19 | Calcium Channel Blockers

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DRUG LIST

The agents commonly called the *calcium channel blockers* comprise an increasing number of agents, including the prototypical verapamil (*Calan, Isoptin*), nifedipine (*Adalat, Procardia*), and diltiazem (*Cardizem*). These agents are a chemically and pharmacologically heterogeneous group of synthetic drugs, but they possess the common property of selectively antagonizing Ca^{++} movements that underlie the process of excitation–contraction coupling in the cardiovascular system. *The primary use of these agents is in the treatment of angina, selected cardiac arrhythmias, and hypertension.*

Although the Ca^{++} channel blockers are potent vasodilating drugs, they lack the fluid-accumulating properties of other vasodilators and the persistent activation of the sympathetic and renin–angiotensin–aldosterone axes. Furthermore, the broad potential range of activities, both within and without the cardiovascular system, suggests that they may be clinically useful in disorders from vertigo to failure of gastrointestinal smooth muscle to relax .

A number of second-generation analogues are known, particularly in the nifedipine (1,4-dihydropyridine) series, including nimodipine (*Nimotop*), nicardip-ine (*Cardene*), felodipine (*Plendil*), nisoldipine (*Sular*), and amlodipine (*Norvasc*). These agents differ from nifedipine principally in their potency, pharmacokinetic characteristics, and selectivity of action. Nimodipine has selectivity for the cerebral vasculature; amlodipine exhibits very slow kinetics of onset and offset of blockade; and felodipine and nisoldipine are vascular-selective 1,4-dihydropyridines.

CALCIUM ANTAGONISM

The concept of calcium antagonism as a specific mechanism of drug action was pioneered by Albrecht Fleckenstein and his colleagues, who observed that verapamil and subsequently other drugs of this class mimicked in reversible fashion the effects of Ca^{++} withdrawal on cardiac excitability. These drugs inhibited the Ca^{++} component of the ionic currents carried in the cardiac action potential. Because of this activity, these drugs are also referred to as *slow channel blockers, calcium channel antagonists, and calcium entry blockers.*

The actions of these drugs must be viewed from the perspective of cellular Ca^{++} regulation (Fig. 19.1). Ca^{++} is fundamentally important as a messenger, linking cellular excitation and cellular response. This role is made possible by the high inwardly directed Ca^{++} concentration and electrochemical gradients, by the existence of specific high-affinity Ca^{++} binding proteins (e.g., calmodulin) that serve as intracellular Ca^{++} receptors, and by the existence of Ca^{++}-specific influx, efflux, and sequestration processes. Calcium, in excess, serves as a mediator of cell destruction and death during myocardial and neuronal ischemia, neuronal degeneration, and cellular toxicity. The control of excess Ca^{++} mobilization is thus an important contributor to cell and tissue protection.

The available Ca^{++} channel blockers exert their effects primarily at voltage-gated Ca^{++} channels of the plasma membrane. There are at least several types of channels—L, T, N, P/Q and R—distinguished by their electrophysiological and pharmacological characteristics. The blockers act at the L-type channel at three distinct receptor sites (Fig. 19.2). These different receptor interactions underlie, in part, the qualitative and quantitative differences exhibited by the three principal classes of channel blockers.

Cellular stimuli that involve Ca^{++} mobilization by processes other than that at the L-type voltage-gated channels will be either completely or relatively insensitive to the channel blockers. This differential sensitivity contributes to the variable sensitivity of vascular and
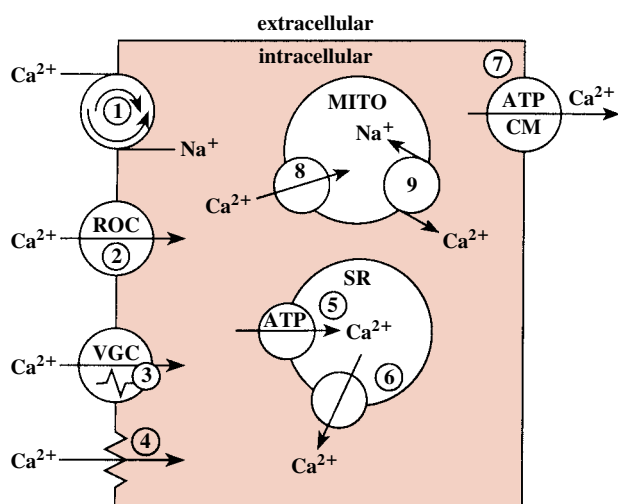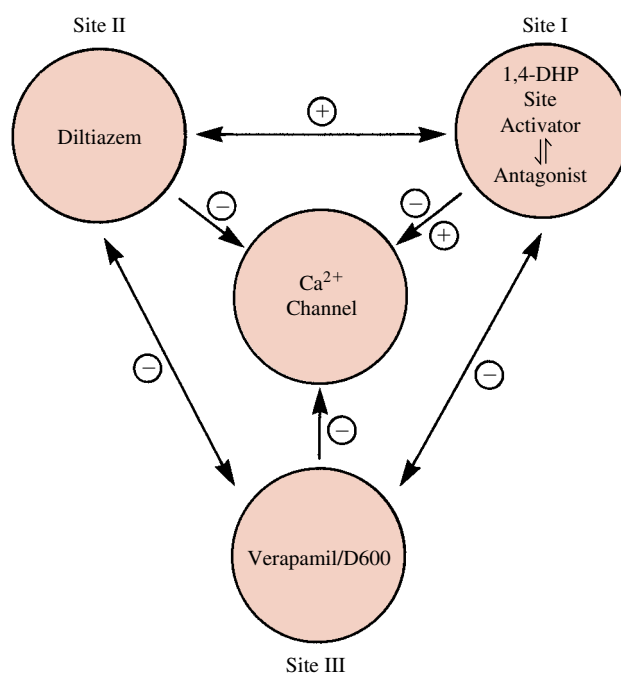
FIGURE 19.2

The principal receptors or drug binding sites at the calcium channel. These sites are linked to the opening and closing of the channel and to each other by activating (+) or inhibiting (−) allosteric mechanisms. The 1,4-DHP site is a receptor site for a number of 1,4-dihydropyridine compounds; D600 is the designation for a close chemical relative of verapamil.

FIGURE 19.1

Cellular calcium regulation. Depicted are several sites that control calcium entry, efflux, and sequestration. *1.* Na^+, Ca^{++} exchange. *2.* Receptor-operated channels. *3.* Voltage-gated channels. *4.* Leak pathways. *5, 6.* Entry and efflux in sarcoplasmic reticulum. *7.* Plasma membrane pump. *8, 9.* Entry and efflux in mitochondria. ATP, adenosine triphosphate; CM, cell membrane.

nonvascular smooth muscle to the actions of these drugs, for example, the regional vascular selectivity and the general lack of activity of these agents in respiratory or gastrointestinal smooth muscle disorders.

The Selectivity of Action of Calcium Channel Blockers

Although the available Ca^{++} channel blockers exert their effects through an interaction at one type of channel, they do so at different sites. Figure 19.2 shows that the channel blockers act at three discrete receptor sites to mediate channel blockade indirectly rather than by a direct or physical channel block. The existence of the different receptor sites is one basis for the different pharmacological profiles exhibited by these agents.

The activity of the Ca^{++} channel blockers increases with increasing frequency of stimulation or intensity and duration of membrane depolarization. *This use-dependent activity is consistent with a preferred interaction of the antagonists with the open or inactivated states of the Ca^{++} channel rather than with the resting state.* This activity is not shared equally by all Ca^{++} blockers and so may provide a further basis for the therapeutic differences between them. For example, verapamil and

diltiazem are approximately equipotent in cardiac and vascular smooth muscle, whereas nifedipine and all other agents of the 1,4-dihydropyridine class are significantly more active in vascular smooth muscle. Furthermore, different members of the 1,4-dihydropyridine class have different degrees of vascular selectivity. These differences are broadly consistent with the observation that verapamil and diltiazem act preferentially through the open channel state, and nifedipine and its analogues act through the inactivated state.

The clinically available calcium channel antagonists have also proved to be invaluable as molecular probes with which to identify, isolate, and characterize calcium channels of the voltage-gated family. In particular, the 1,4-dihydropyridines with their high affinity, agonist–antagonist properties, and selectivity have become defined as molecular markers for the L-type channel.

Synthetic drugs of comparable selectivity and affinity to the 1,4-dihydropyridines do not yet exist for the other channel types, T, N, P/Q, and R; these remain characterized by complex polypeptide toxins of the aga- and conotoxin classes. Neuronal pharmacology, including that of the central nervous system (CNS), is dominated by the N, P/Q, and R channels. This underscores the normally weak effect of L-channel antagonists on CNS function. Drugs that act at the N, P, and R channels with comparable selectivity and affinity to the 1,4-dihydropyridines may be expected to offer major potential for a variety of CNS disorders, including neuronal damage and death from ischemic insults.

The Ca^{++} channel blockers also differ in the extent of their additional pharmacological properties. Verapamil and to a lesser extent diltiazem possess a number of receptor-blocking properties, together with Na^+ and K^+ channel–blocking activities, that may contribute to their pharmacological profile. Nifedipine and other 1,4-dihydropyridines are more selective for the voltage-gated Ca^{++} channel, but they may also affect other pharmacological properties because their nonpolar properties may lead to cellular accumulation. Together with their channel-blocking properties, these properties may con-

tribute to the recently described antiatherogenic actions seen in experimental and clinical states.

PHARMACOLOGICAL EFFECTS ON THE CARDIOVASCULAR SYSTEM

The effects of the prototypical calcium channel blockers are seen most prominently in the cardiovascular system (Table 19.1), although calcium channels are widely distributed among excitable cells. The following calcium channel–blocking drugs are clinically the most widely used compounds in this very extensive class of pharmacological agents: amlodipine, diltiazem, isradipine, nifedipine, nicardipine, nimodipine, and verapamil.

Vascular Effects

Vascular tone and contraction are determined largely by the availability of calcium from extracellular sources (influx via calcium channels) or intracellular stores. *Drug-induced inhibition of calcium influx via voltage-gated channels results in widespread dilation and a decrease in contractile responses to stimulatory agents.* In general, arteries and arterioles are more sensitive to the relaxant actions of these drugs than are the veins, and some arterial beds (e.g., coronary and cerebral vessels) show greater sensitivity than others. Peripheral vasodilation and the consequent fall in blood pressure are commonly accompanied by reflex tachycardia when nifedipine and its analogues are used; this is in contrast to verapamil and diltiazem, whose effects on peripheral vessels are accompanied by cardiodepressant effects.

Cardiac Effects

Calcium currents in cardiac tissues serve the functions of inotropy, pacemaker activity (sinoatrial (SA) node), and conduction at the atrioventricular (A-V) node. In principle, the blockade of calcium currents should result in decreased function at these sites. In clinical use, how-

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T A B L E **19.1** Cardiovascular Effects of Calcium Channel Blockers*

	Nifedipine	Diltiazem	Verapamil
Blood pressure	−	−	−
Vasodilation	+++	++	++
Heart rate	++	−	±
Contractility	0/+	0	0/−
Coronary vascular resistance	−	−	−
Blood flow	+++	+++	++

Key: + = increase; − = decrease; 0 = no significant effect.
*Changes are those seen commonly following oral doses used in therapy of hypertension or angina.
The magnitude of response is indicated by number of symbols.

ever, dose-dependent depression is seen only with verapamil and diltiazem and not with nifedipine, reflecting mainly differences in the kinetics of their interaction at calcium channels (see section on calcium antagonism). *Characteristic cardiac effects include a variable slowing of the heart rate, strong depression of conduction at the A-V node, and inhibition of contractility, especially in the presence of preexisting heart failure.*

THERAPEUTIC APPLICATIONS

The calcium channel–blocking drugs have been investigated for an unusually wide number of clinical applications. Verapamil-induced improvement of diastolic function has proved to be beneficial in the treatment of hypertrophic cardiomyopathy. Vasodilatory properties of these drugs are used in the treatment of peripheral vasoconstrictive disorders (Raynaud's disease) and in relieving vasospasm following subarachnoid hemorrhage. There is ongoing interest in investigating protective effects on renal function and in the ability to reduce deleterious vascular changes in diabetes mellitus. Similarly, the potential benefit afforded by their selective vasodilatory action (especially the second-generation agents) in the management of heart failure is an area of interest. These drugs are of some benefit in a variety of noncardiovascular conditions characterized by hyperactivity of smooth muscle (e.g., achalasia). However, their main applications are as follows.

Hypertension

The calcium channel–blocking drugs are effective antihypertensive agents and enjoy widespread use as single medication or in combination. *Their effectiveness is related to a decrease in peripheral resistance accompanied by increases in cardiac index.* The magnitude of their effects is determined partly by pretreatment blood pressure levels; maximum blood pressure lowering generally is seen 3 to 4 weeks after the start of treatment. These drugs possess some distinct advantages relative to other vasodilators, including the following:

1. Their relaxant effect on large arteries results in greater compliance, which is beneficial in older persons.
2. Tolerance associated with renal retention of fluid does not occur; an initial natriuretic effect is often observed, especially with the nifedipine group of blockers.
3. They do not have significant effects on the release of renin or cause long-term changes in lipid or glucose metabolism.
4. Postural hypotension, first-dose effect, and rebound phenomenon are not commonly seen.

Their antihypertensive efficacy is comparable to that of β-adrenergic blockers and angiotensin-converting enzyme (ACE) inhibitors. The choice of a calcium channel blocker, especially for combination therapy, is largely influenced by the effect of the drug on cardiac pacemakers and contractility and coexisting diseases, such as angina, asthma, and peripheral vascular disease.

Ischemic Heart Disease

The effectiveness and use of calcium channel blockers in the management of angina are well established (see Chapter 17); their benefit in postinfarction stages is less certain. Efficacy in angina is largely derived from their hemodynamic effects, which influence the supply and demand components of the ischemic balance (1) by increasing blood flow directly or by increasing collateral blood flow and (2) by decreasing afterload and reducing oxygen demand. *All three agents are useful in the management of stable exertional angina,* with their vasodilatory and cardiac effects making beneficial contributions. Given the differences in their relative effects (Table 19.1), the response of the patient can vary with the agent used and the preexisting cardiac status.

All agents are also effective in the control of variant (Prinzmetal's) angina, in which spasm of the coronary arteries is the main factor. Their usefulness in the more complex unstable (preinfarction) angina is less definite, depending on the hemodynamic status and the susceptibility of the patient to infarction.

Cardiac Arrhythmias

The prominent depressant action of verapamil and diltiazem at the SA and A-V nodes finds use in specific arrhythmias. *They are of proven efficacy in acute control and long-term management of paroxysmal supraventricular tachycardia* (see Chapter 16). Their ability to inhibit conduction at the A-V node is employed in protecting ventricles from atrial tachyarrhythmias, often in combination with digitalis or propranolol.

PHARMACOKINETICS

A comparison of the pharmacokinetic properties of these agents is listed in Table 19.2. All three drugs are well absorbed following oral administration. Verapamil and diltiazem undergo greater first-pass metabolism relative to nifedipine, resulting in lower bioavailability of the former two drugs. Hepatic metabolism of nifedipine is complete, yielding inactive metabolites; this is unlike verapamil and diltiazem, whose metabolites have pharmacological activity. Verapamil is metabolized stereoselectively in favor of the more active (−) enantiomer, thus requiring higher plasma concentrations after oral administration.

TABLE 19.2 Pharmacokinetics of Calcium Channel Blockers

	Verapamil	Nifedipine	Diltiazem
Absorption, oral (%)	>90	>90	>90
Bioavailability (%)	20	60–80	~40
Onset of action: oral (min)	90–120	<20	<30
Peak effect	5 hr	1–2 hr	3–5 hr
Protein binding (%)	90	90	90
Plasma half-life	4–8 hr	5 hr*	5 hr
Metabolism	80% 1st-pass active metabolites	Inactive metabolites	60% of 1st dose: 10% steady state
Excretion			
Renal (%)	70	90	30
Fecal (%)	15	10	70

*Six to 11 hours after oral tablets: above value for capsules.

TOXICITY

The common side effects seen in chronic therapy (Table 19.3) are mostly related to vasodilation—headaches, dizziness, facial flushing, hypotension, and so forth. High doses of verapamil in elderly patients are known to cause constipation. Serious side effects, especially following the intravenous use of verapamil, include marked negative inotropic effects and depression of preexisting sick sinus syndrome, A-V nodal disease, and enhancement of the action of other cardiodepressant drugs. Their use is generally contraindicated in obstructive conditions (e.g., aortic stenosis). No consistent or significant changes in lipid and glucose levels have been reported with chronic therapy. Non–sustained release formulations of nifedipine are contraindicated in hypertension because of sympathetic rebound that may aggravate existing left ventricular dysfunction.

TABLE 19.3 Adverse Effects of Calcium Channel Blockers

	Verapamil	Diltiazem	Nifedipine
Tachycardia	0	0	+
Decreased heart rate*	+	+	0
Depressed A-V nodal conduction*	+++	++	0
Negative inotropy	++	+	0
Vasodilation (flushing, edema, hypotension, headaches)	+	+/0	+++
Constipation, nausea	++	+	+/0

Key: + = increase; 0 = no change.
*Marked effect in presence of sick sinus syndrome and A-V nodal disease.

Study Questions

1. Which of the following statements most accurately characterize the cellular action of the calcium channel blockers?
   (A) Their interaction with membrane phospholipids results in a nonselective decrease of ion transport.
   (B) They inhibit the Na^+–Ca^{++} exchanger in cardiac and smooth muscle.
   (C) They interact at three distinct sites at the L-type voltage-gated calcium channels.
   (D) Their interaction with the sodium pump results in an inhibition of calcium transport.

2. Which of the following calcium channel blockers would be most likely to suppress atrial tachyarrhythmias involving the A-V node?
   (A) Nifedipine
   (B) Verapamil
   (C) Nicardipine
   (D) Amlodipine

3. All of the following statements are applicable with regard to the systemic effects caused by nifedipine EXCEPT:
   (A) It typically causes peripheral vasodilation.
   (B) It often elicits reflex tachycardia.
   (C) It causes coronary vasodilatation and an increase in coronary blood flow.
   (D) Its benefit in the management of angina is related to the reduction in preload that it induces.

4. All of the following statements regarding the pharmacokinetics of calcium channel blockers are correct EXCEPT
   (A) They are characterized by significant amount (~ 90%) of protein binding.
   (B) They undergo significant first-pass metabolism.
   (C) Their half-life is not altered by hepatic cirrhosis.
   (D) They can be administered orally.

5. All of the following adverse effects are likely to occur with long-term use of calcium channel blockers EXCEPT
   (A) Skeletal muscle weakness
   (B) Flushing
   (C) Dizziness
   (D) Headache

ANSWERS

1. **C.** The available blockers act primarily at voltage-gated calcium channels of the L type. The three prototypes, verapamil, nifedipine, and diltiazem, act at three discrete sites at this channel.
2. **B.** The other three drugs (dihydropyridines) are characterized by relatively selective vasodilator effects with little if any cardiac effects at doses employed clinically for hypertension or angina.
3. **D.** The vasodilatory effects of nifedipine are largely restricted to arteries (and consequently the afterload). It does not alter venous tone (and thus preload) significantly.
4. **C.** Since they are metabolized in the liver, hepatic cirrhosis can be expected to alter their half-life.
5. **A.** Skeletal muscles depend on the mobilization of intracellular stores of calcium for their contractile responses rather than transmembrane flux of calcium through the calcium channels. Therefore, skeletal muscle weakness is not likely to occur.

SUPPLEMENTAL READING

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Case **Study** Nifedipine-Induced Vasodilatation

A 65-year-old recently retired man is being evaluated for elevated blood pressure. He occasionally has angina precipitated by physical exertion and rapidly controlled by sublingual use of nitroglycerin. His blood pressure is 160/100 mm Hg. He is advised to take nifedipine 80 mg/day, which he does, in divided doses of 20 mg (capsules). He develops flushing, dizziness, and nervousness shortly (<30 minutes) after taking the drug, and these symptoms persist for approximately 1 hour. The number of anginal episodes have increased during this period. QUESTION: How do the properties of nifedipine relate to the above development?

ANSWER: Nifedipine, unless formulated for slow, sustained release, is characterized by relatively rapid onset of vasodilatory effects. This man's side effects reflect the rapid and intense fall in blood pressure and consequent reflex increases in sympathetic tone. The increase in anginal episodes also is a result of drug-induced periodic increases in heart rate.