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**Review Article**

# A REVIEW ON CALCIUM CHANNEL & ITS BLOCKERS

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**ABSTRACT**

Calcium channel is a specific ion channel which has selective permeability to calcium ions. In resting stage calcium is mainly stored in endoplasmic or sarcoplasmic reticulum (ER / SR) in cell. Calcium release from ER / SR is controlled by *inositol trisphosphate receptor* ($IP_3R$) and *ryanodine receptor* (RyR).

Voltage-gated calcium channels, Ligand-gated calcium channels, $Na^+$-$Ca^{2+}$ exchange, Store-operated calcium channels (SOCs) are four main routes by which $Ca^{2+}$ enters cells across the plasma membrane. Calcium is extruded from cells in exchange for $Na^+$, by $Na^+$-$Ca^{2+}$ exchange.

There are so many calcium channel blockers are using for treatment of hyper tension, angina, arrhythmia and also using for treatment of epileptic, nausea and some other diseases.

Calcium plays an important role in contraction of smooth muscle, cardiac muscle and skeletal muscles. It is also involved in release of neurotransmitters as well as hormones and also in initiation of action potential or impulse generation in the heart.

**Keywords:** Calcium channel, Calcium channel blockers, Hypertension, Arrhythmia, Angina, Epileptic, Nausea.

## INTRODUCTION

Ions are unable to penetrate the lipid bilayer of the cell membrane, and can get across only with the help of membrane-spanning proteins in the form of channels or transporters. The concept of ion channels was developed more than 50 years ago on the basis of electrophysiological studies on the mechanism of membrane excitation[1].

Ion channels consist of protein molecules designed to form water-filled pores that span the membrane, and can switch between open and closed states. The rate and direction of ion movement through the pore is governed by the electrochemical gradient of ions. Ion channels are characterized by:

- Their *selectivity* for particular ion species, determined by the size of the pore and the nature of its lining.
- Their *gating* properties (i.e. the nature of the stimulus that controls the transition between open and closed states of the channel).
- Their molecular architecture.

In all types of cells, the calcium ion ($Ca^{2+}$) is an important second messenger for intracellular signal transduction, while a high concentration of free Ca2+ $Ca^{2+}$ can also be a cellular toxin as has been demonstrated in ischemic brain damage. The intracellular concentration of free $Ca^{2+}$ {$[Ca^{2+}]_i$} is, therefore, precisely controlled at a low level, and each cell/tissue/ organ can express its function such as secretion and contraction, leading to memory, movement, pain, etc. In a resting condition, $[Ca^{2+}]_i$ is maintained at approximately 100 nM, which is 1/10,000 of the extracellular concentration of free $Ca^{2+}$ (approximately 1 mM). There are generally three mechanisms for maintenance of a large gradient of $Ca^{2+}$ concentrations. Those are (1) the cell membrane, which consists of a $Ca^{2+}$-impermeable lipid bilayer; (2) powerful systems to excrete $Ca^{2+}$outside to the extracellular space [$Ca^{2+}$ pump ($Ca^{2+}$-$H^+$-ATPase) and $Na^+$-$Ca^{2+}$ exchanger]; and (3) intracellular organelles such as endoplasmic reticulum and mitochondria for the $Ca^{2+}$ uptake.[1]

A membrane channel that is specific for calcium, which displays selective permeability to calcium ions. It is sometimes synonymous as voltage-dependent calcium channel, although there are also legend-gated calcium channel. They are categorized as L, T, N, P, Q and R types based on the activation and inactivation kinetics, ion specificity, and sensitivity to drugs and toxins.

A calcium channel is a structure in the body which allows cells to transmit electrical charges. These charges are carried on a calcium ion which can travel freely back and forth through the calcium channel. There are a number of different types of calcium channels, broken up by sensitivity and how they behave. This anatomical structure is part of a family of similar structures known collectively as ion channels[2].

Calcium channels are found in places like muscles, glial cells, and neurons. These types of cells are known as "excitable" cells. Different calcium channels work in different ways, but the general idea is that the structure is made from proteins which are sensitive to electrical impulses. When the proteins receive the right signal, they open the calcium channel, allowing an ion to flow across the channel to another cell.

## REGULATION OF INTRACELLULAR CALCIUM LEVELS[1]

Many drugs and physiological mechanisms operate, directly or indirectly, by influencing $[Ca^{2+}]_i$. The study of $Ca^{2+}$ regulation took a big step forward in the 1970s with the development of fluorescent techniques based on the $Ca^{2+}$-sensitive photo protein *aequorin*, and dyes such as Fura-2, which, for the first time, allowed free $[Ca^{2+}]_i$ to be continuously monitored in living cells with a high level of temporal and spatial resolution.

Most of the $Ca^{2+}$ in a resting cell is sequestered in organelles, particularly the endoplasmic or sarcoplasmic reticulum (ER / SR) and the mitochondria, and the free $[Ca^{2+}]_i$ is kept to a low level.

## CALCIUM ENTRY MECHANISMS

There are four main routes by which $Ca^{2+}$ enters cells across the plasma membrane:

- Voltage-gated calcium channels
- Ligand-gated calcium channels
- $Na^+$-$Ca^{2+}$ exchange
- Store-operated calcium channels (SOCs).

Voltage-gated calcium channels mediate calcium influx in response to membrane depolarization and regulate intracellular processes such as contraction, secretion, neurotransmission, and gene expression in many different cell types. Their activity is essential to couple electrical signals in the cell surface to physiological events in cells[12].

**Table 1: Different types of calcium channels, their locations, functions and drug effects**

| Cee | Main types | Characteristics | Location and function | Drug effects |
|---|---|---|---|---|
| Voltage | L | High activation threshold; slow inactivation. | Plasma membrane of many cells; main $Ca^{2+}$ source for contraction in smooth and cardiac muscle. | Blocked by dihydro-pyridines, verapamil, ditiazem; activated by BayK8644 |
| | N | Low activation threshold; slow inactivation. | Main $Ca^{2+}$ source for transmitter release by nerve terminals. | Blocked by ω-contoxin (component of Conus snail venom) |
| | T | Low activation threshold; fast inactivation. | Widely distributed; important in cardiac pacemaker atria (role in dysrhythmias) | Blocked by mibefradil |
| | P/Q | Low activation threshold; slow inactivation. | Nerve terminals; transmitter release | Blocked by ω-agatoxin (component of funnel web spider venom) |
| | R | Low activation threshold; fast inactivation. | ? | Not directly targeted by drugs; some experimental blocking agents Known; responds to GPCR agonist and antagonist in many cells. |
| Inositol triphosphate | $IP_3$ receptor | - | Location in ER/SR; mediated $Ca^{2+}$release in response to $IP_3$ produced by GPCR activation. | Not directly targeted by drugs; some experimental blocking agents known; responds to GPCR agonists in many cells. |
| Calcium ions | Ryanodine receptor | Directly activated in striated muscle via dihydropyridine receptor of T-tubules. | Location in ER/SR; mediated $Ca^{2+}$ evoked $Ca^{2+}$ release in muscle; also activated by second messenger cADP-ribose. | Activated by caffine (high concentrations), blocked by ryanodine; mutations may lead drug-induced malignant hypothermia. |
| Store depletion | Store-operated channels | Indirectly coupled ER/SR $Ca^{2+}$ Store. | Located in plasma membrane. | Activated indirectly by agents that deplete intracellular store (e.g. GPCR agonists, thapsigargin); not directly targeted by drugs. |

(Source of table: Rang & Dale 5th edition.)

**CALCIUM EXTRUSION MECHANISMS**

Active transport of $Ca^{2+}$ outwards across the plasma membrane, and inwards across the membranes of the ER or SR, depends on the activity of a $Ca^{2+}$-dependent ATPase, similar to the $Na^+/K^+$-dependent ATPase that pumps $Na^+$ out of the cell in exchange for $K^+$. Several subtypes of the $Ca^{2+}$-dependent ATPase have been cloned, but the physiological significance of this heterogeneity remains unclear. They have not been implicated in pharmacological responses, with the exception that thapsigargin (derived from a Mediterranean plant, *Thapsia garganica*) specifically blocks the ER pump, causing loss of $Ca^{2+}$ from the ER. It is a useful experimental tool but has no therapeutic significance. [1]

Calcium is also extruded from cells in exchange for $Na^+$, by $Na^+$-$Ca^{2+}$ exchange. The transporter that does this has been fully characterized and cloned, and comes in several molecular subtypes whose functions remain to be worked out. The exchanger transfers three $Na^+$ ions for one $Ca^{2+}$, and therefore produces a net depolarizing current when it is extruding $Ca^{2+}$. The energy for $Ca^{2+}$ extrusion comes from the electrochemical gradient for $Na^+$, not directly from ATP hydrolysis. This means that a reduction in the $Na^+$ concentration gradient resulting from $Na^+$ entry will reduce $Ca^{2+}$ extrusion by the exchanger, causing a secondary rise in $[Ca^{2+}]_i$, a mechanism that is particularly important in cardiac muscle. The exchanger can actually function in reverse if $[Na^+]_i$ rises excessively, resulting in increased $Ca^{2+}$ entry into the cell . The effect of digoxin on cardiac muscle is produced in this way. [1]

**CALCIUM RELEASE MECHANISMS**

There are two main types of calcium channel in the ER and SR membrane, which play an important part in controlling the release of $Ca^{2+}$ from these stores.

- The *inositol trisphosphate receptor* ($IP_3R$) is activated by inositol trisphosphate ($IP_3$), a second messenger produced by the action of many ligands on G-protein-coupled receptors. $IP_3R$ is a ligand-gated ion channel, although its molecular structure differs from that of ligand-gated channels in the plasma membrane. This is the main mechanism by which activation of G-protein-coupled receptors causes an increase in $[Ca^{2+}]_i$.

- The *ryanodine receptor* (RyR) is so called because it was first identified through the specific blocking action of the plant alkaloid ryanodine. It is particularly important in skeletal muscle, where there is direct coupling between the RyRs of the SR and the dihydropyridine receptors of the T-tubules (see below); this coupling result in $Ca^{2+}$ release following the action potential in the muscle fibre. RyRs are also present in other types of cell that lack T tubules; they are activated by a small rise in $[Ca^{2+}]_i$, producing the effect known as *calcium-induced calcium release* (*CICR*), which serves to amplify the $Ca^{2+}$ signal produced by other mechanisms such as opening of calcium channels in the plasma membrane. CICR means that release tends to be regenerative, because an initial puff of $Ca^{2+}$ releases more, resulting in localized 'sparks' or 'waves' of $Ca^{2+}$ release. [1]

**CALCIUM CHANNEL BLOCKERS**

Calcium channel blockers (CCBs) are drugs which block the calcium channels; they are classified based on their chemical structure.

**Table 2: Classification of Calcium channel blockers;**

| Class | Examples |
|---|---|
| 1. Phenyl alkyl amines | Verapamil |
| 2. Benzodiazepines | Diltiazem |
| 3. 1,4-dihydro pyridine derivatives | Nifedipine |
| | Nicardipine |
| | Isradipine |
| | Felodipine |
| | Amlodipine |

(Source of table: KD Tripathi 6th edition.)

**PHARMACOKINETICS**

Calcium antagonists in clinical use are all well absorbed from the gastrointestinal tract, and are given by mouth except for some special indications, such as following subarachnoid haemorrhage, for which intravenous preparations are available. They are extensively metabolised. Pharmacokinetic differences between different drugs and different pharmaceutical preparations are clinically important, because they determine the dose interval and also the intensity of some of the unwanted effects, such as headache and flushing. Amlodipine has a long elimination half-life and is given once daily, whereas nifedipine , diltiazem and verapamil have shorter elimination half-lives and are either given more frequently

or are formulated in various slow-release preparations to permit once-daily dosing. [1]

**USES OF CALCIUM CHANNEL BLOCKERS**

**A. Uses of CCBs in CVS**

**a. In treatment of angina[3]**

Verapamil was developed in Germany in 1962 as a coronary dilator. It had additional cardio depressant property but its mechanism of action is not known. Fleckenstien (1967) showed that it interfered with calcium movements into the cell.

All of three categories of CCBs verapamil, diltiazem and dihyropyridine derivatives are used in the treatment of angina.

The common properties of all three sub classes of CCBs is to invade calcium mediated slow channel component of action potential (AP) in smooth or cardiac muscle cell.

Two most important actions of CCBs which aids in the treatment of angina are-

1. Smooth muscle (specially vascular) relaxation.

2. Negative chronotropic, inotropic and dromotropic action on heart.

**On smooth muscle:** Smooth muscle depolarizes primarily by inward calcium movement through voltage sensitive channel. The calcium ion triggers release of more calcium from intracellular stores and together brings about excitation contraction coupling through phosphorylation of myosin light chain. CCBs cause relaxation by decreasing intracellular availability of calcium. They markedly relax arterioles but have mild effect on veins. Extra vascular smooth muscle is also relaxed (bronchial, bilary, intestinal, vesicle, uterine is also relaxed).

Nitrindipine and other DHPs have been shown to release NO from endothelium and inhibit cAMP – phosphodiesterase resulting in raised smooth muscle cAMP. This additional mechanism account for their predominant smooth muscle relaxant action. Released endothelial NO may exert anti atherosclerotic action.

**On heart:** In the working atrial and ventricular fibers calcium moves in during plateau phase of AP- releases more calcium from sarcoplasmic reticulum. Contraction through binding to troponin. Allowing of interaction of myosin with actin. The CCBs would thus have negative inotropic action. The 0 phase depolarization in SA and AV nodes is largely calcium mediated automaticity and conductivity of these cells appears to be dependent of the rate of the recovery of the calcium channels.

The L-type calcium channels activate as well inactivate at show rate. Consequently calcium depolarize cells (SA and AV nodes) have a considerably less steep 0 phase and longer refractory period. The recovery process which restores to the state from which it can again be activated by membrane depolarization is delayed by verapamil into a lesser extent by diltiazm (resulting in depression of pace maker activity and conduction) but not by DHPs (they have no negative chronotropic/dromotropic action).

Moreover channel blockade by verapamil is higher rate of stimulation that by nifedipine is independent of frequency, while diltiazem is intermediate. Thus verpamil slow sinus rate and AV conduction but nifedipine does not. Effect of diltiazem of sinus node automaticity and AV conduction is similar to that of verapamil. The DHPs are more selective for smooth muscle L-channels at contraction which cause vasodilation they have negligible negative inotropic action. Diltiazem cause less depression of contractility than verapamil.

**b. In treatment of arrythmia[3]**

Verapamil and Dilatiazem are preferred. The primary action of these drugs is to inhibit calcium-mediated slow channel inward current.

**Verapamil:** Of the many calcium channel blockers, verapamil, has the most prominent cardiac electrophysiological action. It blocks L-type Ca2+ and delays their recovery. The basic action of verapamil is to depress $ca^{2+}$ mediated depolarization. This suppresses automaticity or reentry dependant on slow response. Phase-4 depolarization in SA-node and PFs is reduced resulting in bradycardia and extinction of latent pacemakers. Reflex sympathetic stimulation due to vasodilatation particularly counteracts the direct bradycardia producing action. Delayed after depolarization in PFs is dampened. The most prominent action of verapamil is prolongation of AV-nodal ERP, as a result A-V conduction is markedly slowed and recently involving AV node is terminated.

**Use & Precautions:**

1. PSVT- verapamil can terminate attacks of PSVT.
2. To control ventricular rate in AF or AFI.

Reentrant supraventricular and nodal arrhythmias (WPW) are susceptible to verapamil, but it should not be used because of risk of increased ventricular rate due to reflex sympathetic stimulation and reduction of ERP of the bypass tract in some cases. Verapamil has poor efficacy in ventricular arrhythmias. In contrast to β blockers, verapamil prophylaxis does not reduce mortality in post MI patients.

**Table 3: Electrophysiological actions of calcium channel blockers:**

| | VERAPAMIL | DILTIAZEM | NIFEDIPINE |
|---|---|---|---|
| SA node Automatically | ↓ | ↓- | - |
| Ventricular automaticity | ↓ | - | - |
| ERP: Atrial | - | - | - |
| : Av Nodal | ↑↑ | ↑ | ↑↓ |
| : Ventricular | - | - | - |
| : By-pass t act | ↑ | ↑- | - |
| ECG: | ↑ | ↑↓ | ↓ |
| R-R Interval :P-R Interval | ↑ | ↑ | - |

(Source of table: Rang & Dale 5th edition.)

**Diltiazem**: The direct cardiac action of diltiazem is similar to those of verapamil. However, they are less marked. It is alternative to verapamil for PSVT.

For rapid control of ventricular rate in AF or AFI, IV diltiazem is preferred over verapamil, because it can be more easily titrate to the target heart rate, cause less hypotension and myocardial depression can be used even in the presence of mild to moderate CHF.

**c. In treatment of hypertension[3]**

CCBs are the first line drugs for the treatment of hypertension even though all three categories are equally efficacious antihypertensives. They lower B.P. by decreasing peripheral resistance without compromising cardiac output despite vasodilatation, fluid retention is insignificant. Ankle edema that occurs in some patients is due to increased hydrostatic pressure across capillaries of the dependent

parts as a result of reflex constriction of post capillary vessels in these vascular beds.

**Mechanism of action[4]:** The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enter muscle cell through special voltage-sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium. Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channel in the heart and in the smooth muscle of the coronary or peripheral vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.

The onset of antihypertensive effect is quick, with the availability of long acting preparations most agents can be administered once a day.

In the past few years large amount of data from controlled trial and meta analysis has consistently indicated increased mortality/reinfarction in patients treated with standard nifedipine (other short acting DHPs) formulations. This increase in mortality is dose related. Worsening of unstable angina and CHF has also been noted.

The systolic hypertension in Europe (syst-eup) trial has shown that nitrendipine (long acting DHP) reduce cardiovascular morbidity and mortality in elderly hypertensivse. The hypertension optimal treatment (hot) and sweedish trial in old patients with hypertension - 2 (STOP-2) studied have also found CCB are equally effective as diuretic/beta-blocker/ACE inhibitors in reducing cardio vascular total mortality.

The long acting DHPs are next to ACE-inhibitors in reducing albuminuria and slowing disease progression in hypertension/diabetic neuropathy, they are the most useful anti hypertensives in cyclosporine induced hypertension in renal transplant recipients.

Other concerns in the use of CCBs as antihypertensive agents are:

1. The negative inotropic /dromotropic action of verapamil / diltiazm may worsen CHF and cardiac conduction defect.
2. By their smooth muscle relaxant action the DHPs can worsen gastroesophagial reflex CCBs (especially DHPs) may accentuate bladder voiding difficulty in elderly males.

**B. Use of CCBs in CNS**

**a. As antinociceptives**

L-type calcium channels can modulate neuronal transduction in the spinal cord. However, their role in noxious information processing in animals that are physiologically intact has not been elucidated. The effects of L-type calcium channel blockers diltiazem and verapamil on somatic and visceral nociception at the level of the spinal cord was evaluated. Intrathecal catheters were inserted at the L4-5 level in Sprague-Dawley rats. The tail flick (TF) test and colorectal distension (CD) tests were used to assess somatic and visceral antinociceptive effects, respectively. Motor function was assessed by posture and muscle tone in the limbs. TF latency and CD threshold were measured before and for 180 min after the intrathecal administration of verapamil (50, 100, 300, and 500 pg), diltiazem (100, 300, 500, and 1000 pg), or isotonic sodium chloride solution. The percent maximal possible effect (%MPE) was calculated by transforming response threshold in TF and CD tests. Intrathecally administered diltiazem or verapamil increased both TF latency and CD threshold in a dose dependent fashion. Isotonic sodium chloride solution, diltiazem 100 pg, and verapamil50 pg did not increase %MPE in either test. Diltiazem 300 or 500 pg or verapamil 300 or 500 pg significantly ($P < 0.05$) increased %MPE, with the peak effects 5 min after administration and short-duration antinociception. %MPE was 100% until 15 min after the administration of diltiazem 1000 pg, and significant antinociception continued until 180 min in the TF test. Motor paralysis was observed after the administration of the larger dose of each drug. Intrathecally administered L-type calcium channel blockers diltiazem or verapamil produced both somatic and visceral antinociception and motor block dose-dependently. Implications: The effects of intrathecally administered L-type calcium channel blockers diltiazem and verapamil on somatic and visceral nociception in rats. L-type calcium channel blockers produced antinociceptive effects, suggesting a possible clinical application to control pain[5].

N- and P-type, but not L-type, are involved in facilitated nociceptive processing at the spinal level[6].

**b. As antiepileptics**

Absence seizures are a leading form of childhood epilepsy. Human and mouse P/Q-type calcium channel gene mutations initiate a complex absence epilepsy and ataxia phenotype, and in mice, secondarily elevate neuronal low-voltage-activated T-type calcium currents. These currents influence thalamocortical network activity and contribute to the generation of cortical spike-wave discharges (SWDs) associated with absence seizures[7]. Recently, a novel series of piperidine-based molecules has been shown to selectively block recombinant T-type but not high-voltage-activated (HVA) $Ca^{2+}$ channels and to affect a number of physiological and pathological T-type channel-dependent behaviors. 3,5-dichloro-*N*-[1-(2,2-dimethyl-tetrahydro-pyran-4-ylmethyl)-4-fluoro-piperidin-4-ylmethyl]-benzamide (TTA-P2), exerts a specific, potent ($IC_{50}$ 22 nM), and reversible inhibition of T-type $Ca^{2+}$ currents of thalamocortical and reticular thalamic neurons[8].

**OTHER ACTION OF CCBs**

In a study involving comparision of CCBs, Autonomic nervous system blockers, and free radical scavangers on diazinon-induced hyposecretion of insulin from isolated islet of langarhans in rats, Nifedipine was found to decrease glucose-stimulated insulin secretion to 21.4% of control. Nifedipine plus diazinon did not alter insulin secretion in comparison with diazinon alone[9].

**UNWANTED EFFECTS**

Most of the unwanted effects of calcium antagonists are extensions of their main pharmacological actions. Short-acting dihydropyridines cause flushing and headache because of their vasodilator action, and in chronic use dihydropyridines often cause ankle swelling related to arteriolar dilatation and increased permeability of postcapillary venules. Verapamil can cause constipation, probably because of effects on calcium channels in gastrointestinal nerves or smooth muscle. Effects on cardiac rhythm (e.g. heart block) and force of contraction (e.g. worsening heart fail)[1]. Most important toxic effects reported for CCBs are direct extensions of their therapeutic action. Excessive inhibition of calcium influx can cause serious cardiac depression, including cardiac arrest, bradycardia, atrioventricular block, and heart failure. Nifedipine increased the risk of myocardial infarction in patients with hypertension[10].

**CONCLUSION**

Calcium plays an important role in contraction of smooth muscle, cardiac muscle and skeletal muscles. It is also involved in release of neurotransmitters as well as hormones and also in initiation of action potential or impulse generation in the heart. The calcium channels are categorized as L,T, N, P, Q, R types, based on the activation and inactivation kinetics, ion specificity, and sensitivity to drugs and toxins. CCBs have a major role in treatment of hypertension, angina and cardiac arrhythmias. They are also found to have anti-nociceptive and anti-epileptic action. In coming times other indications of CCBs may be revealed.

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