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COMMENTARY

MEMBRANE INTERACTION OF CALCIUM CHANNEL ANTAGONISTS MODULATED BY CHOLESTEROL

IMPLICATIONS FOR DRUG ACTIVITY

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Overview

The plasma membrane is a highly specialized structure which regulates and maintains the internal milieu of the cell. The membrane lipid bilayer forms an amphipathic environment for protein molecules which mediate various functions of the cell. A subset of these membrane proteins serves as receptors to which a ligand (synthetic or natural) binds to initiate its effect on the cell.

Certain hydrophobic and amphiphilic drugs may necessarily partition into the lipid bilayer of the membrane prior to protein receptor binding. The membrane lipid bilayer may assist successful drug–receptor recognition and binding by optimizing the location, orientation and concentration of the drug molecule with respect to a hydrophobic receptor site. This "membrane bilayer pathway" has been described for local anesthetics [1], general anesthetics [2], 1,4-dihydropyridine (DHP)† calcium channel antagonists [3], and others. In this article, evidence will be given to support the concept that membrane lipid composition changes (e.g. cholesterol content) substantially modulate the partitioning of highly lipophilic calcium channel antagonists to both model and native membranes. These findings may have broad implications for the bioavailability and pharmacological activity of drug molecules which interact with the membrane lipid bilayer as part of their overall mechanism of action.

Pharmacological role of DHP calcium channel antagonists

DHP calcium channel antagonists (see Fig. 1) are potent modulators of the contraction initiation mechanisms of cardiac and smooth muscle by regulating the influx of calcium across the plasma membrane (Fig. 1). The binding site for DHPs is the voltage-sensitive calcium channel (VSCC) found in the plasma membrane of these myocytes. DHPs can both activate and inhibit VSCC in a highly stereoselective, saturable, and reversible manner [4]. The other two chemical groups of calcium channel antagonists are phenylalkyamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem) which also bind to the VSCC with high affinity and can allosterically modulate the binding of the DHPs.

Structural properties of the membrane bound voltage-sensitive calcium channel and the DHP receptor site

The VSCC is a complex of five subunit proteins. The central core of the VSCC is the α_1 subunit which can function alone as a voltage-sensitive channel when expressed in certain cell lines [5, 6]. The mRNA encoding the α_1 subunit predicts a polypeptide of 212 kDa having four highly conserved regions each composed of six putative α-helical transmembrane segments [7]. The other subunits of VSCC are the β subunit of 55 kDa, a glycosylated transmembrane γ subunit of 30 kDa, and a disulfide-linked glycoprotein complex of α_2 (143 kDa) and δ (27 kDa) [5, 6].

Covalent labeling of skeletal muscle VSCC with DHP photoaffinity probes demonstrates that the α_1 subunit constitutes the binding site for DHPs [8–12]. To further resolve the location of the DHP receptor, site-directed anti-peptide antibodies were used in conjunction with α_1 subunits labeled with DHP analogs. The results of these studies indicate that amino acid sequences associated with two transmembrane helices near the extracellular membrane surface of the α_1 subunit participate in the DHP binding site. Moreover, the DHP receptor subunit was heavily labeled by a hydrophobic photoaffinity probe, consistent with a possible intramembrane binding site [13].

Role of the membrane lipid bilayer in DHP receptor recognition and binding

Rhodes and coworkers [3] have described a membrane pathway for the binding of DHPs to the VSCC. This two-step pathway postulates that specific binding of DHPs to a site on the VSCC is preceded by partitioning into and diffusion through the plasma membrane lipid bilayer of the target cell (e.g. cardiac, smooth muscle myocytes), as illustrated in Fig. 2 for an amphipathic drug such as the DHPs.

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† Abbreviations: DHP, 1,4-dihydropyridine; VSCC, voltage-sensitive calcium channel; FC, free cholesterol; PL, phospholipid; ASM, arterial smooth muscle; PC, phosphatidylcholine; BCPC, bovine cardiac phosphatidylcholine; DOPC, dioleoyl phosphatidylcholine; and LSR, light sarcoplasmic reticulum.

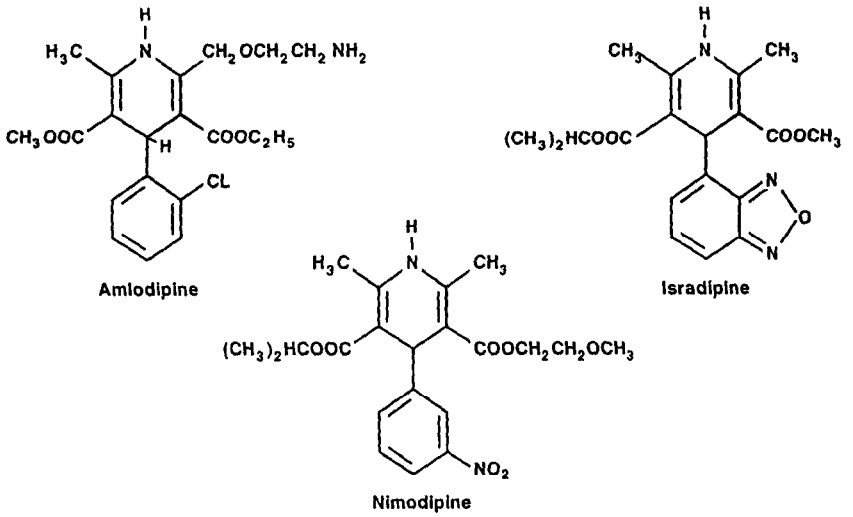

Fig. 1. Structural formulas for three 1,4-dihydropyridine calcium channel antagonists. The amine group of amlopidine is charged at physiological pH ($pK_a = 9.02$). Nimodipine and isradipine (also PN 200–110) are unchanged at physiological pH.

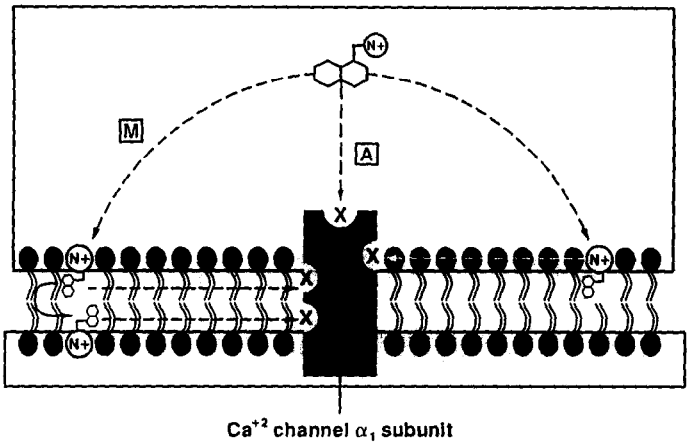

Fig. 2. Schematic diagram of the molecular pathway by which an amphiphilic drug molecule may reach its membrane bound receptor site: a single-step aqueous pathway (A) or a two-step membrane pathway (M) as described in the text. According to the membrane pathway, a drug may enter the bulk lipid phase on the side of the membrane to which it was added and diffuse laterally to a hydrophobic (left side) or hydrophilic (right side) binding site. Alternatively, a drug could diffuse or flip-flop across the bilayer to gain access to the opposite side of the membrane. (Reproduced from Ref. 3 with permission of the authors and the copyright holder The American Society for Pharmacology and Experimental Therapeutics.)

For a diffusion-limited binding rate, two-dimensional transport through the membrane bilayer has a substantial rate advantage if the ligand has an appropriate location and orientation for binding to the receptor site [14]. This pathway would be especially favorable for DHPs as they have both a low receptor site density in the plasma membrane [15] and have binding characteristics which are highly specific and stereoselective. By imposing certain molecular constraints on DHPs, the membrane lipid bilayer could significantly increase the probability of successful receptor site recognition and binding.

There are several lines of experimental support for a DHP calcium channel antagonist "membrane pathway" for receptor binding. The DHPs have high membrane-based partition coefficients ($K_{P[mem]} > 10^3$) and occupy discrete, equilibrium positions in the membrane lipid bilayer [16–19]. The membrane may orient and concentrate the DHP with respect to a receptor site. The concentration of drug in the

Table 1. Drug partition coefficients into DOPC membranes as a function of the C:PL mole ratio*

Drug	Partition coefficient		
	0:1 (C:PL)	0.3:1 (C:PL)	0.6:1 (C:PL)
Amlodipine	34,400 ± 1,300	21,800 ± 700	12,000 ± 400
Isradipine	11,400 ± 100	6,000 ± 400	2,200 ± 200
Nimodipine	6,300 ± 300	2,700 ± 200	1,200 ± 100
Verapamil	5,600 ± 300	2,700 ± 400	800 ± 300
Diltiazem	900 ± 30	600 ± 30	200 ± 10

* Drug concentrations were maintained at 5×10^{-10} M. Phospholipid concentration was 20 μg/mL: (pH 7.0, 21°). Values are means ± SEM (N = 12). This table was reproduced from Ref. 19 with permission of the copyright holder The American Society for Pharmacology and Experimental Therapeutics.

membrane, which is at least three orders of magnitude higher than in surrounding aqueous milieu, may be relevant for determining the actual affinity (i.e. equilibrium dissociation constant) of DHPs for their receptor [20]. Membrane binding is characterized by an extremely rapid membrane association rate and a relatively slow membrane dissociation rate [16–19]. Moreover, DHPs laterally diffuse through the membrane as quickly as lipid molecules, $D = 3.8 \times 10^{-8}$ cm^2/sec [21, 22]. These findings support the idea that DHPs have strong affinity for the membrane lipid bilayer, a well-defined membrane location, and a rapid rate of membrane lateral diffusion.

The molecular interaction of DHPs with the membrane bilayer can be correlated with certain functional parameters. Valdivia and Coronado [23] observed that the affinity of a positively charged DHP analog increased by an order of magnitude when the ratio of charged to uncharged phospholipids was increased 2-fold. In addition, the charged DHP amlodipine has a high membrane partition coefficient ($K_{P[mem]} > 10^4$) and a slow nonspecific membrane dissociation rate (Table 1 and Fig. 3) which correlate directly with certain pharmacokinetic properties [18]. The crystal structure and membrane location of amlodipine would predict that this molecule has both hydrophobic interactions with the lipid bilayer hydrocarbon core and electrostatic bonding with phospholipid headgroups, as illustrated in Fig. 4 [18]. These interactions may provide a rational for the functional properties of amlodipine, such as the long duration of calcium channel antagonist activity relative to that of certain uncharged DHPs [24, 25]. Thus, the interaction of DHPs with the membrane lipid bilayer appears to be related to drug pharmacokinetics (e.g. duration of activity).

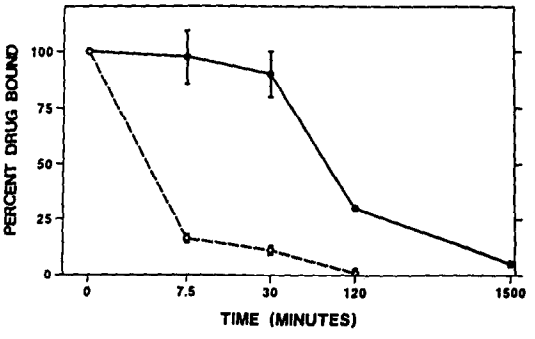

Fig. 3. Membrane "washout" of nimodipine and amlodipine. This figure shows the percentage of initial concentration (100%) of drug bound nonspecifically to light sarcoplasmic reticulum (LSR) membrane vesicles as a function of time up to 25 hr. LSR membranes were used as they did not contain specific receptor sites for DHPs. Key: (●) [^{3}H]amlodipine (4×10^{-9} M) and (○) [^{3}H]nimodipine (1×10^{-9} M). Values are means ± SD, N = 6. (Reproduced from Ref. 18 with permission of the copyright holder The American Society for Pharmacology and Experimental Therapeutics).

Cholesterol, a major membrane constituent which is altered by dietary atherosclerosis

Cholesterol is a major lipid constituent of cardiac and vascular smooth muscle plasma membrane. The concentration of cholesterol within the plasma membrane, commonly expressed as the free cholesterol to phospholipid (FC:PL) mole ratio, correlates with membrane microviscosity and is influenced by cholesterol content in the surrounding environment. In cell culture experiments, the plasma membrane FC:PL mole ratio in cardiac and smooth muscle cells can be efficiently and reproducibly modified in culture with cholesterol-enriched liposomes [26–28]. Cholesterol is rapidly transferred, in a concentration-dependent manner, from the high cholesterol-containing liposomes to the cell plasma membrane, or in the reverse direction when the concentration gradient is reversed [27, 28].

Animal models provide evidence which indicates that dietary atherosclerosis affects cardiovascular cell membrane cholesterol content. In New Zealand rabbits fed a high cholesterol (2% by weight) diet for 10 weeks, the arterial smooth muscle (ASM) cell plasma membrane FC:PL mole ratio was elevated from 0.38:1 to 0.68:1, an increase of 80% [29]. This increase in ASM plasma membrane cholesterol content was accompanied by severe atherosclerotic

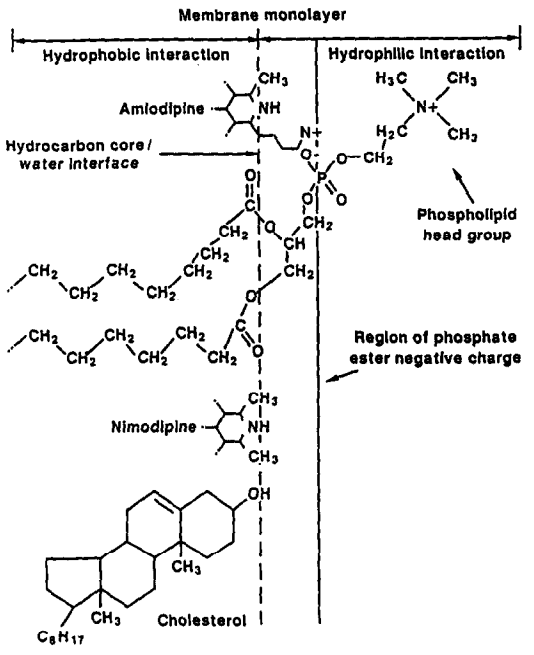

Fig. 4. Proposed interactions of amlodipine and nimodipine with a cholesterol/phospholipid monolayer. This model is based on the observed location of these drugs in the membrane bilayer [16, 18]. The location of amlodipine near the hydrocarbon core/water interface allows both hydrophobic interactions with phospholipid fatty acyl chains and electrostatic bonding between the charged ethanolamine side group and anionic oxygen of the phosphate moiety. These interactions may account for amlodipine's high $K_{P[mem]}$ values and slow dissociation from the membrane. The steroid nucleus of cholesterol would be expected to occupy a region of the membrane which overlaps the location of DHPs. By ordering the lipid hydrocarbon chains adjacent to the glycerol backbone, cholesterol would affect the partitioning of DHPs to this region of the membrane. The electrostatic interactions of amlodipine with the phospholipid headgroup may account for the weaker dependence of its partitioning on membrane cholesterol content, compared with nimodipine. (Reproduced from Ref. 19 with permission of the copyright holder The American Society for Pharmacology and Experimental Therapeutics.)

lesion development in the thoracic aorta. Consistent with this finding, Gillies and Robinson [30] reported a significant increase in the microviscosity of arterial cell membranes isolated from dietary atherosclerotic animals. These findings support the conclusion that changes in dietary cholesterol significantly alter plasma membrane cholesterol content and biophysical properties.

Alteration of the molecular structure of the membrane lipid bilayer by cholesterol

Cholesterol modulates membrane structure due to its unique interactions with phospholipid molecules. The cholesterol molecule favors hydrogen-bond formations with the 3β-hydroxyl group and has hydrophobic steric contact with the condensed steroid ring [31]. This hydrophobic molecule is incorporated into the membrane hydrocarbon core where it reduces freedom of motion in lipid hydrocarbon chains near the glycerol backbone for membranes in the lipid crystalline state [32].

The effect of cholesterol on overall membrane structure is illustrated in Fig. 5. The data for Fig. 5 were obtained by X-ray diffraction analysis of bovine cardiac phosphatidylcholine (BCPC) lipid bilayers prepared in the presence and absence of cholesterol. At the resolution of these experiments (8 Å), the effect of cholesterol on the structure of the membrane was clear. There was a substantial increase in the electron density within the hydrocarbon core of BCPC membranes from approximately 4 to 14 Å from the bilayer center. This increase over an extent of approximately 10 Å is consistent with the cholesterol molecule oriented in the membrane with its long axis parallel to the phospholipid acyl chains and the hydroxyl group located in the vicinity of the phospholipid carbonyl group [31, 33, 34]. The increase in electron density through this large region of the hydrocarbon core would be attributed to the contribution of the electron-rich conjugated ring structure of cholesterol as well as the effect of cholesterol on ordering the acyl chain region of the bilayer (i.e. decreasing *trans-gauche* isomerizations) in the portion of the hydrocarbon core region near the glycerol backbone.

In addition to modulating the packing of phospholipid acyl chains, the increase in membrane cholesterol content resulted in a greater membrane width. This finding is consistent with previous membrane X-ray and neutron diffraction studies [31, 33–35] as well as ^{2}H-NMR spectroscopy work [32]. In the latter study, a change in the effective acyl-chain length of egg phosphatidylcholine by approximately 2.5 Å (or 5 Å for the bilayer) was reported following the addition of 25 mol% cholesterol, consistent with X-ray diffraction data [35]. The implication of changes in membrane structure (e.g. width) on the conformation and function of integral membrane proteins is important to consider. A transmembrane protein has hydrophobic and hydrophilic amino acids in register with the amphipathic membrane lipid bilayer. In an α-helical conformation, the distance between adjacent amino acids is ~1.5 Å. An expansion of the membrane width by an average of 5 Å with the enrichment of cholesterol could force the displacement of several amino acids (i.e. hydrophilic amino acids could be moved into contact with the hydrophobic core of the lipid bilayer), thereby altering the conformation and structure of the integral membrane protein. These effects of cholesterol on the lipid bilayer structure may provide a molecular rationale for changes in activity of certain membrane proteins, as will be described.

Cholesterol modulation of the cell plasma function and pharmacology

Changes in cell membrane cholesterol content modulate membrane function (for review, see Ref. 36). Both increases and decreases in cardiovascular cell membrane cholesterol content have been shown to modify the activity of certain integral membrane proteins, including ion channels [26, 28], as well as

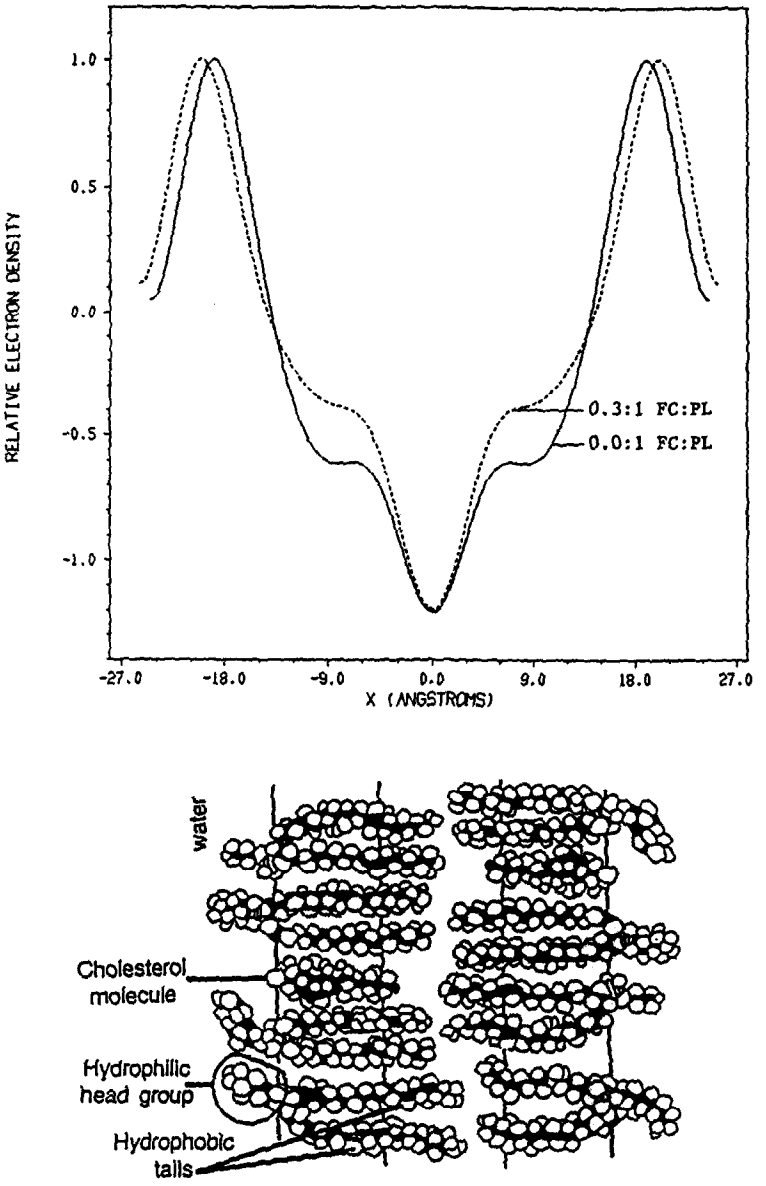

Fig. 5. Membrane bilayer electron density profiles generated from X-ray diffraction analysis. The upper panel shows electron density profiles for bovine cardiac phosphatidylcholine (BCPC) oriented membrane multilayers in the absence (solid line) and presence of a 0.3:1 (short dash) cholesterol:phospholipid mole ratio. The profiles correspond to the phospholipid/cholesterol membrane bilayer illustrated in the lower panel. The maxima of electron density at either side of the electron density profiles correspond to the electron dense phosphate headgroups while the minimum of electron density in the center of the figure corresponds to the membrane bilayer center. The profiles were placed on the same scale to match the peaks of electron density with the electron density minima. The addition of cholesterol to the lipid bilayer produced a broad increase in electron density within the hydrocarbon core in a region approximately 10 Å in width, approximately the length of cholesterol's heterocyclic ring structure. Further, there was an outward displacement in the phosphate headgroups following the addition of cholesterol.

the pharmacological properties of the β-adrenergic [37, 38] and DHP receptor [26]. By altering the physical properties of the membrane (Fig. 6), cholesterol may perturb the conformation of integral proteins and/or the energetics associated with their functional activity (e.g. ion conductance, ligand binding). These findings may provide a molecular basis for alterations in certain vascular cell membrane functions during disease processes, including atherosclerosis [29], in which plasma membrane cholesterol content changes. Plasma membrane cholesterol content has also been shown to change substantially

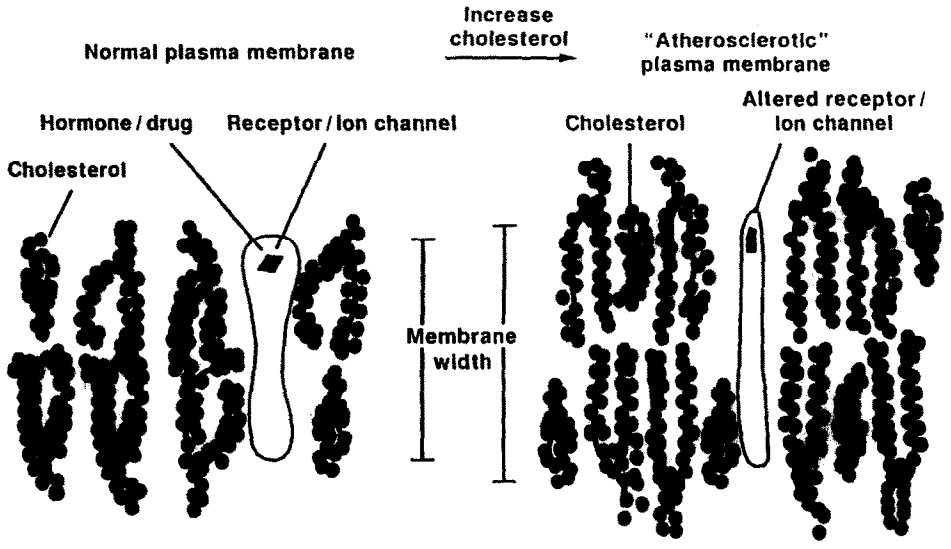

Fig. 6. A highly schematic model for the potential effect of cholesterol enrichment on arterial smooth muscle plasma structure following cholesterol enrichment. The structural consequence of membrane cholesterol enrichment during dietary atherosclerosis is a marked increase in the membrane hydrocarbon core width [19, 32, 34]. An increase in membrane width, moreover, would be expected to perturb the structure and conformation of membrane-bound amphiphilic proteins. This may provide a molecular rationale for altered membrane function in cardiovascular cells as a result of cholesterol enrichment [30, 32].

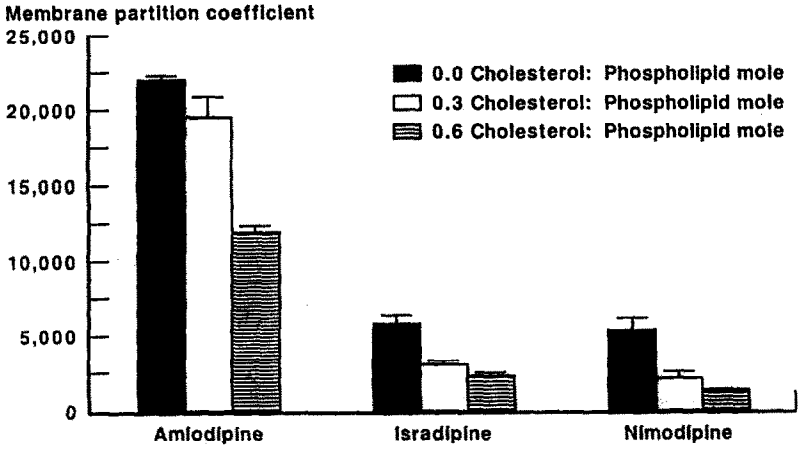

Fig. 7. Effect of cholesterol on binding of DHPs to bovine cardiac phosphatidylcholine membranes. There was a strong negative correlation between membrane cholesterol content and the partition coefficients for DHPs. The effect of cholesterol on DHP membrane partitioning was different for the charged DHP amlodipine and the uncharged analogs, isradipine and nimodipine. The drug concentration was maintained at 5×10^{-10} M and the phospholipid concentration was 20 μg/mL (pH 7.0, 21°). Each value represents the mean ± SEM (N = 12).

in arterial smooth muscle as a function of age [39], experimental diabetes [40] and chronic cigarette smoking [41].

Cholesterol modulation of the binding of calcium channel antagonists to the membrane bilayer

Previous X-ray and neutron diffraction studies [16, 17] show that DHPs, including amlodipine and nimodipine, have a similar time-averaged location near the hydrocarbon core/water interface, a region which overlaps the location of free cholesterol in the membrane (Fig. 4). It was not surprising, therefore, that membrane cholesterol content significantly affected the binding or partitioning of these drugs to the membrane lipid bilayer.

Table 1 summarizes the effect of cholesterol

Table 2. Comparison of drug partition coefficients in native versus model systems*

Drug	Partition coefficient: Sarcoplasmic reticulum (0.1:1 C:PL)	Partition coefficient: Cardiac PC membranes (0.1:1 C:PL)	Partition coefficient: Octanol
Amlodipine	19,000 ± 700†	19,900 ± 1,200§	30 ± 4†
Nimodipine	5,200 ± 400‡	4,800 ± 400§	260 ± 50‡

* This table was from Ref. 19 with permission of the copyright holder The American Society for Pharmacology and Experimental Therapeutics.
† From Ref. 18; mean ± SD (N = 6).
‡ From Ref. 17; mean ± SD (N = 6).
§ Means ± SEM, N = 12.

content on the partitioning of various calcium channel blockers including DHPs (amlodipine, isradipine and nimodipine), verapamil and diltiazem. These results showed a strong negative correlation between membrane cholesterol content and drug partition coefficients. Interestingly, the effect of membrane cholesterol content on amlodipine partitioning was substantially less than that of other calcium channel antagonists between 0:1 FC:PL and 0.3:1 FC:PL while the overall $K_{P[mem]}$ values for amlodipine were much higher. Thus, even modest chemical differences between 1,4-dihydropyridines substantially affected their binding to membranes of varying lipid composition. These findings demonstrate the complex nature of drug interaction with the anisotropic membrane lipid bilayer.

The partitioning of these drugs into a synthetic phosphatidylcholine (PC) lipid system (dioleoyl phosphatidylcholine or DOPC) was then compared to that in a native cardiac PC lipid membrane composed of heterogenous acyl chains (Fig. 7). Although absolute $K_{P[mem]}$ values were lower overall, the effect of cholesterol was similar. The difference in $K_{P[mem]}$ values when measured in the cardiac PC lipid system versus synthetic lipids (DOPC) may be attributed to the acyl chain composition. The cardiac PC lipids have a high percentage of diunsaturated linoleic acid (~30%) and saturated palmitic acid (~20%) which may increase the density of the hydrocarbon acyl chain packing when compared with the very fluid monounsaturated DOPC acyl chains [42].

The high $K_{P[mem]}$ values for amlodipine suggest that this molecule has more favorable chemical and physical interactions with the membrane bilayer than do other calcium channel antagonists. Amlodipine is an amphipathic molecule with a charged, 2-aminoethoxymethyl substituent at the 2-position of the dihydropyridine ring ($pK_a = 9.02$) which, in its crystal structure, extends away from the hydrophobic portion of the molecule [18]. Although amlodipine is soluble in water and has a low partition coefficient in a hydrophobic octanol/buffer system ($K_{P[oct]} = 30$), its $K_{P[mem]}$ values were substantially higher than those of neutral DHPs which are nearly insoluble in water (Table 2). Based on the experimentally determined membrane location of amlodipine and its crystal structure, it would be expected that the charged portion of the drug molecule interacts with the anionic oxygen of the phospholipid headgroup while the hydrophobic dihydropyridine and chlorophenyl ring structures penetrate into the hydrocarbon core, as illustrated in Fig. 4. The combination of ionic and hydrophobic bonding between amlodipine and phospholipid molecules may help to explain high $K_{P[mem]}$ values observed for this drug.

The $K_{P[mem]}$ values measured for amlodipine and nimodipine in BCPC/cholesterol multilamellar vesicles were very similar to $K_{P[mem]}$ measurements in intact, skeletal light sarcoplasmic reticulum (LSR) despite the fact that LSR contains protein (0.9 ± 0.1 nmol lipid/μg protein) and a heterogeneous phospholipid headgroup composition (Table 2). Further, the dependence of nimodipine $K_{P[mem]}$ on membrane FC:PL mole ratios was independent of tissue source (Table 3, Fig. 8).

Potential effect of cholesterol on drug bioavailability

The bioavailability of a drug is a term which describes the extent to which a drug reaches the biological compartment from which it then has access to its site of action. For lipophilic and amphipathic drugs which target receptor sites via the membrane lipid bilayer, including certain anesthetics and DHP calcium channel blockers, the ability of these drugs to partition into the membrane is a critical determinant of their bioavailability. Thus, perturbation of membrane cholesterol content in various tissues during aging or in pathological states would be expected to substantially alter the bioavailability of certain drugs. For example, the membrane concentration of certain calcium channel antagonists would be highly affected by dietary atherosclerosis in which the cholesterol content has been shown to increase by 80% in isolated arterial smooth muscle plasma membranes [29] and by 50% in cardiac membranes [37]. An 80% increase in the FC:PL mole ratio from 0.38:1 to 0.68:1 [29] would be expected to reduce the membrane concentration of nimodipine by at least 4-fold. Based on the measured concentration of DHP receptors in cardiac sarcolemma of approximately one calcium channel receptor per 10^6 phospholipid molecules [15], a $K_{P[mem]}$ of 500 for nimodipine at a 0.6:1 FC:PL mole ratio would result in a drug:receptor ratio of approximately 0.5:1 at the nimodipine K_d (4×10^{-10} M aqueous concentration, see also Ref.

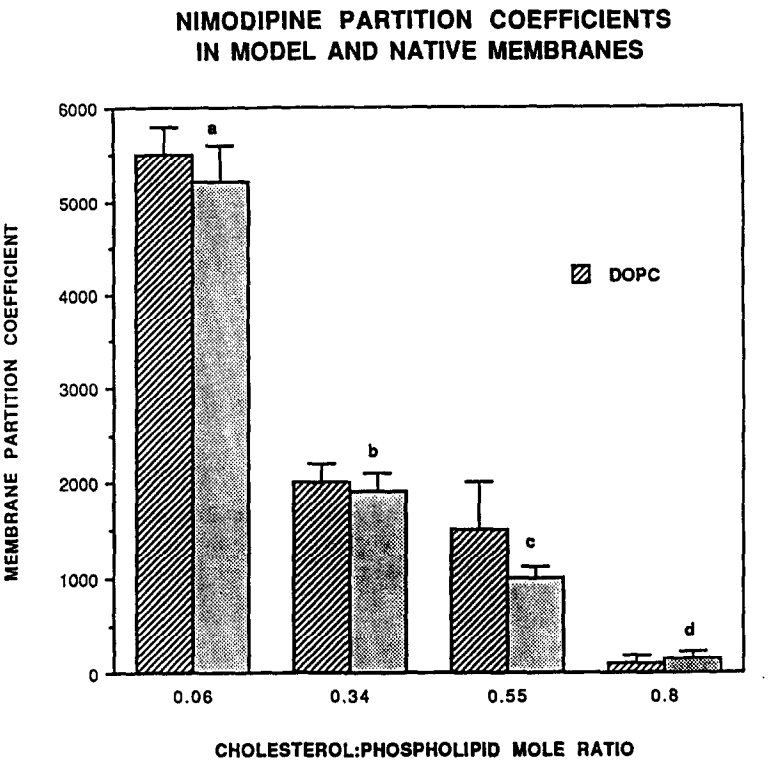

Fig. 8. Partitioning of nimodipine into model (dioleoyl phosphatidylcholine) and native membranes with varying C:PL mole ratios. These data suggest that membrane cholesterol content is an important determinant for the membrane interactions of nimodipine and may be independent of tissue or species source. The concentration of nimodipine for these experiments was 5×10^{-10} M. The membrane concentration was 2.5 μM except for LSR (2 μM) as was reported previously [17]. Values are means ± SEM (N = 12).

Table 3. Nimodipine partition coefficients into membranes from various tissues

Membrane system	C:PL mole ratio	Membrane partition coefficient
Rabbit skeletal light sarcoplasmic reticulum	0.1:1	5200 ± 400*
Rat cerebral cortex synaptosomes†	0.55:1	1900 ± 200‡
Cholesterol enriched rat synaptoneurones†	0.80:1	140 ± 70‡

* From Ref. 17; mean ± SD (N = 6).
† Drug concentrations were maintained at 5×10^{-10} M. Phospholipid concentration was 20 μg/mL (pH 7.0, 21°).
‡ Values are means ± SEM (N = 12).

17). This was calculated directly from the amount of drug in the membrane at these FC:PL mole ratios with the concentration of nimodipine in the buffer being 5×10^{-10} M. By contrast, the extrapolated membrane partition coefficient for amlodipine ($K_{P[mem]} > 7.7 \times 10^5$) at a 0.6:1 FC:PL mole ratio would result in a drug:receptor ratio of 8:1 when the aqueous concentration is 5×10^{-10} M. Thus, after its depletion from plasma and interstitial compartments, amlodipine can remain sequestered

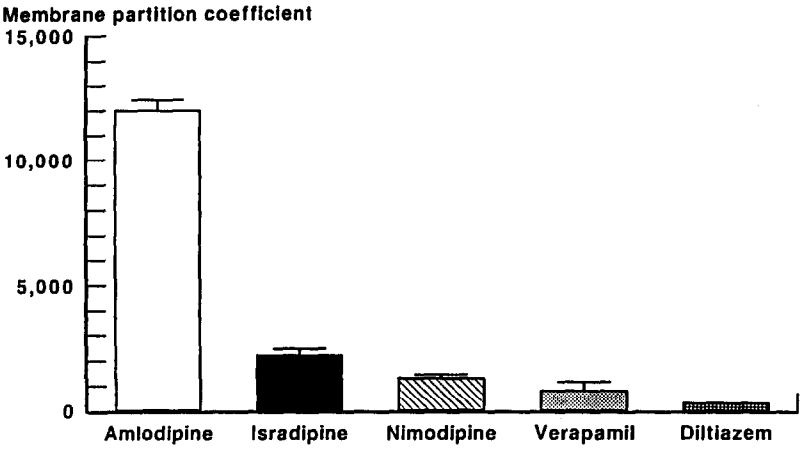

Fig. 9. Summary of membrane partition coefficients for several calcium channel antagonists into dioleoyl phosphatidylcholine membranes with elevated cholesterol (0.6:1, FC:PL mole ratio) to mimic the reported conditions of dietary atherosclerosis [29]. The drug concentration was maintained at 5×10^{-10} M and the phospholipid concentration was 20 μg/mL (pH 7.0, 21°). Each value represents the mean ± SEM of two trials (N = 12).

in the membrane bilayer of the normal or atherosclerotic target tissue at sufficient concentrations for activity [43, 44].

Summary

The interactions of lipophilic calcium channel antagonists with the membrane lipid bilayer are complex and highly dependent on membrane composition and structure. Variability in membrane lipid composition (e.g. cholesterol content, acyl chain saturation) can dramatically affect the membrane partitioning of calcium channel antagonists. The membrane binding properties of these drugs did not correlate with traditional measurements of drug lipophilicity, such as a simple hydrocarbon system (Table 2). These data indicate the need for directly measuring the binding of drug molecules to membranes in order to understand better certain pharmacological parameters, including bioavailability, under both normal and pathological conditions in which membrane composition is altered.

The interaction of certain lipophilic amphipathic drugs with the membrane lipid bilayer may be an important component of their overall receptor binding mechanism. Specifically, the membrane bilayer may serve to concentrate and orient these drug molecules with respect to a hydrophobic receptor site at the protein receptor/membrane bilayer interface. Thus, the design of drugs which target membrane bound receptors should take into consideration the interaction of the drug molecule with the membrane lipid compartment. This understanding of drug/membrane interactions may lead to the development of drugs with more desirable pharmacokinetics, greater efficacy, and reduced side effects.

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