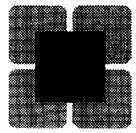

DONALD G. VIDT, MD, AND ALAN BAKST, PharmD, EDITORS

Calcium-channel antagonists: mechanisms of action, vascular selectivities, and clinical relevance

DAVID J. TRIGGLE, PhD

■ The calcium-channel antagonists represent three separate structural categories of drugs. They share a common action—the blockade of calcium-ion flow through one specific type of calcium channel. The chemical heterogeneity of these agents is reflected in their pharmacologic and therapeutic diversity. The calcium-channel antagonists enjoy significant use in cardiovascular medicine for the treatment of hypertension, angina, and some cardiac arrhythmias. However, the 1,4-dihydropyridines, the most potent antihypertensive calcium-channel blockers, lack antiarrhythmic properties. The selectivity of action of calcium-channel antagonists rests upon a number of factors, including pathways of calcium mobilization, types of channel activated, state-dependent interactions, and the pathological state of the tissue. An understanding of these factors is important to the rational application of these drugs and to the development of newer agents with different specificities.

□ INDEX TERMS: CALCIUM-CHANNEL BLOCKERS; CALCIUM CHANNELS; CARDIOVASCULAR DISEASES □ CLEVE CLIN J MED 1992; 59:617–627

CALCIUM PLAYS CRITICAL roles in cellular communication and regulation. Under physiological conditions, the cell maintains a low intracellular concentration of free ionized calcium against large, inwardly directed concentration and electrochemical gradients. The transmembrane flow of calcium serves a dual role as a depolarizing signal and as an intracellular second messenger. The stimulus-evoked inward flow of calcium is coupled to cellular response by intracellular calcium-binding proteins, including the ubiquitous calmodulin.[1] Under pathological conditions, the uncontrolled mobilization of calcium may constitute a lethal signal, and such movements subsequent to cellular insult or injury can lead irreversibly to cell destruction and death.[2] The control of calcium homeostasis therefore represents a powerful route for the modulation of cellular excitability and response.[3,4]

Calcium moves in and out of the cell and intracellular storage sites in response to chemical, electrical, pressure, and other physical stimuli (*Figure 1*). The loci for these events are key sites at which to modulate cellular excitability. Experimental agents are known[5] that interact with all of the sites depicted in *Figure 1*; however, for the purposes of this discussion, we will consider only the voltage-gated calcium channels located on excitable cells, since these are the therapeutic targets of the calcium-channel antagonists. These channels are not unique to the cardiovascular system,

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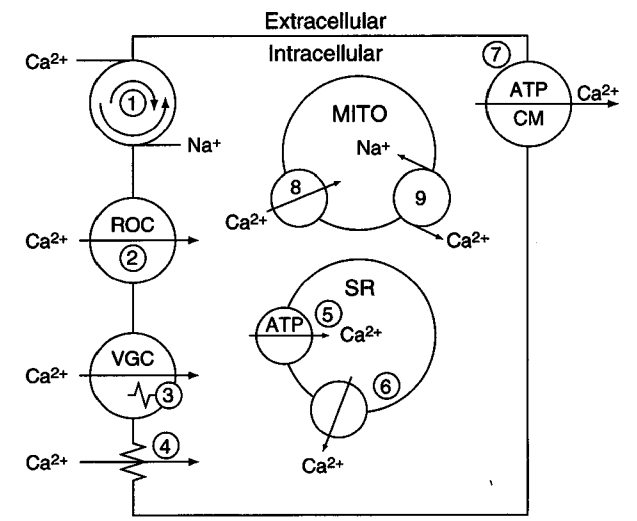

FIGURE 1. Cellular regulation of calcium, showing sites of calcium control at plasma membrane and intracellular sites. (1) Sodium-calcium exchanger; (2) receptor-operated channels (ROC); (3) voltage-gated channels (VGC); (4) "leak" and nonselective cation channels; (5) adenosine triphosphate (ATP)-dependent calcium uptake (pump) into sarcoplasmic reticulum (SR); (6) calcium-release channel in SR; (7) ATP-dependent calcium uptake (pump) in calmodulin (CM); and (8 and 9) calcium uptake and release in mitochondria (MITO).

TABLE 1
THERAPEUTIC USES OF CALCIUM-CHANNEL ANTAGONISTS

Uses	Antagonists		
	Verapamil (Class I)*	Nifedipine (Class II)	Diltiazem (Class III)
Angina:			
exertional	+++	+++	+++
Prinzmetal's	+++	+++	+++
variant	+++	+++	+++
Paroxysmal supraventricular tachyarrhythmias	+++	–	+++
Atrial fibrillation and flutter	++	–	++
Hypertension	++	+++	+
Hypertrophic cardiomyopathy	+	–	–
Raynaud's phenomenon	++	++	++
Cardioplegia	+	+	+
Cerebral vasospasm (posthemorrhage)	–	+†	–

*Provisional and preliminary classification by World Health Organization
†Refers to nimodipine

+++, very common use
++, common use
+, less common use
–, not used

but their activation and blockade are particularly important to the control of cardiovascular function.

Calcium-channel activation in response to depolarizing stimuli is an important excitation-contraction coupling process in vascular smooth muscle. Calcium entry also triggers the release of intracellular calcium through release channels and storage sites in the sarcoplasmic reticulum. Calcium entry through these voltage-gated calcium channels contributes to the plateau phase of the cardiac action potential underlying inotropic events and is the dominant inward current at the sinoatrial and atrioventricular nodes underlying pacemaker function.[3,4]

The calcium-channel antagonists verapamil, nifedipine, and diltiazem (*Figure 2*) block voltage-gated calcium channels in vascular smooth muscle to decrease tone and lower blood pressure. In cardiac muscle, verapamil blocks conduction and reduces cardiac rate and contractility—properties shared by diltiazem but lacking in the 1,4-dihydropyridines, which as a class have very little direct effect on the heart. These properties of verapamil underlie its class IV antiarrhythmic activity. The therapeutic profiles of these agents have both quantitative and qualitative differences (*Table 1*).

Several lines of biochemical evidence indicate that the three major therapeutic groups of calcium-channel antagonists—1,4-dihydropyridines (nifedipine), phenylalkylamines (verapamil), and benzothiazepines (diltiazem)—act at separate sites.[5–7] These sites are linked to one another (by complex allosteric interactions) and to the permeation and gating machinery of the channel (*Figure 3*). Despite these biochemical and therapeutic differences, the calcium-channel antagonist binding sites are located on a single protein, the alpha$_1$ subunit of the oligomeric assembly that constitutes the voltage-gated calcium channel (*Figure 4*).[7]

Some newly developed experimental groups of calcium-channel antagonists probably act at sites distinct from the three already described.[5,8] In fact, there may be as many as six or seven completely separate drug-binding sites associated with the calcium channel. Drugs that act at these other sites may reasonably be expected to exhibit different therapeutic activities from those currently available. The 1,4-dihydropyridine site is also home to a group of experimental drugs, the calcium-channel activators (*Figure 2*). Although structurally similar to nifedipine, these activators or agonists have exactly opposing properties: they open or maintain the opening of calcium channels and so are positive-inotropic vasoconstrictive species.[5,9]

The calcium channel may be regarded as a pharmacologic receptor[10]: it possesses specific binding sites for both activators and antagonists. These sites are coupled to channel function, and we expect to find that they are regulated in experimental and clinical disease states. These latter expectations are being increasingly realized.

SELECTIVITY OF ACTION

An important expression of the selectivity of action of calcium-channel antagonists is seen in their relative cardiac and vascular effects (*Table 2*).

Verapamil, and to a lesser extent diltiazem, exhibit both cardiac depressant and vasodilating properties over similar therapeutic dose ranges.[11–13] With normal ventricular function, the direct myocardial depressant effects of verapamil and diltiazem are counterbalanced by afterload reduction and are of little clinical significance. However, these cardiac depressant properties underlie the limitations of combining verapamil with beta-blockers. They also underlie the deleterious effects of administering verapamil or diltiazem to patients with left ventricular dysfunction.

In marked contrast, the cardiovascular pharmacology of the 1,4-dihydropyridines is generally dominated by their vasodilatory properties that can generate reflex cardiac activation.[14] However, nifedipine can also exhibit cardiodepression; this can limit its application in some patients with severe left ventricular dysfunction.[15]

These differences can be quantified by a vascular-cardiac selectivity ratio that reflects vascular relaxing and cardiac depressant activities under defined conditions (*Table 3*).[16,17] One specific determination of the ratio is a comparison of inhibitory potencies in rat portal vein and papillary muscle. The ratio changes according to experimental conditions and species: rat myocardium is significantly less sensitive to the calcium-channel antagonists than that of other species,[18] and other vascular tissues will show different sensitivity than the portal vein. However, the ratio does indicate the qualitative directions of the vascular-cardiac selectivity profile. These differences in selectivity of action are also accompanied by different side-effect profiles (*Table 4*), those for the 1,4-dihydropyridines being dominated by vascular actions.

The cardiovascular selectivities of action of the calcium-channel antagonists differ not only between the major structural groups, but also within a single structural group. Second-generation calcium antagonists of

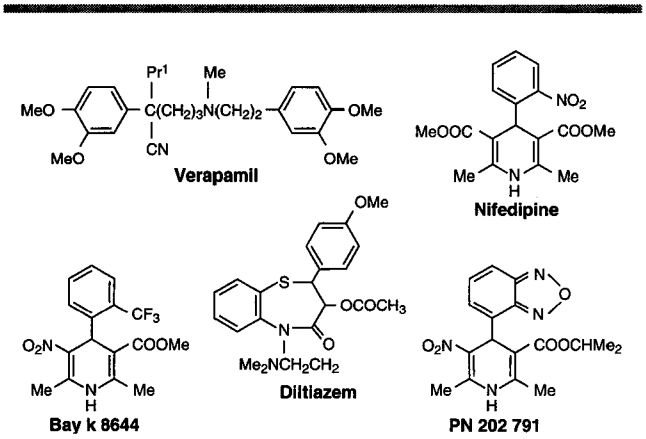

FIGURE 2. Chemical structures of the calcium antagonists nifedipine, verapamil, and diltiazem, and the 1,4-dihydropyridine calcium-channel activators Bay K 8644 and PN 202 791.

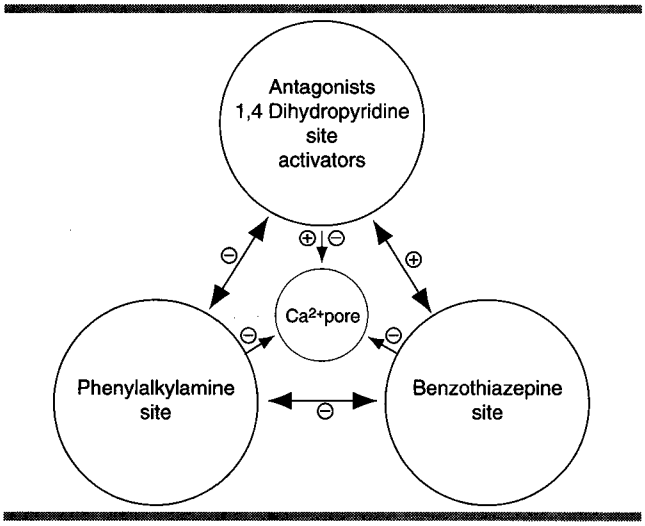

FIGURE 3. Proposed arrangement of the three primary drug binding sites at the L-type calcium channel.

TABLE 2
PHARMACOLOGICAL EFFECTS
OF CALCIUM-CHANNEL ANTAGONISTS

Drug	Heart rate	AV nodal conduction	Myocardial contractility	Arteriolar vasodilation
Verapamil	↓↓	↓↓	↓↓	↑↑
Nifedipine	↑	—	↓↑	↑↑↑
Diltiazem	↓	↓	↓	↑

Number of arrows designates extent of effect

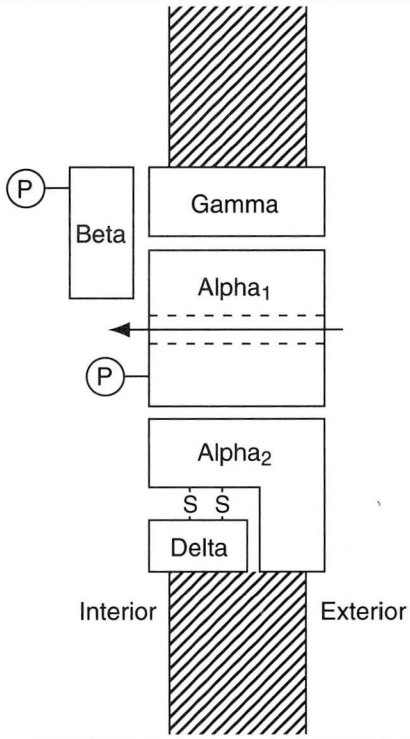

FIGURE 4. Schematic arrangement of the subunits making up the voltage-gated calcium channel. The alpha$_1$ subunit carries the drug binding sites and channel function. The other subunits also play important roles in channel function (reference 7). P, sites of phosphorylation; S-S, disulfide bridges.

TABLE 3
VASCULAR-CARDIAC SELECTIVITY RATIOS OF SELECTED CALCIUM-CHANNEL ANTAGONISTS

Calcium-channel antagonist	Vascular-cardiac selectivity ratio
Verapamil	1
Diltiazem	5
Nifedipine	15
Felodipine	120

TABLE 4
SIDE EFFECTS OF CALCIUM-CHANNEL ANTAGONISTS

	Diltiazem	Nifedipine	Verapamil
Ankle edema	5%-10%	5%-10%	5%-10%
Constipation	0%-5%	0%	>20%
Dizziness	5%-10%	0%-10%	5%-10%
Facial flushing	0%-5%	10%-20%	5%-10%
Headaches	0%-5%	5%-10%	0%-5%
Ischemia	0%	0%-5%	0%
Rash	0%-5%	0%	0%-5%
Tachycardia	0%	5%-10%	0%

the 1,4-dihydropyridine class (*Figure 5*), including felodipine, may have significantly higher vascular-cardiac selectivity ratios than nifedipine (*Table 3*). This enhanced vascular selectivity may offer clinical advantage in the treatment of hypertension, particularly in patients with compromised cardiac contractile or conductive function. Other 1,4-dihydropyridines may exhibit a regional vascular selectivity. Nimodipine has preferential actions on the cerebral vasculature[11,19,20] and nisoldipine is reported to have selectivity for the coronary vasculature.[21,22]

Selectivity of action of the calcium-channel antagonists may arise from a number of factors either alone or in combination, including (1) pharmacokinetic factors; (2) mode of calcium mobilization, (3) class and subclass of calcium channel activated; (4) state-dependent interactions; and (5) pathological state of the tissue.

Pharmacokinetic factors

Calcium-channel antagonists share both similarities and differences in their pharmacokinetic properties. They are all protein-bound species, and they all show extensive first-pass metabolism.[4,23] However, they present a wide range of structures; for example, verapamil and diltiazem are largely protonated at physiological pH, whereas nifedipine and most other 1,4-dihydropyridines are neutral and nonpolar. The partition coefficients and distribution properties differ significantly among 1,4-dihydropyridines, and selective accumulation within different vascular beds or organ systems may contribute to the observed selectivity of action.[24] The higher membrane-water partition coefficient of nimodipine relative to nifedipine may underlie its higher apparent distribution volume in the brain and its cerebral selectivity.[25] Similarly, the very high partition coefficient of amlodipine likely contributes to its slow onset and prolonged duration of action.[26]

Mode of calcium mobilization

Calcium-channel antagonists affect only calcium entry through voltage-gated calcium channels, and antagonism will occur only at activated calcium channels. Direct mobilization of calcium through receptor-operated channels or from intracellular stores is generally unaffected by these agents. Since different calcium mobilizing systems frequently coexist in excitable tissues, the effects of calcium-channel antagonists depend upon the balance of activities in these systems according to physiologic state and

demands.[4,10,27] Furthermore, the vasodilatory effects of calcium antagonists activate cardiovascular reflex effects that may mask the effects on individual organ systems.

A tissue whose response depends only on pathways that are not voltage-gated will be insensitive to calcium-channel antagonists. Calcium-channel antagonists have not achieved clinical significance as antiasthmatic agents despite the presence of voltage-gated calcium channels and calcium-channel antagonist binding sites in respiratory smooth muscle.[28,29] This is almost certainly due to the dominance of calcium mobilization by other pathways, notably those linked to phosphatidylinositol turnover and the production of inositol triphosphate.[30]

Differential activation and blockade of calcium-mobilizing pathways may also underlie the actions of calcium-channel antagonists on kidney hemodynamics and function.[31,32] Total renal vascular resistance is determined by the sum of the (series-arranged) segmental resistances of the preglomerular afferent arterioles and postglomerular efferent arterioles serving the glomerular capillary bed. Calcium-channel antagonists may affect primarily the afferent arterioles after renal vasoconstriction by norepinephrine or angiotensin II and, thus, partially relieve renal vasoconstriction produced by these agents (*Figure* 6). However, the glomerular filtration rate is generally restored or even augmented by calcium-channel antagonists because selective dilation of the afferent arteriole increases glomerular filtration pressure in the face of maintained efferent tone. These differential effects of calcium-channel antagonists are very stimulus-dependent and vary according to physiologic and pathologic state.

Whether these effects of calcium-channel antagonists on renal hemodynamics underlie their natriuretic and diuretic actions in hypertensive individuals remains to be determined.[33] These effects, desirable in an antihypertensive agent, may arise from

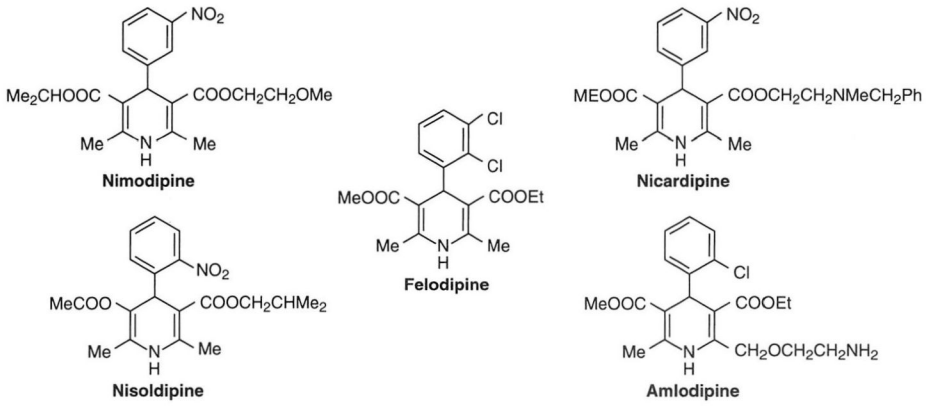

FIGURE 5. Structural formulas of some second-generation 1,4-dihydropyridine calcium-channel antagonists.

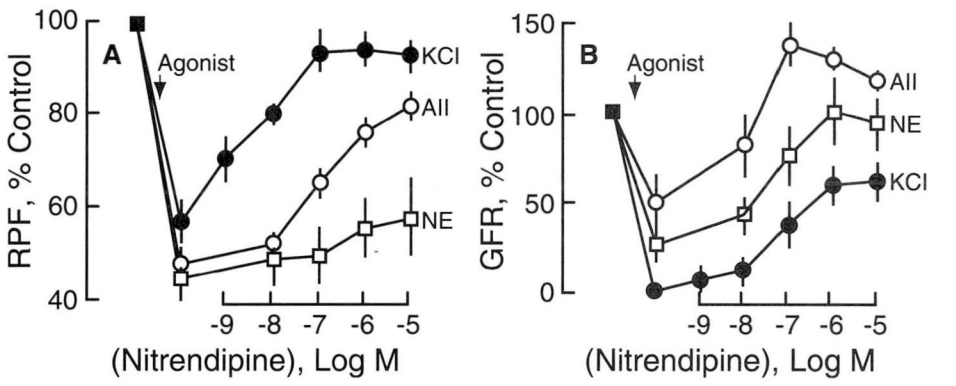

FIGURE 6. The effect of the 1,4-dihydropyridine nitrendipine on renal hemodynamics in the isolated perfused rat kidney. The kidneys were treated with nitrendipine following potassium chloride (KCl), angiotensin II (AII), or norepinephrine (NE). Graph A shows renal perfusate flow (RPF), and graph B shows the glomerular filtration rate (GFR). Reproduced with permission from Loutzenhiser R, Epstein M, Horton C. Modification by dihydropyridine-type calcium antagonists of the renal hemodynamic response to vasoconstrictors. J Cardiovas Pharmacol 1987; 9(Suppl 1):S70–S75.

TABLE 5
CLASSIFICATION OF VOLTAGE-GATED CALCIUM CHANNELS

Property	Channel class			
	L	T	N	P
Conductance (pS)	25	8	12-20	10-12
Activation threshold	high	low	high	moderate
Inactivation rate	slow	fast	moderate	rapid
Permeation	$Ba^{2+}>Ca^{2+}$	$Ba^{2+}=Ca^{2+}$	$Ba^{2+}>Ca^{2+}$	$Ba^{2+}>Ca^{2+}$
Function	E-Coupling in cardiovascular system, smooth muscle, endocrine cells and some neurons	Cardiac SA node: neuronal spiking repetitive spike activity in neurons and endocrine cells	Neuronal only: neurotransmitter release	Neuronal only?: neurotransmitter release
Pharmacologic sensitivity				
1,4-Dihydropyridines (Activators/antagonists) Phenylalkylamines Benzothiazepines	Sensitive	Insensitive	Insensitive	Insensitive
w-Conotoxin	Sensitive? (some)	Insensitive	Sensitive	Insensitive
Octanol, amiloride	Insensitive?	Sensitive	Insensitive	?
Funnel web spider toxin	Insensitive	Insensitive	Insensitiven	Sensitive

a redistribution of blood flow, from direct effects on the calcium-dependent tubular reabsorption of sodium, or from inhibition of the tubuloglomerular feedback response of the macula densa.[34,35] Calcium-channel antagonists may also exert clinically different effects on urinary protein excretion. For example, in diabetic patients, diltiazem and nifedipine had opposing effects (decreasing and increasing protein excretion, respectively, with corresponding changes in renal dysfunction).[36] In other studies, nifedipine and nicardipine also either decreased protein excretion or left it unchanged.[37–39] Since protein excretion is determined in part by glomerular capillary pressure, any difference in effects among calcium-channel antagonists may be associated either with different origins of arteriolar tone according to the disease state and its severity, or with different effects on the preglomerular and postglomerular arteries.

Classes and subclasses of calcium channels

There are at least four major classes of voltage-gated calcium channels, each with its unique electrophysiologic and pharmacologic profile (*Table 5*).[40] Channels with large, long-lasting conductances (L channels) dominate in the cardiovascular system. L channels are sensitive to the clinically available calcium-channel antagonists, and they support excitation-contraction coupling in vascular and cardiac muscle. A transient (T) channel, probably involved in both peripheral and central pacemaker processes, opens and closes rapidly and is insensitive to the calcium-channel antagonists. A third channel, the N channel, is of particular importance in the central nervous system and is also insensitive to the calcium-channel antagonists. This may explain the general lack of effectiveness of these agents under most conditions of use. P channels, sensitive to funnel web spider toxin (FTX), are also found only in neurons.

Molecular biology studies permit the tentative construction of an evolutionary tree of calcium channels, from an ancestral type of considerable antiquity to at least half a dozen types and subtypes, including those found in skeletal, cardiac, and smooth muscle, and in neuronal and endocrine cells, with a correspondingly diverse pharmacology.[41] This pharmacological classification will be of importance in the future generation of new categories of calcium-channel drugs with therapeutic properties and uses substantially different from those currently available.[42]

State-dependent interactions

State-dependent interactions of channel antagonists with channels constitute an important base for selectivity of action. Moreover, this base is susceptible to both coarse and fine tuning.

The voltage-gated calcium channel exists in three states or families of states—resting, open and activated, and closed and inactivated (*Figure 7*). Equi-

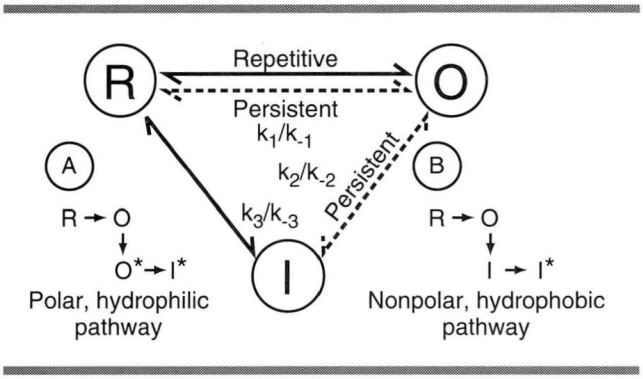

FIGURE 7. The voltage-gated calcium-channel cycle of resting (R), open (O), and inactivated (I) states. Each state may offer preferential affinity or access to drug species (routes A and B). The distribution between the states is determined by membrane potential and frequency of stimulation. K indicates rate constant (forward and backward) for interconversion between states. "Persistent" and "repetitive" refer to depolarization and indicate maintained and rhythmic changes, respectively, in membrane potential. The asterisks indicate the drug-bound state.

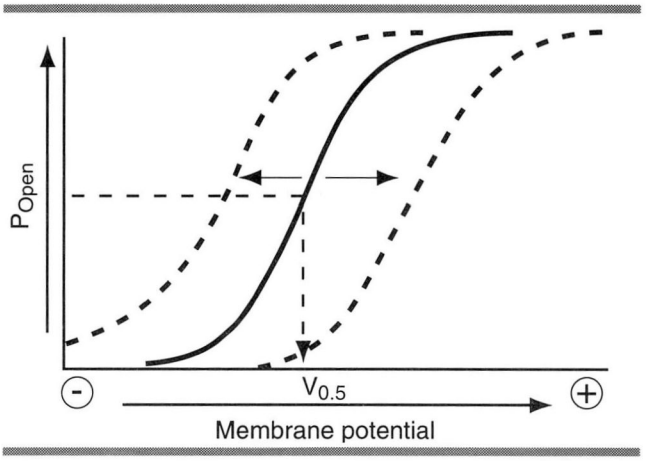

FIGURE 8. Relationship between membrane potential and channel-opening probability (P_{Open}). The relationship (solid line) may be shifted in hyperpolarizing or depolarizing directions (dashed lines) by the influence of neurotransmitters and other modulators.

librium between these states is determined by several factors, including channel phosphorylation and membrane potential. Membrane depolarization opens the channel and prolonged membrane depolarization causes channel inactivation. Drugs may have different affinities and different access to their specific binding sites depending on channel state,[43,44] and the apparent affinity of a drug may be determined by its specific affinity for or access to each of the separate states and the distribution between these states. The latter is determined by physiologic and pathologic factors including membrane potential, modulation by neurotransmitter-directed phosphorylation, G protein interaction or other biochemical change, and tissue pathology.

Calcium-channel antagonists show voltage-dependent binding: their affinity increases with decreasing membrane potential. This is consistent with selective binding or access to the inactivated state of the channel (increasing depolarization increases drug affinity).[44,45] Additionally, some calcium-channel antagonists, notably the charged verapamil and diltiazem, show frequency-dependent interactions whereby apparent affinity increases with increasing frequency of depolarizing stimulus.[46] This property underlies the selective class IV antiarrhythmic properties of verapamil and diltiazem that are absent in nifedipine and other 1,4-dihydropyridines (*Figure 2*). Similar considerations underlie the antiarrhythmic activities of class I agents at the cardiac Na^+ channel.[47] This important difference between the three structural classes of antagonist likely reflects the necessity of verapamil and diltiazem, as charged and more polar species, to access the inactivated state through the open state of the channel. In contrast, the nonpolar and noncharged 1,4-dihydropyridines can access their preferential binding state directly through the membrane phase.

State-dependent interactions can account for both quantitative and qualitative differences in selectivity of the calcium-channel antagonists. The greater potency of the antagonists in hypertensive vs normotensive vascular smooth muscle likely arises from the greater tone and depolarization in the former. Similarly, differential dilation of vascular beds may arise from similar differences in existing tone.[48] These effects of membrane potential upon drug interactions at the voltage-gated L channel have been measured largely by electrophysiologic techniques. However, a number of studies using direct radioligand binding techniques have shown that cardiac and vascular cell depolarization increases drug affinity.[49,50]

Voltage-dependent interactions can be fine-tuned through the use of neurotransmitters and hormones to modulate the voltage-dependence of channel kinetics. The channel-opening probability is determined by membrane potential (*Figure 8*). This curve can be shifted in the depolarizing or hyperpolarizing directions by neurotransmitters and other modulators to

TABLE 6
ADDITIONAL AND POTENTIAL USES OF CALCIUM-CHANNEL ANTAGONISTS

Cardiovascular
Atherosclerosis
Cardioplegia
Cerebral ischemia, focal
Cerebral ischemia, global
Congestive heart failure
Hypertrophic cardiomyopathy
Migraine
Myocardial infarction
Peripheral vascular diseases
Pulmonary hypertension
Subarachnoid hemorrhage
Nonvascular smooth muscle
Achalasia
Asthma
Dysmenorrhea
Eclampsia
Esophageal spasm
Intestinal hypermotility
Obstructive lung disease
Premature labor
Urinary incontinence
Other
Aldosteronism
Antimalarial drug resistance
Cancer chemotherapy (multiple drug resistance)
Epilepsy
Glaucoma
Manic syndrome
Motion sickness
Spinal cord injury
Tinnitus
Tourette's disorder
Vertigo

TABLE 7
CALCIUM-CHANNEL DEPENDENCY OF ATHEROSCLEROTIC EVENTS

Calcium-channel-dependent events
Smooth muscle events
contraction
migration
proliferation
transformation
Neurotransmitter release
Growth factor release
Growth factor response
Calcium-channel-independent events
Endothelial cell function
Platelet function
Cholesterol processing
Low-density lipoprotein processing
Macrophage function

produce attendant changes in voltage-dependent drug interactions.[48] A shift in the hyperpolarizing direction will move the channel equilibrium at a given membrane potential to the open and inactivated state and will increase the apparent affinity of the calcium-channel antagonist.

Pathologic state of tissue

A number of disorders are associated with specific alterations in the numbers and functions of voltage-gated calcium channels.[10,51,52] Lambert-Eaton syndrome, associated with small lung-cell carcinoma, is an autoimmune disorder in which circulating antibodies directed against nerve-terminal calcium channels are associated with a dysfunction in neurotransmitter release. Also, some reports indicate that the Syrian cardiomyopathic hamster has an overexpression of cardiac calcium channels, and a rodent model of congestive heart failure exhibits down-regulation of cardiac calcium-channel numbers.

Neuronal calcium channels increase in experimental lead intoxication and also after chronic alcohol ingestion.[51] The latter observation probably accounts for the clinical utility of calcium antagonists for patients suffering seizures from alcohol withdrawal. Neuronal calcium channels also show very large decreases as a function of age in experimental animals; it is tempting to speculate that these changes are associated with the cognitive and behavioral deficits that accompany aging.[53]

The selectivity of action of the calcium-channel antagonists is determined by the extent to which channel number and function are affected by pathological states. It is likely that specific diseases will be associated with defined changes in calcium channel function as a contributory or causal factor.

EXPERIMENTAL USES

Calcium-channel antagonists have been used experimentally in a wide range of disorders outside the cardiovascular system, including disorders of nonvascular smooth muscle, central nervous system disorders (eg, vertigo, tinnitus, Tourette's syndrome), and indications that are not related to voltage-gated calcium channels, such as multiple drug resistance for cancer chemotherapeutic agents and antimalarial drug resistance (*Table 6*).

Effects on atherogenesis

In recent years, clinical trials have indicated that these agents may affect atherogenesis.[54] In the International Nifedipine Trial on Antiatherosclerotic Therapy,

nifedipine modestly reduced the incidence of new lesions in coronary arteries but was without effect on existing lesions.[55] Clinical studies with nifedipine and the other classes of calcium-channel antagonists parallel earlier experimental studies, principally in cholesterol-fed rabbits, with these agents.[56] At issue is the extent to which the antiatherogenic properties of the calcium-channel antagonists are related to calcium-channel antagonism.

The "atherogenic cascade"—the sequence of events that lead or contribute to atherosclerosis (*Figure 9*)—contains a number of processes that are calcium-dependent and sensitive to calcium-channel antagonists, including smooth muscle cell proliferation and migration, the actions of growth factors, and, possibly, processes that depend on chemotactic factor. These may be targets for the clinical antiatherogenic actions of calcium-channel antagonists. However, other properties of calcium-channel antagonists (including antioxidative effects, inhibition of platelet function, enhancement of LDL receptor function, and promotion of cholesterol ester metabolism) that are not obviously related to calcium-channel antagonism may also contribute to the antiatherogenic activities observed experimentally and clinically. It remains to be determined whether long-term administration of calcium antagonists influences processes other than voltage-gated calcium channels, and whether these processes contribute to the antiatherogenic actions and other possible long-term effects of calcium-channel antagonist administration. Such processes (*Table 7*) may also contribute to the selectivity of action of the calcium-channel antagonists.

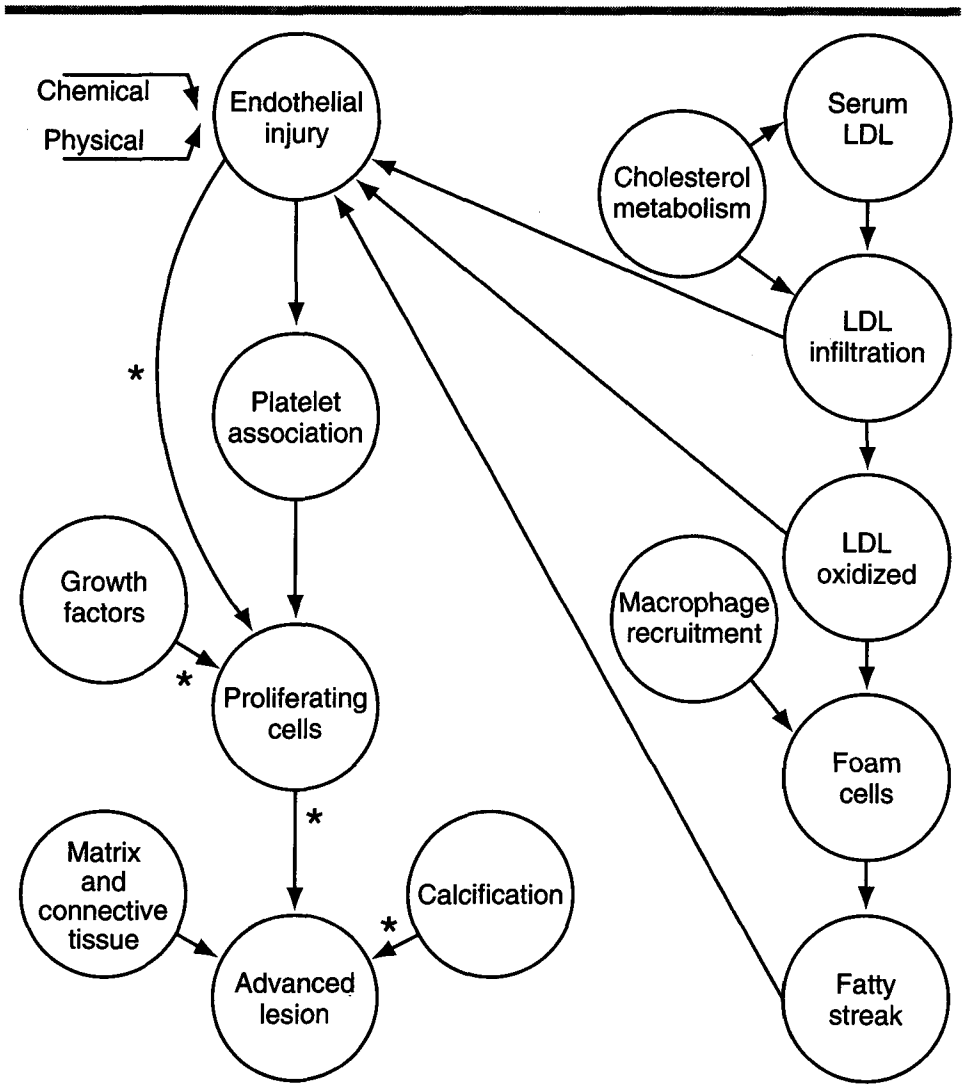

FIGURE 9. The "atherogenic cascade"—the sequence of events that lead or contribute to atherosclerosis. Steps known or believed to be sensitive to calcium-channel antagonists at cardiovascular concentrations are marked with an asterisk. Reproduced with permission from Born GVR, Poole-Wilson P, Triggle DJ. Calcium antagonists and atherosclerosis. London: Science Press, 1991.

SUMMARY

Calcium-channel antagonists interact specifically at a set of binding sites associated with a single class of voltage-gated calcium channel. They differ quantitatively and qualitatively in their activities. In the car-

diovascular system (their primary therapeutic target), verapamil, diltiazem, and nifedipine present a broad range of vascular-cardiac selectivities that define their general therapeutic applications, their contraindications with other classes of cardiovascular drugs, and their side-effect profiles.

The new generation of calcium-channel antagonists, particularly the 1,4-dihydropyridine class, indicates that vascular-cardiac selectivity differs not only between the three major structural classes of drug but also within a structural class. Enhanced vascular-cardiac selectivity is observed with some 1,4-dihydropyridines, including felodipine, and enhanced regional vascular selectivity is observed with other 1,4-dihydropyridines including nimodipine and nisoldipine. A number of factors, including voltage-dependent actions and pharmacologically distinct channel subtypes, contribute to the observed selectivity profiles.

Second-generation calcium-channel antagonists

The specific cardiovascular advantages gained from the new generation of vascular-selective calcium-channel antagonists are twofold. Regional vascular selectivity permits selective vasodilation without generalized hemodynamic changes. This quality underlies the cerebral selectivity of nimodipine, and vascular selective antagonists may be developed for other regions, including the pulmonary and renal beds.

Agents with generalized vascular selectivity can reduce negative inotropic potency. Cardiac depression limits the use of verapamil and diltiazem in patients with hypertension and in patients with congestive heart failure and ventricular dysfunction,[57–59] and it becomes a significant factor when nifedipine is applied to patients with left ventricular dysfunction. Patients with congestive heart failure have both a reduced calcium mobilization system and a compromised sympathetic system[52]: under such conditions, the cardiodepressant properties of the calcium-channel antagonists are exaggerated. Thus, calcium antagonists with enhanced vascular selectivity may prove useful as vasodilator therapy for patients with congestive heart failure;[60] consistent with this rationale, they have produced greater hemodynamic benefits in patients with chronic heart failure and with fewer detrimental effects than with first-generation agents.[61–64] Whether the enhanced vascular selectivity of some new generation calcium-channel antagonists is the dominant factor in determining their clinical acceptability is under evaluation.[59]

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