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A Review

Crosstalk between L-type calcium channels and protein kinases in cardiovascular diseases

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Cardiovascular diseases (CVDs) represent the primary cause of mortality globally, accounting for around 17.9 million fatalities annually. These conditions frequently arise from structural and functional injuries in heart, including cardiac hypertrophy, vascular stiffening and impaired muscle contraction. A major contributor to many forms of CVD is dysregulation of calcium-dependent cardiomyocyte contraction. The entry of calcium ions (Ca^{2+}) *via* L-type voltage-dependent calcium channels (L-VDCCs) is essential for contraction of cardiac and smooth muscle cells. These channels are on plasma membrane and T-tubules in cardiomyocytes, along with trafficking and scaffold proteins. A range of transmitters and hormones are known for regulating $Ca_v1.2$ and have been linked to CVDs, many of which also involve protein kinase C (PKC). Activation of Gq-coupled receptors and subsequent activation of protein lipase C (PLC) are among the most common mechanisms of PKC activation in cardiac and smooth muscle cells. Both *in vitro* and *in vivo*, $Ca_v1.2$ found to be regulated, phosphorylated, and linked with PKC. In addition to PKC-mediated regulation, β-adrenergic receptors are stimulated, and adenylate cyclase produces more cyclic adenosine monophosphate, which activates protein kinase A (PKA) and phosphorylates L-VDCC. This review highlights functional significance of L-VDCCs in cardiac physiology and examines therapeutic potential of calcium channel blockers (CCBs) in clinical trials.

Keywords: Calcium channel blockers, Cardiac hypertrophy, L-VDCCs, Protein kinase C, Therapeutic targets

Introduction

Calcium channels play a crucial role in many physiological processes in cells. They include all calcium-permeable pore-forming membrane proteins that transport ions through the cellular membrane, which contribute to membrane potentials, electrical impulses, and cell signalling; crucial for diverse biological systems[1]. The most widely expressed intracellular Ca^{2+} release channels are inositol 1,4,5-trisphosphate (IP_3) receptors. Ca^{2+} can quickly move from the endoplasmic reticulum (ER) lumen to the cytosol after being activated by IP_3 and Ca^{2+}. The increased cytosolic calcium may regulate cytosolic effectors or fuel Ca^{2+} intake by other organelles, whereas the decreased ER luminal calcium drives store-operated Ca^{2+} entry[2]. The primary function of calcium channels is to regulate calcium levels within the cell and across cellular compartments. Depending on the location of the cell, calcium concentrations can vary significantly. These channels are essential for maintaining a low cytoplasmic calcium concentration, which is crucial for proper cellular function. The relationship between calcium influx and efflux, governed by channels, signalling molecules, membrane depolarization, and external influences, is vital to cellular homeostasis. Dysregulation of calcium levels can lead to severe consequences, such as apoptosis and cell death[3].

Ten different types of voltage-gated calcium channels (VGCCs) are categorized into three families in cells with excitable membranes [Ca_V1 family ($Ca_V1.1$, $Ca_V1.2$, $Ca_V1.3$, and $Ca_V1.4$), Ca_V2 family ($Ca_V2.1$, $Ca_V2.2$ and $Ca_V2.3$), and Ca_V3 family ($Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$)][4]. These channels serve a crucial role in calcium entry into cells that control many physiological processes, such as gene transcription, neurotransmitter/ hormone release, and muscle contraction. Ca_V1 or Ca_V2 channels are triggered by high voltage and are generally made up of subunits featuring $\alpha_2\delta$, β subunits, and γ in cardiac and skeletal muscles[5].

The pore-forming subunit 1 dictates electro-physiological features of the subtypes. Low voltage-activated Ca_V3 channels, on the other hand, do not couple with any of the typical auxiliary subunits

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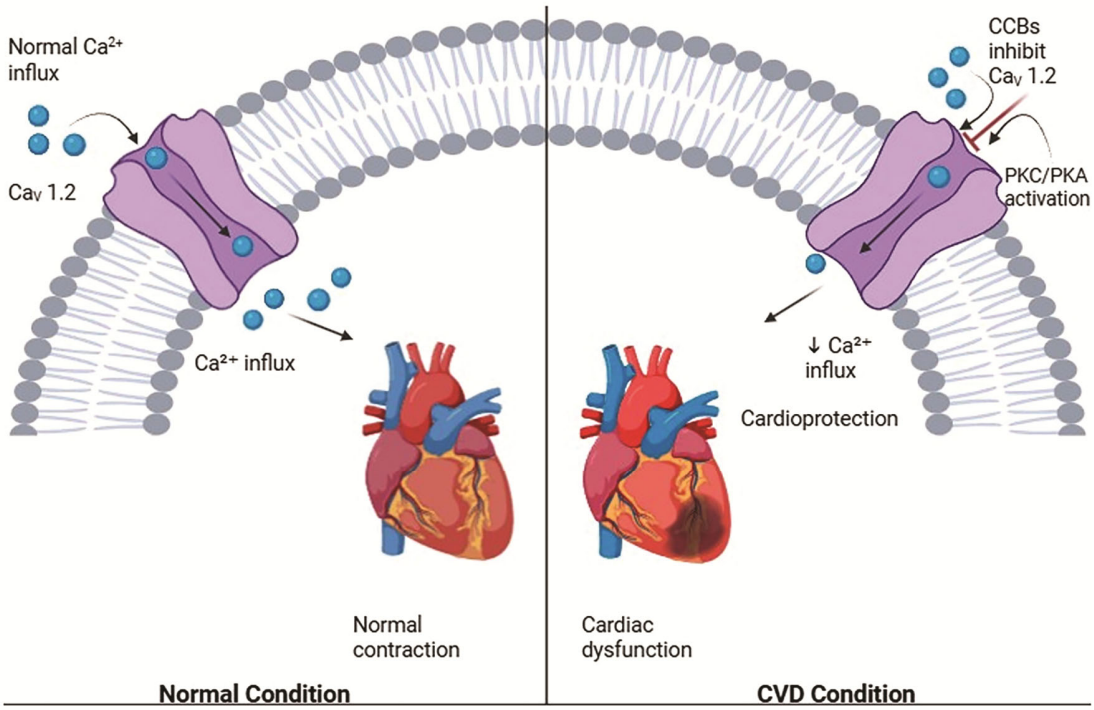

Graphical abstract

required for the typical functioning of the channel[6]. Ca_V1 channels belong to the L-VDCCs, which comprises four members, namely $Ca_V1.1$ (α_1S), $Ca_V1.2$ (α_1C), $Ca_V1.3$ (α_1D), and $Ca_V1.4$ (α_1F) channels[7]. $Ca_V1.2$ channels are found to be expressed in all cardiac and smooth muscle cells in the cardiovascular system, and $Ca_V1.4$ and $Ca_V1.1$ are identified in retinal and skeletal muscle, whereas $Ca_V1.3$ channels have predominantly been located in sinoatrial pacemaker cells. The CACNA1C (calcium voltage-gated channel subunit alpha1 C) gene encodes for α_1C, a major subunit of $Ca_V1.2$ L-type VDCC which is found in smooth muscle, cardiac tissue, and brain cells. As a result, conventional L-type CCBs, which primarily target $Ca_V1.2$ and $Ca_V1.3$, are used to treat cardiovascular illnesses such as angina pectoris, arrhythmia, and hypertension. Understanding the varied activities of $Ca_V1.2$ or $Ca_V1.3$ calcium channels in diverse cardiovascular diseases (CVDs) scenarios is crucial for more effective pharmaceutical development targeting these channels[8].

$Ca_V3.1$ (α_1G), $Ca_V3.2$ (α_1H), and $Ca_V3.3$ (α_1I) calcium channels belong to the Ca_V3 family, which are categorized as T-type voltage-dependent calcium channels (T-VDCCs). $Ca_V3.1$ and $Ca_V3.2$ calcium channels are the main T-VDCCs present in pacemakers, smooth muscle cells, and sinoatrial in the cardiovascular system, but $Ca_V3.3$ calcium channels are abundant in thalamic reticular neurons, basal ganglia in the brain, and in the reticularis thalami nuclei[9]. T-type Ca^{2+} currents are involved in various physiological processes, ranging from myoblast fusion, smooth muscle contraction, to cardiac tissue cell proliferation[10]. Only Ca_V1 and Ca_V3 calcium channels have been characterized in cardiomyocytes ($Ca_V1.2$, $Ca_V3.1$, and $Ca_V3.2$), smooth muscle cells ($Ca_V1.2$, $Ca_V3.1$, and $Ca_V3.2$), and cardiac pacemaker cells ($Ca_V1.3$, $Ca_V3.1$ and $Ca_V3.2$) till date. Post-translational alterations of these channels critically regulate their function, influencing cardiac hypertrophy and alternative splicing in hypertension and heart failure (HF)[11-13]. $Ca_V\beta$ subunits may modulate the response to neurochemicals in affecting the channel and current kinetics[14]. For instance, stimulation of β-adrenergic receptors enhances L-type calcium currents and increases excitation-contraction coupling, raising cardiac output. Conversely, vasoconstrictors like angiotensin II can increase L-type Ca^{2+} channel activity *via* PKC signaling, thereby elevating vascular resistance.

Outline of L-Type ($Ca_V1.2$ and $Ca_V1.3$) and T-type ($Ca_V3.1$ and $Ca_V3.2$) channels in heart

The principal signal that drives contraction in smooth muscle cells and ventricular/atrial myocytes is

Ca^{2+} inflow from L-VDCCs (predominantly $Ca_V1.2$ channels), which open in response to membrane depolarization[15]. Although the functions of ventricular $Ca_V1.2$ channels in rodent models of heart failure and cardiac hypertrophy are still up for debate, $Ca_V1.3$ channels have usually been assumed to be protective in pace making and atrial function[16]. Both α_{1c} and β_{2a} subunits are overexpressed in mice with enhanced calcium currents, and $\alpha_{1c}^{+/-}$ in mice showed decreased calcium currents in cardiomyocytes, established in heart hypertrophy and cardiomyopathy[17-19]. These studies demonstrate the regulatory complexity of cardiac $Ca_V1.2$ channel activation under pathological circumstances. The functions of $Ca_V1.2$ channels in blood pressure (BP) and smooth muscle regulation are well understood. In animals, smooth muscle-specific removal of $Ca_V1.2$ channels or negative control of $Ca_V1.2$ channels significantly reduces BP[20].

CCBs have been shown to significantly reduce BP, making them an integral first-line BP medication[21]. Nevertheless, because CCBs non selectively block cardiac $Ca_V1.3$ and $Ca_V1.2$ channels, unpleasant side effects are common during antihypertensive treatment. Consequently, the pursuit of $Ca_V1.2$-targeted anti-hypertensive therapies remains interesting, and the progression of negative regulators or smooth muscle-selective delivery of channel blockers rather than pure channel blockers is a promising avenue to pursue. $Ca_V3.1$ and $Ca_V3.2$ are re-expressed in the ventricles and atria in multiple rodent models of myocardial infarction, HF, and cardiac hypertrophy[22], which may have various impacts on heart function since both $Ca_V3.2$ deficiencies and $Ca_V3.1$ overexpression in cardiomyocytes can ameliorate pressure overload-stimulated cardiac hypertrophy in the mouse model. Therefore, it remains unclear how $Ca_V3.1$- or $Ca_V3.2$-dependent T-VDCCs contribute to heart-related disorders. However, 4 weeks after post-transverse aortic constriction surgery or angiotensin II (AngII) infusion, total T-type calcium current was dramatically elevated in the left ventricular cardiomyocytes in mouse models, potentially owing to overexpression of $Ca_V3.1$ and $Ca_V3.2$ transcripts[23].

Low-voltage-activated calcium channels are re-expressed in ventricular myocytes under medical conditions, including hypoxic episodes; however, oxidative stress and T-VDCCs function and regulation in cardiomyocytes are not directly related[24]. The ER/sarcoplasmic reticulum (SR), an intracellular calcium compartment in skeletal muscle, releases calcium upon activation of ryanodine receptors. Ca^{2+} release through ryanodine is driven by voltage-sensitive dihydropyridine receptors, also known as L-type Ca^{2+} channels, either directly or indirectly. Intracellular Ca^{2+} concentration is directly related to ryanodine activity; low concentrations open the channel, and high concentrations close the channel. Asparagine-linked glycosylation is a critical post-translational modification that regulates many plasma membrane-anchored channels and their functional gating properties[25].

Role of Protein Kinases in CVDs

Protein kinases mediate various G protein-coupled receptor (GPCR) signaling pathways in the cardiovascular system and, as such, are also essential regulators of cardiovascular function. Some key protein kinases include PKA, protein kinase G (PKG), and PKC, which belong to the family of serine/threonine kinases. PKA is pivotal in CVDs by facilitating beta-adrenergic signaling and modulating cardiac muscle contractility. Abnormal activation or inhibition of PKA can disrupt calcium handling, leading to impaired contractility, arrhythmias, and cardiomyocyte apoptosis. Dysregulation of PKA signaling is linked with myocardial ischemia, hypertrophy, heart failure, and diabetic hypertrophy[26]. PKG mediates the nitric oxide (NO)-cGMP pathway, which plays an important role in cardiovascular protection by promoting vasodilation, inhibiting cardiomyocyte hypertrophy, and reducing apoptosis. Reduced PKG activity can lead to increased vascular constriction, loss of cardiomyocyte homeostasis, and enhanced fibrosis. This dysregulation in the PKG signaling is associated with conditions like hypertension, heart failure, and myocardial hypertrophy[27]. PKC is essential in ischemic preconditioning of the myocardium and participates in GPCR signaling in the normal heart. The PKC isoforms are classified into three main classes based on their activation mechanism and structural characteristics. Various isoforms of PKC, which exist, are: few [Classical or conventional PKC - cPKC (PKC-α, PKC-βI, PKC-βII, and PKC-γ)] are calcium-dependent and activated by β-phorbol 12-myristate 13-acetate (PMA) and Diacyl-glycerol (DAG), others [Novel PKC - nPKC (PKC-δ, PKC-ε, PKC-η, and PKC-θ)] are calcium-independent but require DAG and a third group [A typical PKC - aPKC (PKC-ι, PKC-ζ)] are not activated by DAG or calcium. These different PKC isoforms are differentially expressed and activated in the heart, contributing to cardiac hypertrophy, ischemia-reperfusion injury, and heart failure[28].

PKC is responsible for $Ca_v1.2$ regulation

Calcium inflow and outflow through Ca^{2+} ATPases are controlled by PKC phosphorylation. Chronic stimulation of PKC, either directly by PMA or indirectly by hormones and neurotransmitters acting through Gq-coupled receptors, has been found to cause cardiac hypertrophy and HF in adult and neonatal hearts. PKC isozymes have been connected to a range of cardiac diseases, including cardiac inflammation and fibrosis. One mechanism contributing to these cardiac disorders has been identified as Ca^{2+} mishandling in cardiomyocytes[30].

The cPKC subclass (e.g., PKCα, PKCβI, and PKCβII) is the predominant modulator in the cardiovascular system. Upon Gαq activation by agonists, phosphatidylinositol 4,5-bisphosphate is hydrolyzed to produce DAG and IP_3, initiating the classic PKC activation pathway. PKC phosphorylates Ser^{1928} at the distal C-terminus of α_1C subunit, with Ser^{1928} being crucial for PKC's full effect. Mutating Ser^{1928} to alanine significantly reduced the expression of $Ca_V1.2$, induced by Gq activation and PMA in *Xenopus oocytes* of *Xenopus laevis* frogs, highlighting its vital role in $Ca_V1.2$ regulation by PKC. The enhanced activity of L-type Ca^{2+} currents by PKC through the activation of Gq-coupled receptors such as AngII and Acetylcholine (ACh) constitutes a significant modulatory mechanism in the cardiovascular system. PKC is triggered by this signaling cascade and is required for the increase in Ca^{2+} current[28]. Voltage-dependent inhibition occurs when Gβγ binds directly to the Ca^{2+} channel α_1 subunit, influenced by factors such as channel subunit composition, membrane potential, splice variations, firing patterns, and Gβγ heterodimer composition. Moreover, voltage-independent blockage of Ca_V2 channels involves interactions with GPCRs, channel phosphorylation, and inhibition through lipid signaling pathways, among other pathways[29].

The regulation of $Ca_V1.2$ is one of PKC's well-known functions in the cardiovascular system. PKC activation plays an important role in the actions of Gq-coupled receptors and other $Ca_V1.2$ modulators. Vasoconstrictors, including ACh, ET-1, and AngII, which act mostly through Gq-coupled receptors in smooth muscle, trigger Ca^{2+} release from intracellular storage and increase L-VDCC currents[31,32]. PKC is activated in this signaling pathway and is necessary for Ca^{2+} augmentation. PKCα is involved in the stimulation of $Ca_V2.3$ currents by acetyl-beta-methylcholine, and PKC ε and βII in the stimulation of $Ca_V2.3$ currents by PMA[31]. Differential activation of PKC isozymes enables independent regulation of different calcium channel family members. Different combinations of PKC isozymes can activate or inhibit a channel, even of the same type, resulting in graded levels of modulation. This variability influences the channel's susceptibility or resistance to subsequent stimulatory events[33] (Table 1).

The Transient Receptor Potential Channel (TRPC), which significantly contributes to Ca^{2+} inflow in cardiac and vascular cells, is another effector of the Gq-PLC system[34,35]. Ang-II-stimulated vasoconstriction is blocked by PKC inhibitors[36-38]. PKC phosphorylates α_1C subunit *in vivo* (mouse and rat) cardiac lysates and *in vitro* by utilizing the glutathione-S-transferase (GST)-fused portions of α_1C subunit as per the investigations. PKC interacts with α_1C on a variety of residues, most significantly on Ser^{1928}[39]. However, the effects of PKC isozymes are not solely dependent on the target Ser/Thr PKC phosphorylation sites[38]. Upon PKC activation, smooth muscle myocytes in mice and humans showed increased Ca^{2+} conductance. This is attributed to enhanced $Ca_V1.2$ availability (open time), reduced closure rate of $Ca_V1.2$, and improved voltage sensitivity while the activation curve switched towards more negative potentials[39].

β-Adrenergic regulation of $Ca_v1.2$ channels

The favorable inotropic impact of β-adrenergic agonists on the heart is a well-known physiological mechanism that occurs during exercise, excitement, and fight-or-flight situations. PKA is activated by β-adrenergic stimuli, resulting in enhanced calcium

Table 1 — Summary of key protein kinase isoforms regulating Ca_V 1.2 channels and their cardiovascular effects

Kinase	Isoform	Target channel	Effect	Pathological Implication	References
PKG	Iα, Iβ	Ca_V 3.1 and Ca_V3.3	Decreases Ca^{2+} entry and vasodilation happen	Protective in hypertension	27
PKC	α, βI, βII, ε	Ca_V 1.2	Increases $Ca_V1.2$ activity and vasoconstriction	Vascular stiffness, hypertension and cardiac remodeling	28
PKA	Type I & II	Ca_V 1.2, Ca_V 1.3 and Ca_V 3.3	Increases L-type Ca^{2+} current and enhanced contractility	Contributes to β-adrenergic stress, hypertrophy and HF	36,40

influx *via* L-type $Ca_V1.2$ channels in cardiomyocytes. PKA raises the $Ca_V1.2$ currents primarily by phosphorylating $Ca_V1.2\alpha_1C$- and/or β_2B-subunits. Furthermore, potential regulatory residues on the C-termini of α_1C (Ser^{1928}; $Ser/Thr^{1700/1704}$) and β_2B (Ser^{512} and Ser^{570})[40] are ineffective in stimulating Ca^{2+} currents in the heart. Given the various other Ser/Thr residues on α_1C and β_2B, it was still feasible that PKA phosphorylation of a combination of them was responsible for the β-adrenergic regulation of $Ca_V1.2$ in cardiomyocytes. Rad, a monomeric G-protein that inhibits Ca^{2+} channels, is abundant in $Ca_V1.2$ microenvironments but decreases following β-adrenergic stimulation. Rad and Rem are Ras-like G-proteins; the phosphorylation of certain Serine residues on Rad by PKA reduces its affinity for auxiliary subunits and relieves $Ca_V1.2$ the constitutive inhibition of $Ca_V1.2$, which is manifested as a rise in channel open probability. PKA-mediated stimulation of $Ca_V1.3$ and $Ca_V2.2$ was also stimulated by Rad or Rem, a homolog, demonstrating an evolutionarily conserved mechanism for adrenergic modulation of voltage-gated Ca^{2+} channels[41].

Studies based on the clinical trials of CCBs and their contribution to CVDs

Amlodipine: A widely prescribed CCB that is also investigated in several clinical trials for various CVDs, such as hypertension, HF, and coronary artery disease. It is being tested in one trial on its effect on diastolic function in hypertensive patients, while another trial examined its effects on myocardial ischemia in patients with coronary artery disease[42,47]. Amlodipine is more effective in preventing CVD than non-calcium channel blocker (non-CCB) antihypertensive therapy, showing significant reductions in myocardial infarction (9%), stroke (16%), and all cardiovascular events and total mortality (10%). It exhibited a comparable risk of HF to β-blockers and diuretics in a meta-analysis of six outcome trials[43].

Verapamil: This CCB is currently under study in clinical trials for CVDs. It works by relaxing the blood arteries, improving the heart's pumping efficiency. The trials are exploring their impact on cardiac function and exercise tolerance in HF patients with preserved ejection fraction, as well as their effects on diastolic function and exercise capacity in patients with hypertension and diastolic dysfunction[44].

Nicardipine: A broadly used CCB in the treatment of hypertension and subarachnoid hemorrhage. In one trial, the effect of nicardipine on cerebral vasospasm and cerebral blood flow in patients with subarachnoid hemorrhage was investigated. Another trial investigated its effects on BP control and vascular function in patients with hypertension and type 2 diabetes[45].

Mibefradil: A new CCB has been shown to have potent effects on both vascular smooth muscle and cardiac muscle. For example, one trial investigated its effects on exercise capacity and symptoms in patients with HF with preserved ejection fraction. Similarly, another trial investigated its effects on endothelial function and vascular stiffness in patients with hypertension and type 2 diabetes[46].

Diltiazem: A CCB that is commonly employed in the treatment of hypertension and angina. The trials investigate the effects of diltiazem on diastolic function and exercise capacity in patients with hypertension and diastolic dysfunction and one more trial investigated its effects on the incidence of atrial fibrillation in patients undergoing cardiac surgery[43].

Nifedipine: A commonly used CCB in the treatment of hypertension and angina. One trial investigated the effects of nifedipine on left ventricular hypertrophy and diastolic function in patients with hypertension and left ventricular hypertrophy. Another trial investigated its effects on BP control and vascular function in patients with hypertension and type 2 diabetes[47].

Researchers suggest that traditional CCBs, such as diltiazem, verapamil, and amlodipine, are widely used across a range of indications due to their lipophilicity and calcium channel-blocking properties. Nevertheless, the new L/T-type and L/N-type CCBs have potential advantages over traditional L-type CCBs (Table 2). However, the contribution of L-VDCCs in cardiovascular and neuronal physio-pathology is due to the lack of specific organic (verapamil and diltiazem) and inorganic (La^{3+}, Co^{2+}, Mn^{2+}, Ni^{2+}, Mg^{2+}) blockers[48]. The regulation of L-VDCCs and their inhibition by CCBs in CVD.

Interplay between L-VDCCs, Protein kinases and emerging therapeutics in CVD

L-type particularly Ca_V 1.2, are crucial for controlling blood pressure, cardiac contractility, and vascular tone through calcium influx. While CCBs, such as amlodipine and nifedipine, encourage vasodilation. Under physiological conditions, protein kinases such as PKA and CaMKII tightly regulate L-type channel function. The maladaptive of L-type channel remodeling is caused by dysregulated kinase signaling in CVD[49]. In HFrEF, reduced L-type channel expression and current

Table 2 — Clinical Trials and Applications of CCBs in CVD.

Name of CCB	Target channel	Current Indication	Clinical Trials	References
Amlodipine	$Ca_V1.2/Ca_V1.3$	Coronary Artery Disease, Hypertension	Ischemia, Diastolic function	42,46
Nicardipine	$Ca_V1.2$	Hypertension, Subarachnoid Hemorrhage	Vasospasm	44
Nifedipine	$Ca_V1.2$	Angina	BP control	46

impair systolic Ca^{2+} signaling and contractility. T-tubule disruption decreases excitation-contraction efficiency by further dissociating L-type channels from RyR2. Long-term β-adrenergic stimulation produces desensitization after initially increasing L-type channel activity. Oxidative stress and calcium overload cause CaMKII to become chronically active. It prolongs activity, raises the probability of channel opening and encourages excessive Ca^{2+} influx. Additionally, CaMKII phosphorylates RyR2, resulting in arrhythmias and SR Ca^{2+} leakage. L-type channel expression is maintained in HFrEF; however, relaxation is hampered by diastolic Ca^{2+} overload. Adaptive channel modulation and cardiac reserve are limited by decreased β-adrenergic reactivity. Drug binding and CCB efficacy can be affected by genetic mutations in $Ca_V1.2$. Emerging approaches like digital twin models and AI-driven drug discovery enable personalized LTCC-targeted therapies[50,51].

Calcium channel subunits as therapeutic targets in CVD

Ca^{2+}-dependent cardiomyocyte functions, such as transcription and EC coupling, and L-VDCCs (Ca_V 1.2, Ca_V 1.3, β, $\alpha_2\delta$), regulating channel activity, are reliant on Ca^{2+}. Myocardial damage results from MI/RI's disruption of calcium homeostasis, whereas arrhythmias and Ca^{2+}-dependent abnormalities are caused by L-VDCCs malfunction. Ca^{2+} influx causes vascular contraction in hypertension through pathways such as RhoA-Rho kinase and DAG-PLC-PKC. Mutations in $Ca_V1.2$ and its subunits, specifically α_1C (CACNA1C) and β_2b (CACNB2), can cause cardiac dysfunction, leading to Brugada syndrome (BrS) and sinoatrial node dysfunction. Twelve percent of cases related to BrS are caused by mutations[52]. For smooth and cardiac muscle contraction, L-VDCCs control the influx of calcium ions. Cardiovascular conditions such as long QT syndrome (LQTS), atrial fibrillation, and hypertension are associated with malfunction in these channels. Channel function is influenced by post-translational modifications, such as trafficking modifications, polyubiquitination by E3 ligases (Rfp2, Mdm2), and changes in biophysical properties, such as CDI *via* calmodulin. S-nitrosylation, phosphorylation, or interactions with proteins such as galectin-1 and Rem may also cause modification. Treatments for cardiovascular disorders linked to calcium channels can be improved by understanding these modifications under disease conditions[16].

Conclusion

Calcium channels are principal regulators of smooth muscle and cardiac contraction, BP, and CVDs, as they are the main pathways for intracellular calcium in smooth muscle cells and cardiomyocytes. The effects of Gq-coupled receptors on the $Ca_V1.2$ channel are mediated primarily by activated PKC. L-VDCCs ($Ca_V1.2$, α_1C), which are important in cardiovascular physiology and CVDs, are controlled by GPCRs and then PKC. Facts provided by many authors enhance global collaboration between the fundamental and clinical biomedical communities in analyzing the potential of CCBs for treating a wide range of disorders, from angina pectoris to various forms of dementia. Such long-term effects are thought to be linked to the therapeutic activity of CCBs, which may be explained by both BP-independent actions and decreased vascular tone, which regulates blood pressure. Yet, as with long-term impacts, a strong demonstration must be supported by clinical evidence. Moving forward, substantial work is needed to better understand and characterize the complexities to improve the therapeutic management of CVDs.

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Conflict of interest

All authors declare no conflict of interest.

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