans-gauche transition of the terminal angles defined by the last four carbon atoms in the hydrocarbon chains of the six PL indicated in Fig. 6. Data were obtained without DHP (Control), and in the presence of nifedipine and lacidipine, as indicated in the figure. The continuous curves represent the best fit of the experimental data points by a Lorentzian distribution (Eq. 3). The corresponding cut-off frequencies, f_c, are indicated

We measured the dwell time for each configuration, trans and gauche, of the twelve terminal dihedral angles defined by C26–29 and C43–46 (in the following indicated as "terminal angles") of the six PL close to the DHP (see Fig. 6) in the absence and in the presence of DHPs. The results are shown in Fig. 7, where we present the cumulative probability density plotted against time, measured for the trans and gauche conformation, i.e. the prob-

ability function that a given angle stays in a certain configuration for a time interval longer than t. Results confirm that the gauche-trans isomerisation process is a Markovian first order kinetic process, and the cumulative probability density, $f_{t,g}(t)$, is well fitted by an exponential function:

$$f_{t,g}(t) = \frac{1}{\tau_{t,g}} e^{(-t/\tau_{t,g})} \quad (3)$$

The results of the fitting are presented in Table 2.

As a further control, we have plotted sequentially the time course of the isomerisation as a two state system (|angle| vs. time) measured in the twelve terminal angles, and then we have calculated the power spectra for each set of experimental conditions (with and without DHPs). The results are presented in Fig. 8, where the continuous line represents a fitting of the spectra with a Lorenzian function:

$$S(f) = \frac{2\pi S_0}{(1 + f/f_c)^2} \quad (3)$$

where S(f) is the power density of the signal as a function of f, S_0 is the density at f = 0 and f_c is the cut-off frequency of the signal. For first order kinetics,

$$f_c = \frac{\alpha + \beta}{2\pi} \quad (4)$$

where α and β are the rate constants of isomerisation (see eq. (1)). The values of f_c under control conditions (12.7 GHz) and in the presence of nifedipine (12.6 GHz) and lacidipine (13.6 GHz) are in good agreement with the values derived from direct measurement of the dwell times presented in Table 2, confirming the hypothesis of a Markovian first order kinetic character of the isomerisation.

Discussion

We have constructed a DMPC bilayer by molecular modelling, and compared some parameters (membrane thickness, electron density profile, percentage of trans dihedral angles, dwell time in trans or gauche configuration) with experimental data (Herbette et al. 1986; Levine and Wilkins 1971; Lewis and Engelman 1983; Mabrey and Sturtevant 1976; Mason et al. 1989) and with results obtained from simulations of similar systems (Bassolino-Klimas et al. 1993; Chiu et al. 1995). We concluded that, in spite of the limitations of the system, i.e. the lack of water molecules at the surface of the simulated membrane and the limited number of PL molecules, the model presented here reproduces quite well the general properties of a lipid bilayer. We used the crystalline conformation of the membrane as a starting point. After the transition from the crystal to the liquid-crystal phase, obtained after 550 ps of molecular dynamics, the lipid bilayer core appears disordered, because the hydrocarbon chains are not in the all-trans conformation (see Fig. 2). Moreover, the polar head groups do not appear perfectly aligned to the plane of the membrane, which confers an evident roughness at the membrane-water interface (Chiu et al. 1995).

Nifedipine and lacidipine were inserted into a void in the lipid core of the bilayer at approximately 7 Å from the centre of the bilayer, according to the position deduced from electron density profiles obtained from X-ray diffraction (Bangalore et al. 1994; Herbette et al. 1993). Consistent with the low diffusion coefficient of DHPs in the membrane phase, estimated to be $\approx 4.10^{-8}$ cm^2/s (Chester et al. 1987), we have not observed any lateral diffusion of the DHPs during the small time interval of our simulation. Also, we have not observed any significant change of the membrane thickness induced by DHP, similar to that observed using other membrane-soluble molecules, either experimentally (Mateu and Moran 1986; Mateu et al. 1997; Turner and Oldfield 1979) or from a similar dynamics simulation approach (Bassolino-Klimas et al. 1993). We have observed that at the end of the simulation lacidipine is located slightly deeper in the bilayer compared to nifedipine, and produces a distortion on the high density peak of $\rho(x)$ opposite to the location of the DHP molecule. This fact may be partially explained by the bulkiness of lacidipine, and the tendency of this molecule to attract PL molecules (see Fig. 6). On the other hand, there is a diffusion of PL normal to the plane of the membrane that produces the roughness of the membrane surface mentioned above. This effect could be locally amplified near the lacidipine molecule, particularly under the simulation conditions used here, where the constraints introduced by the external water molecules and the boundary periodic conditions are lacking.

The analysis of the effect of the DHP on the isomerisation of the fatty acid chains of the lipid bilayer was done by measuring the fraction of hydrocarbon-chain dihedral angles in the trans and gauche conformation. The results of the analysis on these two groups of angles are reported in Table 1, where data corresponding the local effects of DHP were used to amplify the local effect of the DHP. The invariance of the ratio of gauche-trans configuration, together with that of the membrane thickness, suggests that DHPs find sufficient space in the middle of the bilayer in which to position themselves and do not appreciably modify the mean organisation of the hydrophobic chains (Herbette et al. 1986).

Evidence have been reported that the fatty acid chains of a lipid bilayer should not be treated as a homogeneous hydrocarbon bulk phase. Studies concerning the diffusion of small molecules through lipid bilayer membranes suggest that the solute molecule are located in voids formed by the hydrocarbon chains, that could serve as gates between voids. When an isomerisation occurs and the lipid chain changes its configuration, the solute can move towards adjacent holes (Bassolino-Klimas et al. 1993). Hence, more frequent isomerisations occur when the diffusion of the solute is higher. Since the isomerisation rate of the terminal angles of the hydrocarbon chains is larger and since they should be particularly sensitive to the presence of drugs positioned in the vicinity of the centre of the bilayer, we have measured the dwell time on the trans (or gauche) state, τ_t, (τ_g) of the terminal angles for the PL surrounding the DHP molecules (Table 2). The dwell times reported in Table 2 are consistent with the isomerisation

rate derived directly from the raw data. The estimated value of the isomerisation rate in the absence of DHP, 46 ± 4 ns^{-1}, was not statistically different from the value of 42 ± 2 ns^{-1}, estimated in the presence of lacidipine. In contrast, nifedipine causes a decrease of the isomerisation rate, to about 37 ± 3 ns^{-1}. Thus we conclude that in the presence of lacidipine the membrane fluidity in the vicinity of the DHP does not change appreciably, while nifedipine induce a sort of rigidity in the vicinity of the ends of the chains. This result suggests that the lateral diffusion rate of the two DHPs could be slightly different.

In conclusion, microscopic properties, revealed by electron density profiles and isomerisation rates of acid chain terminal angles, suggest modification of membrane local properties that are specific for the two DHPs examined. Further investigations in a more complete system, probably containing natural fluidifying molecules, such as cholesterol, will give insight into pharmacological effects of the DHPs on cellular membranes.

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