DRUGS & CALCIUM CHANNELS: THE PAST, THE PRESENT & THE FUTURE

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ABSTRACT
Calcium channels form a significant portion of ionic channels in the human body. They are responsible for various physiological functions, the most important ones being muscle contraction, cardiac contractility, cardiac conduction and maintenance of blood vessel tonicity. Hence, these channels have always been under the microscope so as to develop drugs that will modulate their function. Agents that block these channels are being used very commonly in practice. This review focuses on the basic aspects of calcium channels and the various clinical applications of drugs affecting them.

KEYWORDS: Verapamil, Diltiazem, Dihydropyridines, Nifedipine, Amlodipine, Angina, Hypertension.

INTRODUCTION
Cardiology is one field of medicine where the physician relies heavily on drug treatment, as the conditions they treat usually need lifelong therapeutic or prophylactic pharmacotherapy. Drugs acting on calcium (Ca²⁺) ionic channels form a major portion of the most commonly prescribed drugs in general medical practice, especially in the field of cardiology. These drugs have undergone a wide variety of changes over time, both structurally and functionally. At present, calcium channel blockers (CCBs) are being used for various conditions, and are being investigated for use in several others.
Physiological Basis: Ion channels were studied in the 1950’s and were found to be useful in maintaining membrane potential, through exchange of various ions through the plasma membrane.\textsuperscript{[1]} Ion channels are narrow, water-filled tunnels that are selectively permeable to specific types of ions.\textsuperscript{[2]} The most common ions that are permitted through these ion channels are sodium, calcium, potassium and chloride.

Calcium channels are a battery of ionic channels, which are grouped under these broad categories
a. Voltage gated channels
b. Ligand gated channels
c. Leaky channels

The initial classification system simply grouped the channels into two broad categories, namely, low voltage activated and high voltage activated channels.\textsuperscript{[3]} Later, it was discovered that all $\text{Ca}^{2+}$ channels could not be put under these two broad categories. Of the three current types of $\text{Ca}^{2+}$ channels, voltage gated channels are the most clinically significant ones, and this article will mainly deal with this group of $\text{Ca}^{2+}$ channels.

Voltage – gated calcium channels: Voltage-gated $\text{Ca}^{2+}$ channels are structurally, funnel-shaped glycoproteins that are selectively permeable to $\text{Ca}^{2+}$ ions across the channel, although they also admit the entry of barium ions occasionally (However, this is insignificant clinically). Earlier, these voltage-gated $\text{Ca}^{2+}$ channels were further subdivided into three groups: L – type, T – type, and N – type. Now, two more groups have been added, namely, P/Q and R – types.\textsuperscript{[3]}

Structural architecture of $\text{Ca}^{2+}$ channels: Just like most other voltage activated channels, these $\text{Ca}^{2+}$ channels also have a major subunit (alpha 1) and a few modulatory subunits (alpha 2, beta, gamma, delta). While the alpha unit is responsible for the functional expression of the channel, the other subunits are necessary for the kinetics and voltage selectivity of the channels. Each domain contains six membrane-spanning helices with a P-loop (Pore loop) between the last two helices (i.e., between $S_5$ and $S_6$). There are four such domains per alpha subunit, as shown in the picture 1.\textsuperscript{[4,5]}
Functional architecture of Ca^{2+} channels

Functionally, the Ca^{2+} channel consists of 3 parts: a voltage sensor, a pore or conducting pathway and a selectivity filter, as shown in the picture 2 below. The selectivity filter is responsible for letting in/out of the corresponding ions and for blocking the entry/exit of all other ions.

**Types of voltage-gated Ca^{2+} channels:** As mentioned earlier, the voltage-gated Ca^{2+} channels are subdivided into at least five types.
(a) L-type channels
These are high voltage – activated (having a conductance of 20 to 27 pS (pico Siemens)) “long – lasting” (hence called “L” type) channels that are distributed in skeletal muscles, smooth muscles, osteoblasts, ventricular myocytes, endocrine cells, etc. This subtype is the one that is targeted by clinically used calcium channel blockers. Hence they are also known as dihydropyridine receptors.[7]

(b) T-type channels
These are low voltage – activated “transient” (hence called “T” type) channels that are seen in neurons, osteocytes, pacemaker cells of the heart, placenta, lung, kidney, etc. Drugs that are clinically useful in the treatment of absence seizures target these channels.[8] Mibefradil, a calcium channel blocker that was later withdrawn from the market, also targets the T-type channels.[9]

(c) N-type channels
These channels are high voltage – activated (with a conductance of about 13pS) “neuronal” (hence called “N” type. Literature also suggests these channels could have been named after the scientist, Martha “Nowycky”) channels found in plenty in the brain, peripheral nervous system and in sperm. Omega conotoxin, a toxin from marine cone snails, blocks these channels.[10] Further, ziconotide (a synthetic derivative of peptide toxin from marine cone snails), which is being evaluated for its analgesic property, also blocks these channels.[11]

(d) P/Q-type channels
They are high voltage – activated channels that are present mainly in the “Purkinje” (hence called “P” type; “Q” simply because it is the next alphabet) fibres in the cerebellum. Omega agatoxin, a toxin from spiders, blocks this type of channels.[12]

(e) R-type channels
These are intermediate voltage – activated channels that were not found to have properties matching the other four types of channels. So they are also termed “residual” channels. Also, if the Ca\(^{2+}\) blockers are applied, these channels survive the blockade. Hence, they are also known as “resistant” channels. They are mainly located in the cerebellum and sperm cells.

**Drugs acting on / through calcium channels:** The various drugs that act on / through Ca\(^{2+}\) channels can be grouped into three broad categories
(a) Calcium channel agonists
(b) Calcium channel blockers
(c) Calcium channel sensitizers

**Calcium channel agonists**
There are no clinical implications of the drugs that have agonistic activity on the Ca\(^{2+}\) channels. BayK 8644 is an agent that has agonistic activity on L-type Ca\(^{2+}\) channels. However, it is being employed only for experimental purposes and has no clinical use. The other agents that have similar activity are CGP 28 392, YC 170 and FPL 64176.\(^{[13,14]}\)

**Calcium channel blockers**
Calcium channel blockers (CCBs) block the L-type voltage – activated Ca\(^{2+}\) channels. Since the ultimate result is prevention of Ca\(^{2+}\) ion entry, these agents are also called calcium entry blockers (CEBs). The blockers can be grouped into the following three groups based on their chemical structure.\(^{[15]}\)

(a) **Phenylalkylamines** – Verapamil
(b) **Benzothiazepines** – Diltiazem
(c) **Dihydropyridines (DHPs)**

1. **First generation** – Nifedipine, Nicardipine, Isradipine
2. **Second generation** – Amlodipine, s-Amlodipine, Felodipine, Nisoldipine, Nimodipine, Clevidipine, Cilnidipine, Lercanidipine, Lacidipine, Benidipine, Azelnidipine

There are a few differences in the site at which these 3 groups of CCBs bind to on the alpha subunit of L-type channel, as listed below in Table I.

**Table I, showing the different sites of drug action**

<table>
<thead>
<tr>
<th>Class of CCB</th>
<th>Site of binding</th>
</tr>
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<tbody>
<tr>
<td>Phenylalkylamines</td>
<td>S6 of domain IV</td>
</tr>
<tr>
<td>Benzothiazepines</td>
<td>Between domains III and IV</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>Both domains III and IV</td>
</tr>
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**Kinetics of CCBs:** CCBs are orally well-absorbed drugs that have high first pass metabolism and high plasma protein binding. Most drugs show peak action between 1 and 3 hours after intake, the exception being long-acting CCBs like amlodipine, which shows peak action between 6 and 9 hours after intake. The other long-acting CCBs are isradipine and felodipine.
These drugs are metabolized by the liver and excreted by the kidneys. Verapamil, in particular, shows the phenomenon of auto – inhibition (of its own metabolism). Clevidipine is a novel DHP that is available only as an intravenous formulation.

**Pharmacological actions of CCBs:** The actions of CCBs are mainly limited to the heart and smooth muscles (vascular & non-vascular).

(a) **Vascular smooth muscles**
By blocking the voltage-sensitive Ca$^{2+}$ channels in the vascular smooth muscles, CCBs inhibit the entry of Ca$^{2+}$ ions, hence preventing normal vascular wall constriction. This leads to passive dilatation. This dilatation is more pronounced in the arteries as compared to that in the veins.

(b) **Heart**
CCBs prevent the entry of Ca$^{2+}$ into the myocardial cells. Troponin, which needs to be bound to Ca$^{2+}$ to produce physiological contraction, is not activated. Hence, CCBs exert a negative inotropic action. On the nodal tissues of the heart, non-dihydropyridines exert an inhibitory action, while the DHPs do not have this action. Hence, there is always a reflex tachycardia seen with the use of DHPs but not with verapamil or diltiazem.

(c) **Non-vascular smooth muscles**
CCBs can result in relaxation of other smooth muscles, especially the uterus and bronchi. This action is brought about by the same mechanism as with vasodilatation.

**Adverse effects of CCBs**
The most commonly encountered adverse effects with the use of CCBs are headache and dizziness, majorly due to the vasodilatation caused by the agents. Another significant adverse effect, especially with the use of amlodipine, is peripheral pedal/ankle oedema (seen in 15-30% of patients), which is due to pre-capillary dilatation and reflex post-capillary constriction (The more potent s-enantiomer of amlodipine is preferred to avoid this adverse effect). Other adverse effects are tachycardia (as seen with DHPs) or bradycardia (as seen with phenylalkylamines and with benzothiazepines, as they have negative effects on nodal tissue of the cardium), orthostatic hypotension, leg cramps, skin rashes and gingival hyperplasia. These drugs might precipitate congestive heart failure or cause “coronary steal” phenomenon,
which is diversion of blood away from the ischaemic zone to vasodilatation in the normal heart vessels.\textsuperscript{15}

**Clinical applications of CCBs**

(a) **Angina pectoris**
CCBs are given as they reduce the cardiac afterload and also prevent arterial spasms, hence leading to decrease in cardiac work. Hence, they find use in both classical as well as in variant angina.\textsuperscript{15}

(b) **Hypertension**
According to the recent JNC (Joint National Committee) 8 recommendations\textsuperscript{16}, CCBs can be used as monotherapy as first line therapy in black hypertensives and in the elderly without diabetes mellitus. In India, these agents are used as monotherapy owing to the low cost, high tolerability and good efficacy. CCBs can also be used in hypertension in diabetics, but ACE (angiotensin converting enzyme) inhibitors or ARBs (Angiotensin Receptor Blockers) are first line agents.\textsuperscript{17} Further, in cyclosporine – induced hypertension post – renal transplant, CCBs are being used as first – line therapy.\textsuperscript{18}

(c) **Cardiomyopathy**
CCBs are used for their negative inotropic effect on the heart, hence lowering cardiac work.\textsuperscript{15}

(d) **Arrhythmias**
The main usage of CCBs is in the pharmacotherapy of paroxysmal supraventricular tachycardia (PSVT).\textsuperscript{15} Verapamil and diltiazem are preferred over the DHPs, as the DHPs can cause reflex tachycardia.

(e) **Raynaud’s phenomenon**
Nifedipine, diltiazem, amlodipine and felodipine are used in this condition for their vasodilatory property.\textsuperscript{15}

(f) **Following sub-arachnoid haemorrhage**
Nimodipine is preferred in this scenario as it is highly cerebroselective in its kinetics. Nicardipine has also been tried with some success.\textsuperscript{19}
(g) **Migraine**

All three classes of CCBs have been evaluated for use in migraine. Also, they have been found to be useful in the management of cluster headache.[19]

(h) **Mountain sickness**

CCBs are mainly useful in the treatment of acute pulmonary oedema associated with mountain sickness.[19]

(i) **Tocolysis**[15]

As a tocolytic, nifedipine is preferred over the other CCBs.

(j) **Nocturnal leg cramps**[15]

Verapamil is used for this purpose, based on a few clinical trials. Nifedipine is not preferred for this use as it may itself cause muscle cramps as a side effect.

### Contraindications to CCBs[19]

(a) Tight aortic stenosis  
(b) Severe myocardial infarction  
(c) Heart blocks (especially, non-dihydropyridines)  
(d) Heart failure  
(e) Unstable angina  
(f) Pre-existing hypotension  
(g) Wolff-Parkinson-White (WPW) syndrome  
(h) Pregnancy (Relative contraindication)

### Calcium channels and epilepsy

Agents that inhibit T-type Ca$^{2+}$ current in the thalamo-cortical system of the brain (site of pathology in absence seizures) are useful as antiepileptic drugs in patients suffering from absence seizures / petit mal epilepsy. Ethosuximide, sodium valproate and zonisamide are drugs that act by this mechanism. In children less than 2 years of age, ethosuximide is preferred over valproate, as the latter is highly hepatotoxic. In older children, valproate is considered as the drug of choice.[8]

### Novel / Emerging uses of drugs acting through calcium channels

(a) **Migraine** – CCBs are primarily used for prophylaxis of migraine. Flunarizine, a non-selective CCB, is the drug of choice among this class of drugs, as there have been several
satisfactory trial results. Verapamil and nimodipine are also being used for migraine prophylaxis.\textsuperscript{[20]}

(b) Analgesia – Ziconotide, a synthetic derivative of peptide toxin from marine cone snails is being tested for chronic and intractable pain.\textsuperscript{[11]}

(c) Worm infestation – Praziquantel acts on a variant of calcium channels in tapeworms and flukes, and causes leakage of calcium ions from the membranes, leading to contractures, paralysis and expulsion of the worms.\textsuperscript{[21]}

(d) Atherosclerosis – Studies indicate positive effects of CCBs in mild atherosclerosis. CCBs (mainly, dihydropyridines) are being tried in this case because of their propensity to slow progression of the disease.\textsuperscript{[22]}

(e) Renal failure\textsuperscript{[23]} – There are ongoing clinical trials to evaluate the efficacy of CCBs in renal failure, both in post-transplant and in non-transplant kidney injury patient.

(f) Parkinson’s disease – Isradipine is being tried for adjuvant treatment for Parkinson’s disease, as it has been postulated that CCBs can keep the dopamine-producing cells alive for a longer time, as compared to a placebo.\textsuperscript{[24]}

(g) Cancer – Verapamil might be useful as an adjuvant in cancer chemotherapy, as it may reverse the resistance developed against the chemotherapeutic agents.\textsuperscript{[25]} This could be due to a decrease in the calmodulin activity, leading to loss of extrusion of the anticancer drug from the resistant cells.

(h) Malaria\textsuperscript{[4]} – Verapamil has been tried with some success in reversal of resistance to antimalarial agents. The mechanism could be related to p-glycoprotein and other efflux pumps.

(i) Glaucoma – CCBs might find use in attenuation of disease progression in cases of glaucoma, as evidenced by a study conducted on verapamil. Stress-induced extracellular matrix gene response was found to be reduced with verapamil pre-treatment in the lamina cribrosa cells of the optic nerve head.\textsuperscript{[26]}
(j) **Pulmonary artery hypertension (PAH)** – CCBs are used in PAH in view of their vasodilatory property. However, they are said to be useful only in “responders” who are highly and immediately responsive to venodilatory therapy.[27]

(k) **Fibrotic lung disease** – CCBs might be of therapeutic usefulness in treatment or prevention of fibrotic lung disease. Animal studies on bleomycin-induced lung fibrosis have shown significant response to CCBs. This response was not due to anti-inflammatory property, but secondary to alteration of the profibrotic response to bleomycin usage.[28]

(l) **Antiplatelet activity** – Nifedipine is known to have an antiplatelet activity, although the mechanism involved is unclear. The hypothesis is that nifedipine can activate PPAR (Peroxisome Proliferator Activated Receptors) and result in antiplatelet action.[29]

(m) **Achalasia cardia** – CCBs have been tried in achalasia cardia. Nifedipine was given as primary treatment in a clinical trial but with no satisfactory results.[30]

(n) **Testicular torsion-detorsion injury** – Animal studies have been conducted for the effectiveness of CCBs (nifedipine) in torsion-detorsion injury of testes in rats. Encouraging results were obtained.[31]

(o) **Mental depression** – Flunarizine has been shown to have antidepressant action in a recent preclinical study performed on albino rats.[32]

(p) **Anal fissure** – CCBs have been tried with success as a modality of medical sphincterectomy in chronic anal fissures. Topical nifedipine has been found to have good therapeutic value.[33]

There are a few other studies and trials on the usefulness of CCBs in the treatment of osteoporosis, immune modulation, infertility, male contraception and schistosomiasis. However, CCBs are not approved for these uses yet.

**Toxicity of CCBs**

CCB toxicity is very rare. If it does occur, the effects are usually an extension of their pharmacological actions. In case of minor or trivial toxicity, the common spectrum of features seen includes flushing, dizziness, nausea and peripheral oedema. In such circumstances, discontinuation of the CCBs is not warranted. In more severe cases, direct
cardiac depression can occur, leading to bradycardia, AV block and cardiac arrest. Management of CCB toxicity has been done with high dose insulin and extracorporeal life support. Calcium, dopamine and norepinephrine have also been used in management of the same.\[34\]

**Calcium sensitizers**

Levosimendan and pimobendan are two agents that sensitize Ca\(^{2+}\) channels, and hence are clinically relevant. They do not increase the levels of Ca\(^{2+}\) in the cells, but only sensitize the receptor or end organ to the already-available Ca\(^{2+}\) ions. Levosimendan is more commonly used of the two. The main clinical applications are in refractory heart failure and refractory pulmonary hypertension. The main advantage over other drugs used in heart failure is that levosimendan does not increase the intracellular levels of Ca\(^{2+}\), hence minimizing the risk of arrhythmias. Also, there are no significant drug-to-drug interactions, and this drug can also be tried as a “once weekly” therapy regimen, as evidenced by several trials. On the downside, the drug is very expensive, and not many studies to support its safety are available.\[35,36\]

**REFERENCES**


