

2. Introduction
Hypertension is the most common cardiovascular disease. Hypertension or High Blood Pressure is a medical condition in which constricted arterial blood vessels increase the resistance to blood flow, causing the blood to exert excessive pressure against vessel walls. The heart must work harder to pump blood through the narrowed arteries. If the condition persists, damage to the heart and blood vessels is likely increasing the risk for stroke, heart attack, and kidney or heart failure. Often called the “silent killer,” hypertension usually causes no symptoms until it reaches a life-threatening stage.

2.1 Calcium Channel Blockers

2.1.1 History of calcium channel blockers
Calcium channel blocking drugs represent one of the more important clinical pharmacological advances of this decade. The discovery of calcium antagonism occurred by chance in November 1963 as a new principle of action of coronary drugs, when it was reported that two new compounds, later given the generic names verapamil and prenylamine, mimicked the cardiac effect of simple calcium withdrawal in that they diminished calcium dependent high energy phosphate utilization, contractile force and oxygen requirement of the beating. In 1969, the term calcium antagonists were given a novel drug designation. In an extensive search for other calcium antagonists, a considerable number of substances that also met these criteria were identified in 1975 e.g. nifedipine, nimodipine. In 1975, Japanese pharmacologists introduced diltiazem to this group. Fleckenstein stated that complete blockage of transmembrane calcium ions entry is incompatible with life and therefore the term calcium blockade should be avoided. However, the term calcium antagonist implies that calcium and its antagonists interact at specific receptors. This is probably not the case, as their predominant action is to reduce calcium ions influx at specific sites including cell membrane. For these reasons, the term calcium channel blocking drug was preferred. Also, they were referred to by some authors as calcium entry blockers as their primary action is inhibition of the inward movement of calcium ions through voltage-dependent calcium channels at different sites. The work in the 1960s of Fleckenstein, Godfraind, and their colleagues led to the concept that drugs can alter cardiac and smooth muscle contraction by blocking the entry of Ca$^{2+}$ into myocytes. Hass and Hartfelder reported in 1962 that verapamil, a putative coronary vasodilator. Kolhardt and Fleckenstein reported nifedipine to block the movement of Ca$^{2+}$ through
the cardiac myocyte Ca^{2+} channel.\textsuperscript{3,4} Five classes of compounds are phenylalkylamines, dihydropyridines, benzothiazepines, diphenylpiperazines, and diarylaminopropylamine. At present, verapamil (phenylalkylamines), diltiazem (benzothiazepines), nicardipine, nifedipine, isradipine, amlodipine, felodipine, nisodipine, and nimodipine (dihydropyridines) and bepridil (diarylaminopropylamine) are the widely used drugs as calcium channel blockers. There structures are shown below,
2.1.2 Classification of Calcium channel blockers

Calcium channel blockers comprise three chemical groups, all of them bind the L-type Ca++ channel, but each class binds to different binding sites of the same channel.
Figure 1. Classification of calcium channel blockers

Several thousand compounds are known to have a calcium channel inhibitory effect. Fleckenstein classified calcium antagonists, based on the specificity of inhibition of the slow calcium current, into: Group A: for 90 to 100 percent inhibition of calcium influx without change in the sodium current (verapamil, diltiazem and the dihydropyridines); Group B: for 50 to 70 percent inhibition of calcium influx current without change in the sodium current (bepridil, cinnarizine and prenylamine); Group C: for agents exhibiting some inhibition of calcium influx (phenytoin, indomethacin and propranolol).

Robertson and Robertson divided CCBs into three groups: Group I is the group that blocks VGCCs in the myocardium and arteries. This group was further subdivided into: Group IA, which consists of drugs that affect myocardium with no action on SA or AV nodes and includes dihydropyridines, e.g. amlodipine, nifedipine and nicardipine and Group IB, which has additional action on SA and AV nodes and includes phenylalkylamines (verapamil, anipamilard and gallapamil), benzothiazepines (diltiazem). Group II a drug blocks calcium channels of peripheral arteries, but spare myocardium, and includes diphenylpiperazines, cinnarizine and flunarizine. Group III contains drugs which have action on calcium and fast sodium channels, having selective myocardial effect and includes bepridil, prenylamine and tiapamil (figure 1).

2.1.3 Mechanism of action
The interaction of the calcium channel modulators with calcium channels is complex. Three distinct but allosterically interacting receptors exist for the three different chemical classes of dihydropyridines, phenylalkylamines (verapamil like drugs) and benzothiazepines (diltiazem like drugs). All these receptors are located on the VGCCs. The effects of calcium antagonists are membrane potential (voltage) dependent. The binding and effects of calcium antagonists are stereoselective. Generally, stereoisomers of the same compound produce qualitatively the same effects, with one stereoisomer being more effective than the other. In a few special situations, the stereoisomers produce opposite pharmacological effects. While the (R)-enantiomers of Bay, K-8644 and 202-791 (two recently synthesized experimental 1,4-dihydropyridine derivatives), act like calcium antagonists, the (S)-enantiomers are calcium agonists. It has been postulated that conformational alterations occur in the receptors and/or separate binding sites exist for agonists and antagonists. CCBs exert their effect through either the production of a physical plug-like obstruction or distortion of the membrane through a nonspecific interaction with the membrane phospholipids that surround and functionally modulate ion transport by channel proteins. However, it was found that dihydropyridines, which bind to alpha1 subunit of the calcium channel, affect channel function in a complex way, not simply by physical plugging of the pore. This became clear when some dihydropyridines were found to bind to the same site but to act in the converse way, that is, to promote the opening of VGCCs.

Calcium antagonists exhibit different binding affinities. Depending on the membrane potential (voltage) and the frequency of channel opening, it is thought that calcium antagonists bind with highest affinity to channels in the inactivated state. The channels can exist in one of three distinct states; mode 0, 1, and 2. When a channel is in mode 0, it does not open in response to depolarization. In mode 1, depolarization produces a low opening probability and each opening is brief. In mode 2, depolarization produces a very high opening probability and single openings are prolonged. Under normal conditions, about 70% of the channels at any one moment exist in mode 1, with only 1% or less in mode 2. Each channel switches randomly and quite slowly between the three modes. Dihydropyridines of the antagonist’s type bind selectively to channel in mode, thus favoring this non-opening state. It was found that only the L-type channels were sensitive to calcium channel-inhibiting drugs. Since the distribution of the channel subtypes differs in various tissues, drug sensitivity of the...
tissues is also different. In addition, even the L-type calcium channels are different in various tissues with respect to their affinities for calcium antagonists (figure 2). CCBs bind to the receptors with higher affinity under depolarized rather than polarized conditions. The effects of one calcium antagonist should not be extrapolated to another of a different subtype because drugs belonging to different subtypes have different pharmacological effects\(^\text{10}\).

![Figure 2. Positions of Ca Ions in cell membrane](image)

As the following table 1 shows, there are differences in terms of tissue selectivity between dihydropyridines (nifedipine and others), diltiazem and verapamil:

Table 1. Drugs & their activity in tissue.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peripheral and coronary vasodilation</th>
<th>Depression of cardiac contractility</th>
<th>Depression of SA node</th>
<th>Depression of AV node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>+++</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Verapamil</td>
<td>++++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
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Dihydropiridines have minimal effect on cardiac conduction or heart rate, while they have potent actions as arteriolar vasodilators. This class of drugs can cause reflex tachycardia when peripheral vasodilation is marked. On the other hand, verapamil and diltiazem slow AV conduction and decrease SA node automaticity, they also decrease heart rate. Diltiazem is used in the treatment of variant angina because of its coronary antispasmodic properties.

Figure 3. Effects of CCBs on heart contraction and conduction

2.1.4 Types of Calcium Channels

Three types of calcium channels have been identified: voltage-sensitive, receptor operated (cardiac muscle & vascular smooth muscle) and stretch operated (in some blood vessels) channels. The regulation of calcium ions depends on both the entry and exit of calcium across the plasma membrane and on the sequestration and release of calcium within the cell. At the membrane level, calcium entry into the cell occurs partly through voltage gated calcium channels (VGCCs) which open when the cell membrane is depolarized. VGCCs belong to a family of homologous proteins that also includes channels for sodium and potassium. In addition, there are believed to be receptor-operated calcium channels (ROCCs), which are coupled to excitatory receptors either directly or via G-proteins and open in response to receptor ligands, such as noradrenaline acting on alpha1-adrenoceptor. In general, calcium channels are membrane-spanning, funnel-shaped glycoproteins that function like ion selective
valves. They form a water-filled pore that open and close to permit calcium ions to move in the direction of its electrochemical concentration gradient. Each channel has outer and inner gates: the outer gates are specifically blocked by tetrodotoxin in fast channels and by calcium channel blockers in slow channels. The inner gates, particularly in slow channels, appear to be dependent on the phosphorylation state of the membrane. The position of a channel gate, which is a portion at or near the inner side of the gate, indicates whether the channel is in the closed or opened state. Verapamil and diltiazem block slow channel conduction at the inner gate and possess some fast channel blocking activity as well\(^1\). When conformational changes in the channel macromolecule occur, the activation and inactivation gates move into and out of an occluding position. This determines opening and closing of the channel pore. Calcium binding sites present in the pore ensure ion selectivity of the channels. Phosphorylation sites as well as drug and toxin binding sites of the channel macromolecule play important roles in the regulation of the channel. It should be emphasized that the exact macrostructure of the channel proteins, putative gates and other regulatory sites is unknown at this time\(^1\). Though the direct evidence for ROCCs appears to be strong, they have so far eluded identification experimentally and some even doubt their existence. ROCCs do not appear to be targets for any of the known types of calcium antagonists which act only on VGCCs\(^1\).

### 2.1.5 Types of Voltage gated calcium channel blockers (VGCCs)

Using electrophysiological and pharmacological techniques, Tsien et al. identified three different types of VGCCs which they called L-type (for long lasting, large channels), T-type (for transient, tiny channels) and N-type (for neuronal, neither L nor T). They are classified according to their activation and inactivation kinetics, their conductances, their ion specificity and their sensitivity to drug and toxin. Subsequently, high threshold VGCCs were found to exist in some neurons and were termed P-type channels (for purkinje cells). There are several endogenous and exogenous modulators that inhibit calcium channels, including dependence of the tissue on external calcium ions, existence of calcium channel subtypes, voltage dependence of drug binding and effects, and frequency dependence of drug effects. All excitable tissues contain voltage dependent calcium channels and high affinity, reversible and stereospecific binding sites for calcium channel-inhibiting drugs. However, calcium antagonists do not affect every tissue equally.\(^1\)

### 2.1.5.1 L-type channels
These are widely distributed in many tissues particularly in heart, smooth and skeletal muscles. They are highly sensitive to the dihydropyridines e.g. nifedipine, phenylalkylamines e.g. diltiazem. There appear to be diverse forms of the L-type channels (L1, 2, 3, isoforms) allowing tissue selectivity and diversity of function.\textsuperscript{15-17}

2.1.5.2 N-type channels
These N-type channels generally seemed to be sensitive to W-contoxins and in certain instance may be coupled to transmitter release whereas selective antagonists of L-type channels do not normally modify neurotransmitter release. Like T but unlike L, N-channels, contribute to phasic currents and require strongly negative holding potentials for complete removal of inactivation. Like L but unlike T, N current requires strong depolarization for activation and is relatively sensitive to the inorganic blockers cadmium.\textsuperscript{18}

2.1.5.3 P-type channels
These were proposed by Llinas \textit{et al}\textsuperscript{19} on the basis that, dihydropyridine and contoxin resistant currents present in cerebellar Purkinje and granule cells. The most selective toxin is funnel web spider venom. They may form a larger proportion of calcium channels in the brain. Although several calcium ion channels are known, all presently available CCBs act preferentially or solely on one of them, the L-channel.

2.1.6 Pharmacology
Many drugs affect calcium ion movement in smooth and cardiac muscle. This general monograph focuses on the calcium channel blockers affecting the cardiovascular system. Calcium channel blockers (also referred to as slow channel blockers, calcium entry blockers or calcium antagonists) are a chemically and pharmacologically heterogeneous group of drugs, but physiologically they all share the ability to selectively antagonist the calcium ion movements that are responsible for the excitation-contraction coupling in the cardiovascular system. There are two main classes of calcium channel blockers: dihydropyridines (nifedipine, nicardipine, amlodipine, felodipine and nimodipine) and nondihydropyridines which include diltiazem (a benzothiazepine) and verapamil (a phenylalkylamine). Flunarizine is an antihistamine with calcium channel blocking activity.

Calcium channel blockers exert their effect at the voltage-gated (or slow) calcium channels of the plasma membrane. Calcium channel blockers block transmembrane influx of calcium through the slow channel into the cardiac muscle and vascular smooth muscle, without significantly affecting the transmembrane influx of sodium...
through the fast channel. This results in a reduction of free calcium ions in the muscle tissue and no change in serum calcium concentrations. The effects on the cardiovascular system include depression of mechanical contraction of myocardial and smooth muscle and depression of both impulse formation (automaticity) and conduction velocity. The different pharmacological profiles for these agents are in part based on their ability to bind to different receptor sites at the calcium channel. Dihydropyridines are strong vasodilators acting via relaxation of vascular smooth muscle cells. They have little direct effect on myocardial contractility or SA/AV nodal conduction. However, they cause tachycardia and increased cardiac output via reflex sympathetic activity. These drugs also cause peripheral edema, presumably through precapillary vasodilation. The nondihydropyridines (diltiazem and verapamil) have an increased effect on AV nodal conduction compared to that of the dihydropyridines; while they also cause vasodilation via relaxation of vascular smooth muscle; their vasodilatory effects are only one-tenth the magnitude of nifedipine's. All calcium channel blockers interfere somewhat with blood coagulation by inhibiting platelet aggregation.

Angina: The precise mechanism by which calcium channel blockers relieve angina has not been fully determined but it is believed to be brought about largely by its vasodilatory effects on the coronary and peripheral vasculature. This increases blood flow to the ischemic area of the myocardium and reduces oxygen demand by decreasing the after load.

Arrhythmia: Verapamil and diltiazem depress AV nodal conduction and prolong functional refractory periods, which is the basis for their use in supraventricular arrhythmias.

Hypertension: The mechanism by which calcium channel blockers reduce arterial blood pressure involves direct peripheral arterial vasodilation and reduction in peripheral vascular resistance.

Other Uses: Nimodipine, which has a more marked effect on the cerebral circulation than on the peripheral circulation, is used in the management of subarachnoid hemorrhage. Although the mechanism of action is not fully understood, current evidence suggests that it may be due to an increase in collateral circulation due to dilation of the small cerebral resistance vessels and/or prevention of calcium overload in the neurons. Flunarizine may relieve or prevent reactive vasodilation of migraine sufferers by inhibiting the vasoconstriction during the prodromal phase$^{20}$. 4-Aryl-1,4-
dihydropyridines of the nifedipine type (DHPs, e.g. 1-3) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina. More than 20 years after the introduction of nifedipine, many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market (e.g. Nicardipine and Nitrndipine). In recent years interest has also focused on aza-analogs, which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators. Over the past few years several lead-compounds have been developed (e.g. SQ 32926 and SQ 32547) that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compared favorably with second-generation analogues such as amlodipine and Nicardipine. These inherently asymmetric dihydropyrimidine (DHPM) derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure activity relationships and to get further insight into molecular interactions at the receptor level.

The synthetic potential of DHPM synthesis (now known as Biginelli reaction) remained unexplored for quite some time. In the 1970’s and 1980’s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended, allowing access to a large number of multifunctionalized dihydropyrimidines.
Since that late 1980’s a tremendous increase in activity has occurred, as evidenced by the growing number of publications and patents on the subject. This is mainly due to the fact that the multifunctionalized dihydropyrimidines represented a heterocyclic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives. More recently, appropriately functionalized DHPMs have emerged as e.g. orally active antihypertensive agents or α1a adrenergic-selective antagonists. A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol as a mitotic kinesin Eg5 motor protein inhibitor and potential new lead for the development of anticancer drugs. Apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated. Most notably among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.
Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate
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