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Emerging Role of CaMKII as a Possible Therapeutic Target for Cardiovascular Diseases

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Abstract

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a key regulator of heart function. While some CaMKII activity is beneficial, excessive, or persistent, CaMKII can lead to heart damage. CaMKII is often elevated in conditions like diabetes and heart disease, contributing to various cardiovascular problems. Therefore, CaMKII is considered a potential target for drug therapy, although its complex nature poses challenges. This review summarizes the structure, regulation, and roles of CaMKII in both normal and disease states, mainly focusing on its involvement in heart problems.

Keywords

CaMKII, Cardiovascular Diseases, Heart Failure, Arrhythmias, Diabetes, Inflammation, Cardiac Remodeling, Ion Channels, Therapeutic Target, Drug Development

1. Introduction

Cardiovascular arrhythmia continues to be a primary concern for clinicians because of its high incidence and the inadequacies of the currently available pharmacological therapies. Arrhythmias can be sectioned into supraventricular and ventricular arrhythmias, possibly having dangerous outcomes. For example, atrial fibrillation, the most prevalent prolonged arrhythmia, increases the likelihood of stroke by five times [1]. Because pharmacological therapies are often unsuccessful in averting atrial fibrillation or even exercising severe side effects, intrusive procedures such as pulmonary vein isolation are often required, leading to additional risks for patients [2]. In addition, most patients with atrial fibrillation have to be given anticoagulant therapy and are therefore exposed to a higher risk of hemorrhage

[3].

Type 2 diabetes is often associated with prolonged QT interval, atherosclerotic heart disease, and atrial fibrillation, further encouraging the detrimental effects of CaMKII [4] [5]. Fundamental pathophysiology is complicated and comprises dysfunctional cardiac remodeling, damaged Ca^{2+} handling, mitochondrial dysfunction, increased oxidative stress, decreased bioavailability of endogenous nitric oxide bioavailability, altered insulin signaling, metabolic disorder, myocardial fibrotic scarring, inflammation, and microvascular dysfunction [6].

CaMKII is a serine/threonine kinase that controls physiological functions after β-adrenergic activation [7], pathological signals, and remodeling induced by cardiac stress [8]. CaMKII's role in the pathophysiology of various cardiac disorders, such as ventricular hypertrophy [9], myocardial infarction [10], myocardial ischemia/reperfusion injury, atrial fibrillation [11] [12], and ventricular arrhythmias [13], is firm. Mechanistically comprehending the CaMKII activation processes, its targets, and the consequent functional effects that cause ventricular remodeling and arrhythmias can uncover new therapeutic methods regarding cardiovascular disorders.

2. Understanding CaMKII: Structure, Function, and Regulation

2.1. CamkII Structure and Activation

The multifunctional serine/threonine protein kinase CaMKII exists as various isoforms (α, β, δ, and γ) that are differentially expressed across tissues. In the heart, the predominant isoforms are CaMKIIδ and CaMKIIγ [14]. The structural organization of CaMKII is complex, with twelve subunits assembling into a holoenzyme comprising two hexameric rings. The γ isoform exhibits the highest affinity for calcium ions, followed by the β and α isoforms [15].

The basic functional unit of CaMKII is a monomer, which consists of three distinct domains.

1) The catalytic domain, responsible for the kinase's enzymatic activity, i.e., the transfer of phosphate groups to target proteins.

2) The regulatory domain, which harbors an autoinhibitory region that masks the catalytic domain in the basal state. The binding of calcium-bound calmodulin to this regulatory domain triggers a structural change that removes this inhibition, thus activating the kinase.

3) The association domain, which mediates the oligomerization of CaMKII monomers into the dodecameric holoenzyme.

The relatively low affinity of CaMKII for Ca^{2+} allows it to function as a sensitive detector of intracellular Ca^{2+} fluctuations, particularly within microdomains such as the cardiomyocyte dyadic cleft, where Ca^{2+} transients occur in response to stimuli [16]. When intracellular calcium levels decrease, Ca^{2+} and calmodulin dissociate from the regulatory domain, leading to CaMKII inactivation.

The N-terminal region of the regulatory domain contains Threonine-287, which

can undergo autophosphorylation in response to sustained or rapid elevations in intracellular Ca^{2+} [17]. This autophosphorylation event significantly increases the enzyme's affinity for calmodulin, resulting in a "calmodulin-trapped" state where the kinase remains active even after Ca^{2+} levels decline [18]. The calmodulin trapping state enhances the binding affinity of Ca^{2+}/calmodulin to CaMKII by approximately 105-fold. Under conditions of transient Ca^{2+} elevations and low oxidative stress, CaMKII reverts to an inactive conformation following the dissociation of Ca^{2+}/calmodulin. However, autophosphorylation at an additional site, Threonine-306, can disrupt the CaMKII binding interface and prevent calmodulin trapping [19].

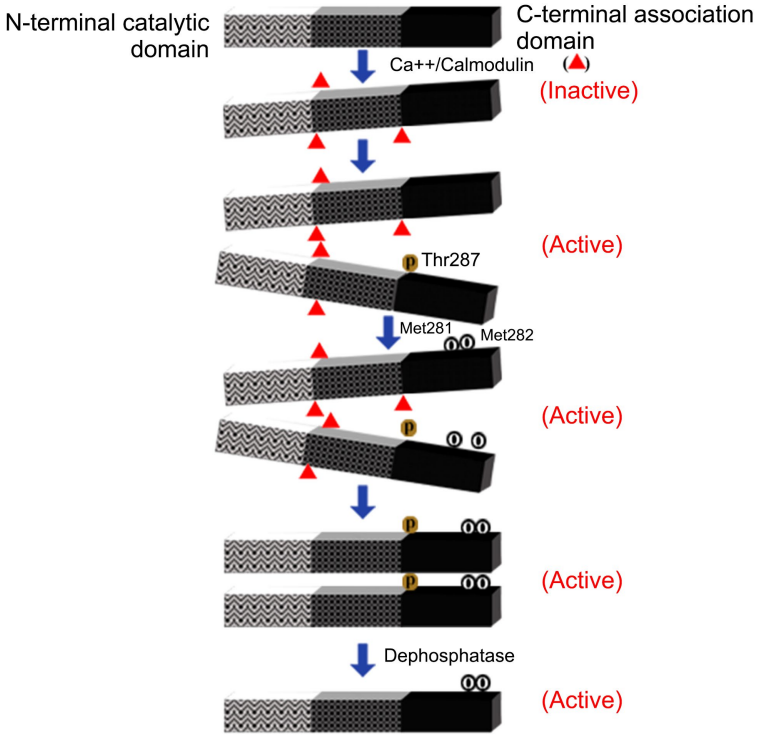

Figure 1. The structure and activation of CaMKII. The image depicts the different domains of the CaMKII monomer, the binding of calcium/calmodulin leading to its activation, and the role of autophosphorylation in maintaining its active state [20]-[22].

In addition to Ca^{2+}/calmodulin-dependent activation and autophosphorylation, CaMKII activity can also be modulated by redox-dependent mechanisms. The enzyme methionine sulfoxide reductase A (MsrA) protects CaMKII from oxidative damage by reducing oxidized methionine residues. MsrA deficiency has been associated with increased susceptibility to heart failure and adverse outcomes following myocardial infarction, suggesting a cardioprotective role for this enzyme [23] [24]. The oxidation of paired methionine residues (Met-281/Met-282) within the regulatory domain can lead to CaMKII activation independent of Ca^{2+}/calmodulin binding. This oxidation-induced activation, while promoting the dissociation of the C-terminal association domains, does not result in calmodulin

trapping.

Beyond autophosphorylation and oxidation, the regulatory region of CaMKII can undergo other post-translational modifications that influence its activity. These include O-GlcNAcylation at Serine-280 and S-nitrosylation at Cysteine-290, both of which can further enhance the calcium-independent activity of CaMKII. Notably, diabetic heart samples have been found to exhibit increased levels of Threonine-281 phosphorylation, Methionine-281/282 oxidation, and Serine-280 GlcNAcylation of CaMKII [25]-[28]. **Figure 1** provides a visual representation of the key steps involved in CaMKII activation and regulation, encompassing Ca^{2+}/calmodulin binding, autophosphorylation, oxidation, and dephosphorylation. It highlights the dynamic interplay of these mechanisms in modulating CaMKII activity, which has profound implications for cardiac physiology and pathophysiology.

2.2. CaMKII-Regulated Channels and Proteins

The activity of CaMKII profoundly influences the function of several key ion channels and proteins that govern cardiac excitation-contraction coupling and electrophysiology. The multifaceted nature of CaMKII regulation is evident in its ability to modulate these targets through both direct phosphorylation and indirect mechanisms, often with distinct consequences in physiological and pathological contexts. The major CaMKII targets and their associated functional outcomes are summarized in **Table 1**.

2.2.1. Ryanodine Channel

The ryanodine receptor 2 (RyR2), responsible for calcium release from the SR in cardiomyocytes, is a major target of CaMKII phosphorylation. CaMKII-mediated phosphorylation of RyR2 at multiple sites, including Ser-2808, Ser-2811, Ser-2814, and Ser-2815, Is associated with the development and progression of heart failure and atrial fibrillation [17] [29] [30].

Phosphorylation of RyR2 by CaMKII increases the channel's open probability, leading to Ca^{2+} leak from the SR, a phenomenon known as a diastolic SR Ca^{2+} leak. This leak can trigger spontaneous Ca^{2+} release events, known as Ca^{2+} sparks, which can summate to generate delayed afterdepolarizations (DADs) and triggered activity, ultimately promoting arrhythmias [31] [32]. The increased Ca^{2+} efflux from the SR also activates the sodium-calcium exchanger (NCX), leading to an inward current (ITi) that further contributes to membrane depolarization and DADs [33] [34]. Studies in transgenic mice overexpressing CaMKII have demonstrated increased diastolic SR Ca^{2+} leak, elevated DADs, and a higher incidence of triggered activity compared to wild-type mice, further supporting the proarrhythmic role of CaMKII-mediated RyR2 phosphorylation [35].

Among the various phosphorylation sites on RyR2, Ser-2814 has emerged as a critical target in the context of heart failure. Knock-in mice expressing a RyR2 mutant with Ser-2814 replaced by alanine (S2814A) were protected against heart

failure progression induced by transverse aortic constriction, a model of non-ischemic heart failure. However, this protection was not observed in myocardial infarction-induced heart failure, suggesting a differential role for CaMKII-mediated RyR2 phosphorylation in distinct heart failure etiologies [36].

Table 1. CaMKII-mediated regulation of cardiac ion channels and proteins.

CaMKII-Regulated Channel/Protein	Effects of CaMKII Modulation	Associated Cardiac Disorders
Ryanodine Receptor 2 (RyR2)	Phosphorylation at multiple sites (Ser-2808, Ser-2811, Ser-2814, Ser-2815)	Heart Failure, Atrial Fibrillation
	Increased RyR2 opening probability, Ca^{2+} leak from sarcoplasmic reticulum, delayed afterdepolarizations, triggered activity	
	Ser-2814 phosphorylation linked to non-ischemic heart failure progression	Heart Failure
Potassium Ion Channels	Stimulates transient outward potassium current (ItKo)	Long QT syndromes, Cardiomyopathy
	Enhances Kv1.4 expression and current	Proarrhythmic action potential, Increased QT intervals
	Biphasic effect on Kir channels: acute increase, chronic downregulation	Arrhythmias
	Enhances Kir6.2 subunit activity, chronic downregulation of Kir6.2	Dysregulation of action potential duration, Myocardial vulnerability
Voltage-gated L-type Calcium Channel (Cav1.2)	Increases amplitude of Cav1.2 current (ICav1.2), slowed inactivation, faster recovery	Arrhythmias
	Prolonged CaMKII activation may decrease Cav1.2 expression	Heart Failure
Phospholamban (PLB)	Phosphorylation at Thr-17	Arrhythmias, Heart Failure
	Increased SERCA activity, Ca^{2+} reuptake into SR	Can offset increased Ca^{2+} release or exacerbate arrhythmias

The table summarizes the key cardiac ion channels and proteins regulated by CaMKII, along with the effects of CaMKII modulation on their function and the associated cardiac disorders.

2.2.2. Potassium Ion Channel

CaMKII also modulates the activity of several potassium channels, which are crucial determinants of cardiac action potential duration and repolarization. Voltage-gated K^+ currents (IK) are the primary drivers of cardiac repolarization, and their dysfunction has been implicated in various arrhythmias, including long QT syndrome and acquired cardiomyopathies. CaMKII has been shown to stimulate the transient outward potassium current (Ito), which contributes to the early phase of repolarization [37] [38].

The potassium current is composed of both the transient outward current (Ito)

and the inward rectifier potassium current (IK1). Ito consists of a fast component (Kv4.2/Kv4.3) and a slow component (Kv1.4) [39] [40]. CaMKII overexpression has been shown to enhance both the current and the expression of Kv1.4 [41], with Thr-602 identified as a target for CaMKII-mediated phosphorylation of the Kv1.4 protein [42].

CaMKII exerts a biphasic effect on the inward rectifier potassium current (IK1). Acute CaMKII activation increases IK1, but chronic activation leads to IK1 down-regulation through reduced expression of KCNJ2/Kir2.1 at both the mRNA and protein levels [40] [43] [44]. This biphasic modulation of IK1 by CaMKII can contribute to arrhythmogenesis by altering action potential duration and refractoriness.

Furthermore, CaMKII has been shown to regulate the ATP-sensitive inward rectifier potassium current (IKATP) in a dual manner. It enhances Kir6.2 subunit activity by reducing the channel's time spent in the long-closed state and facilitating transitions from the closed to open state [45]. However, chronic CaMKII stimulation and activation lead to decreased Kir6.2 expression by promoting its dynamin-dependent internalization [46] [47]. CaMKII phosphorylates Kir6.2 at Thr-180 and Thr-224, which may contribute to these regulatory effects [48].

2.2.3. Voltage-Gated L-Type Calcium Channel

The L-type voltage-gated calcium channel (Cav1.2) is another crucial target of CaMKII-mediated phosphorylation in the heart. CaMKII phosphorylation of Cav1.2 enhances the channel's activity, contributing to the positive force-frequency relationship observed in cardiac muscle during β-adrenergic stimulation [49]. However, this CaMKII-dependent facilitation of ICaL can also have detrimental consequences, promoting arrhythmogenesis under certain conditions.

CaMKII increases the amplitude of the L-type calcium current (ICaL) and slows its inactivation through a process known as Ca^{2+}-dependent facilitation, which occurs after repeated stimulation [50] [51]. Ca^{2+}-dependent facilitation is associated with a shift in channel gating behavior towards mode 2, characterized by frequent long-lasting openings [52]. Additionally, CaMKII accelerates the recovery of ICaL from inactivation [52]. The molecular mechanisms underlying these effects involve CaMKII-mediated phosphorylation of the Cav1.2 C-terminus [53] and the Thr-498 residue in the β2a subunit, which also binds to CaMKII [54]. Conversely, prolonged CaMKII activation can lead to a reduction in Cav1.2 expression [55].

Mode 2 gating and the associated increase in ICaL have been proposed to be proarrhythmic due to their potential to promote early afterdepolarizations (EADs), SR Ca2+ leak, inward NCX current, and delayed afterdepolarizations (DADs) [56]-[60]. The elevated ICaL also plays a role in extending the action potential duration, which can create a favorable environment for arrhythmias, especially when the action potentials are already prolonged [61] [62].

2.2.4. Phospholamban

CaMKII phosphorylates phospholamban (PLB) at the Threonine-17 site, a sole

CaMKII site, is also expended to distinguish the CaMKII-controlled impact from the protein kinase A-dependent on Serine-16 phosphorylation [63]. By reducing PLB-mediated tonic suppression, PLB phosphorylation plays an important role in the induction of calcium ATPase (SERCA) activity. This cycle stimulates the reuptake of Ca^{2+} from the sarcoplasmic reticulum and facilitates the relaxation of myocytes. In this case, phosphorylation at the Threonine-17 site of PLB can offset the increased release of Ca^{2+} and serve as a defensive mechanism. However, when merged with enhanced Ca^{2+} leakage, it can become lethal, and the induced loading of the sarcoplasm reticulum Ca^{2+} can additionally cause spontaneous Ca^{2+} release events that intensify arrhythmias. Adjusting this equilibrium between the release of Ca^{2+} from the sarcoplasm reticulum, the Ca^{2+} stores, and the reuptake of Ca^{2+} by modifying the activity and levels of SERCA2a and PLB has been suggested as regards a possible therapeutic instrument in many heart complications [64].

3. Regulation of Cardiac Contractile Proteins by CaMKII

CaMKII controls numerous proteins essential to control muscle contraction force and kinetics, such as myosin-binding protein C (MyBP-C), cardiac troponin I, and regulatory light chain of myosin (RLC). CaMKII can also phosphorylate the titin protein, which is responsible for passive muscle elasticity, and its mutations or defective phosphorylation are associated with diastolic dysfunction [65].

CaMKII mediates MyBP-C phosphorylation mainly in Serine-302 and, to a minor extent, at Serine-282, adding to the frequency-reliant enhancement in the strength and kinetics of healthy cardiomyocyte contractions [66].

The phosphorylation of RLC at Serine-15 is also connected, grounded on studies with CaMKII suppressor KN-93 in heart muscles, which can lead to positive inotropy by smoothing the development process of cross-bridge development of myofilaments [67].

In addition, CaMKII controls connectin phosphorylation in many serine/threonine locations in the unique N2B sequence, the peculiar domains having sufficient levels of proline, valine, glutamate, and lysine, and this reduces the passive cardiomyocyte force [68]. Titin phosphorylation increases in failing hearts at these sites, but in general, unbalanced titin phosphorylation can lead to changed myocardial diastolic rigidity in heart failure [69].

4. CaMKII and SA Node Dysfunction

Over the last two decades, experimental observations that unfold the function of intracellular Ca^{2+} cycling in cardiac pacemaker activity have improved our understanding of generating unprompted action potentials in sinoatrial node cells. Synchronized events between SERCA and RyR2 in pacemaker cells result in rhythmic Ca^{2+} oscillations, establishing a chain of proceedings resulting in a net cationic cell charge in the second staged ventricular diastole, causing an action potential generation besides increased automaticity [70]. Localized Ca^{2+} releases were shown to be reliant on CaMKII activity [71] since inhibition of CaMKII by automative-2

linked inhibitor peptide (AIP) or KN-93 resulted in a reduced Ca^{2+} current amplitude in Cav1.2 and sinoatrial node action potential.

CaMKII has recently been observed to play a vital role in tachycardia-linked response to a fighting or fleeing situation, causing a faster heart rate due to catecholamine caused by increasing Ca^{2+} concentrations in the sarcoplasmic reticulum and release and inward NCX current, resulting in an increase in the diastolic depolarization rate [72] [73].

Although CaMKII function is vital to ensure the appropriate performance of cardiac pacemaker cells, CaMKII overexpression has shown lethal consequences leading to the sinoatrial node. Intriguingly, congestive heart failure patients with sinoatrial node problems were characterized by enhanced oxidized CaMKII in the right atrium compared to congestive heart failure patients who did not have sinoatrial node dysfunction [74].

Mice exhibiting genetic CaMKII inhibition and lacking an essential subunit p47 of myocardial nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidases) were resistant to angiotensin II stimulated sinoatrial node apoptosis and fibrosis, suggesting that NADPH oxidase-controlled oxidation of CaMKII has a vital role in angiotensin II-stimulated damage in the sinoatrial node. It was also demonstrated that the sinoatrial node-targeted suppression of CaMKII was enough to shield against the detrimental outcomes of angiotensin-II infusion on the sinoatrial node [20].

These results indicate that while CaMKII is essential for cardiac pacemaking and maintaining sinus rhythm homeostasis, overexpressed CaMKII initiates cardiac arrhythmias, particularly in the case of enhanced oxidant stress in congestive heart failure.

5. Role of CaMKII in Apoptosis

The breakdown of cellular Ca^{2+} homeostasis caused by CaMKII suggests its essential function in cardiomyocyte apoptosis [75]. Apoptosis due to overexpressed CaMKII seems to play a vital function in the pathogenesis of heart failure after myocardial infarction. CaMKII causes cardiac cell death through various downstream processes, some of which involve activation of proapoptotic proteins, and the rest involve transcriptional regulation of proapoptotic pathways. CaMKII can activate 24-kD apoptotic protease, causing fragmentation of deoxyribonucleic acid (DNA) [76]. CaMKII can phosphorylate and thus activate proapoptotic factor B-cell lymphoma-10. Furthermore, CaMKII can enhance the expression of genes that encode apoptosis, which is downstream of transforming growth factor β-stimulated kinase 1 (TAK1) [77] and apoptosis signal-regulating kinase 1 (ASK1) [78].

5.1. Role in Apoptotic Mitochondrial Routes (Animal Studies)

CaMKII is involved in mitochondrial-dependent apoptotic pathways. The stimulation of CaMKII through L-type calcium channels (LTCCs) and the SR Ca^{2+}

release pathway has been shown to enhance mitochondrial-mediated myocyte cell death in animal models [79]. The mitochondria-mediated intrinsic pathway appears to be the final common pathway for CaMKII-regulated Ca^{2+}-dependent apoptosis. When cardiomyocytes were engineered to produce excess CaMKII, they exhibited heightened apoptosis in the presence of ROS. This was accompanied by a rise in cytosolic Ca^{2+} and the release of cytochrome c from mitochondria, mirroring the effects seen when mitochondrial cytochrome c upregulates LTCCs [80]. However, the precise CaMKII target proteins responsible for this activity remain to be fully elucidated.

5.2. Role in Endoplasmic Reticulum Stress-Regulated Apoptosis (Animal Studies)

Stress within the endoplasmic reticulum leads to a rise in both cytosolic calcium levels and oxidative stress, which can activate CaMKII, in part through oxidation. This activated CaMKII can then interact with mitochondria, promoting cytochrome c release, loss of mitochondrial membrane potential, and ultimately, mitochondrial-mediated apoptosis [81]. The elevation in cytosolic Ca^{2+} caused by ER stress, coupled with prolonged CaMKII activation, has been identified as a key factor in ER stress-induced cell death in lipid-loaded macrophages [81]. In this context, CaMKII activation by Ca^{2+} overload triggers three distinct pro-apoptotic pathways.

1) Activation of the c-Jun N-terminal kinase (JNK) signaling pathway, leading to upregulation of the FAS ligand and activation of the extrinsic apoptotic pathway [82].

2) Stress within the endoplasmic reticulum leads to a rise in both cytosolic calcium levels and oxidative stress, which can activate CaMKII, in part through oxidation [83].

3) ER stress can activate CaMKII, partly by increasing cytosolic calcium and oxidative stress, which can directly modify the kinase [84].

CaMKII-mediated ER stress-induced cell death has been observed in various organs, including the heart. In a tunicamycin-induced cardiomyopathy model, CaMKII inhibition attenuated ER stress-induced heart failure, although the precise mechanisms involved remain to be fully elucidated [85]. These findings suggest that CaMKII activation, whether through Ca^{2+} overload or oxidation, plays a pivotal role in the transition from ER adaptation to ER stress-induced cell death. Moreover, CaMKII appears to be a central mediator of the crosstalk between the stressed ER and mitochondria.

5.3. Relationship of CaMKII-Induced Apoptosis with Cardiac Remodeling and Arrhythmia (Animal Studies)

The pro-apoptotic effects of CaMKII have been linked to adverse cardiac remodeling and the development of arrhythmias. In mice overexpressing myocardial actin, which develops dilated cardiomyopathy and heart failure, increased levels of

total and autophosphorylated CaMKII were observed, along with enhanced cardiac apoptosis. Inhibition of CaMKII with KN-93 ameliorated these maladaptive changes, suggesting a causal relationship between CaMKII-induced apoptosis and left ventricular remodeling and dysfunction [86].

Furthermore, CaMKII activation has been shown to induce both arrhythmias and apoptosis through the phosphorylation of the Cav1.2 β subunit. CaMKII phosphorylates the β2a subunit at Thr-498, leading to increased Ca^{2+} current, SR Ca^{2+} overload, arrhythmogenic afterdepolarizations, and apoptosis. These effects could be prevented by CaMKII inhibition, suppression of Ca^{2+} release, or mutation of the CaMKII phosphorylation site on the β2a subunit [87]. Transgenic mice with cardiac-specific overexpression of CaMKII exhibited increased myocardial cell death, afterdepolarizations, and cardiac arrhythmias (Sag *et al.*, 2009). These findings further support the notion that the pro-apoptotic consequences of CaMKII overexpression contribute to the development of heart failure and provide a proarrhythmic substrate.

Mice overexpressing myocardial actin produce dilated cardiomyopathy, heart dysfunction, enhanced total and autophosphorylated CaMKII, and increased cardiac apoptosis. CaMKII inhibition with KN-93 improved these maladaptive modifications [87]. These results indicate that CaMKII-caused cell death leads to unfavorable left ventricular remodeling and mechanical dysfunctionality.

The contribution of CaMKII to increased apoptosis may be associated with arrhythmias. Subsequently, it was revealed that CaMKII stimulation could induce arrhythmias and apoptosis through the phosphorylation of the CaV1.2's β subunit. CaMKII encourages the addition of phosphate at Threonine-498 residue, resulting in an enhanced Ca^{2+} current, upsurge sarcoplasmic reticulum, arrhythmias inducing afterdepolarizations, and apoptosis. These could be avoided by inhibiting CaMKII, suppressing Ca^{2+} discharge, or by removing the removing β2a subunit's CaMKII-induced phosphorylation location of the 2a subunit [87]. Mice having CaMKII transgenic overexpression in heart muscles display enhanced myocardial cell death, after-depolarizations, and cardiac arrhythmias [88]. These outcomes are inferred to suggest that proapoptotic consequences of CaMKII overexpression are probable to cause heart failure development and supply proarrhythmic tissue substrates.

6. Role of CaMKII in Inflammation

There is a great deal of work that connects inflammation with cardiovascular complications, such as congestive heart failure and cardiac arrhythmias. Patients with atrial fibrillation exhibit high concentrations of C-reactive protein, interleukins-6, and 8 (IL-6, IL-8) compared to healthy controls. Atrial mass biopsies from atrial fibrillation patients possessed inflammatory infiltrates, indicating a connection between atrial fibrillation and inflammation. Inflammatory biomarkers such as C-reactive protein [89] and chemokines, including IL-8and monocyte chemoattractant protein-1, are increased in patients with ventricular fibrillation [90], indicating

life-endangering ventricular arrhythmias and unexpected mortality are encouraged by a proinflammatory condition. CaMKII regulated the physiology of T cells. CaMKII, which is not dependent on Ca^{2+}, improves recognition of cognate T cell antigens and controls apoptosis [91]. The CaMKII inhibitor KN93 inhibited the phorbol-ester-catalyzed addition of phosphate of the inhibitory kappa B peptides in T cells, modulating the NF-κB activation pathway [92]. CaMKII also affects the production of IL-2, -4, and -10 T cells [93]. Due to the power of CaMKII to promptly influence IL-10 promoter function, upregulation of CaMKII greatly enhances IL-10 concentration and mRNA levels [94]. It also plays a role in Ca^{2+}-stimulated IL-2 transcriptional arrest, which results in immune unresponsiveness and controls IL-4 by directly influencing its promoter [94] [95]. CaMKII increased inflammation-inducing mediators and type I interferon generation in macrophages in response to TLR activation, in addition to participating in the inflammatory reaction regulated by Wnt5A signaling [96]-[98]. CaMKII also affects accessory cell biology, working on many points on MHC class II protein expression and localization, cell differentiation, and antigen presentation potential in response to phagocytosis-induced stimulus [99].

6.1. Myocardial Infarction (Animal Studies)

CaMKII is critical in controlling inflammation in heart attacks due to oxidation due to enhanced β-adrenergic activity, leading to increased intracellular ROS [100]. By boosting NF-κB activity, oxidized CaMKII promoted proinflammatory transcriptional activity (Ling *et al.*, 2013). CaMKII suppression lowered the elevation of inflammation-inducing genes and Factor-B after the post-heart attack. The I/R injury also caused the permeability transition pores in mitochondria to open, increasing intracellular Ca^{2+} and ROS [101]. CaMKIIδ deletion in the heart was shown to protect against I/R by reducing the dimensions of the infarct, inhibiting apoptosis, and improving functional recovery [102]. CaMKIIδ deletion prevented the decrease of IκB and the overexpression of NF-κB target genes, reducing I/R-stimulated inflammation [103].

CaMKII deficiency reduced cardiomyocyte production of monocyte chemoattractant protein 1 and C-C motif ligand 3, reducing leukocyte infiltration positive for common antigen and reducing post-infarction ventricular remodeling [50]. **Figure 2** illustrates the pivotal role of CaMKII in the activation of a pro-inflammatory program that culminates in inflammation-mediated remodeling. The image depicts how various stressors, including arrhythmic syndromes, ischemic diseases, pressure overload/hypertrophy, and reactive oxygen species (ROS), can elevate intracellular calcium (Ca^{2+}) levels. This increase in Ca^{2+} subsequently activates CaMKII, which can also be activated through oxidation. The activated CaMKII then triggers several downstream signaling pathways. One of these pathways involves the direct phosphorylation and activation of the transcription factor NF-kB, a key regulator of pro-inflammatory gene expression. Another pathway involves the phosphorylation and modulation of histone deacetylases (HDACs),

influencing epigenetic gene expression and potentially activating pro-inflammatory genes.

Additionally, CaMKII can activate the p38 mitogen-activated protein kinase (MAPK) pathway, a crucial signaling cascade in the inflammatory response. The activation of these downstream pathways by CaMKII ultimately results in the production of cardiokines, signaling molecules that promote inflammation and cardiac remodeling. The figure underscores the central role of CaMKII in connecting various stressors to the activation of a pro-inflammatory program that contributes to the development of cardiovascular diseases.

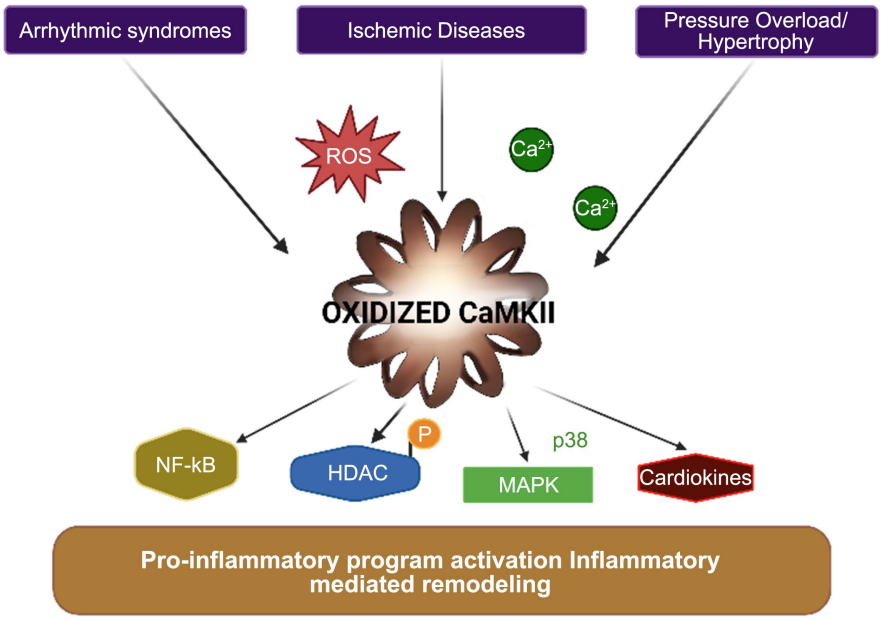

Figure 2. The role of CaMKII in the activation of a pro-inflammatory program that leads to inflammation-mediated remodeling. Created in BioRender. Oroszi, T. (2024) BioRender.com/a16y516.

6.2. Cardiac Hypertrophy (Animal Studies)

Ang II therapy increased NF-κB-modulated inflammatory expressions with inflammasome engagement, which is decreased within a cardiomyocyte-limited CaMKIIδKO animal model [104]. Therefore, inflammation-driven remodeling is mediated by CaMKIIδactivation. As a secondary mechanism, Ang II-induced the production of reactive oxygen species (ROS) and CaMKII oxidation, culminating in the activity of p38 MAPK, a key mediator in the inflammatory response [105]. Hypertrophy is associated with increased fibrosis, inflammation, cardiomyocyte death, and sustained CaMKII stimulation in the TAC model [106]. CaMKIIδactivation activates the inflammasome in cardiomyocytes via NF-κB and oxidative stress signaling, causing chemokine synthesis, which results in macrophage infiltration and the establishment of the fibrotic process [107]. Within the initial 14 days of TAC and after initiation of the inflammatory cell build-up, CaMKIIδdeletion of CaMKII and obstruction of CaMKII stimulation reduced fibrosis and

ventricular dysfunction, affirming active participation in the abnormal response at the time of pressure overload [107].

7. CaMKII and Cardiac Disorders

7.1. Cardiac Arrhythmias (Animal and Human Studies)

Many arrhythmogenic mechanisms have been revealed in diabetes, such as early and delayed after depolarizations [108]. The prime mechanism can be attributed to an enhanced Ca^{2+} leak in the sarcoplasmic reticulum dependent on CaMKII and the parallel inward NCX current [109]. The increased leakage of Ca^{2+} from the sarcoplasmic reticulum also results in increased diastolic Ca^{2+} concentration, decreased sarcoplasmic Ca^{2+} load, and, as a result, reduced systolic intracellular Ca^{2+} transient resulting in diastolic and systolic dysfunctions in patients with diabetes [109].

The decreased gap junction alpha-1 protein (GJA1) expression, subcellular redistribution of GJA1, and enhanced fibrosis considerably reduced cell-to-cell coupling within the diabetic heart [110]. The defected coupling and reduced intracellular sodium further reduce the conductive pace, which encourages reentry formation. Myocardial ischemia can increase cell-to-cell coupling and advance arrhythmia [111].

CaMKII has become a potential antiarrhythmic target in various types of inherited cardiac anomalies, which typically presents a susceptibility to cardiac arrhythmia by altering normal Ca^{2+} cycling at the intracellular level. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an arrhythmic genetic disease illustrated via stress-causing arrhythmias in a normally functioning cardiac structure without electrocardiographic signs in resting conditions. Genetic mutations of RyR2 are the major source of CPVT. Recently, pharmacological inhibition of CaMKII has been indicated to eradicate stress-induced arrhythmias and increase activity in the mouse model R4496C [112].

Timothy syndrome is an autosomal dominant disorder produced by Cav1.2 mutations and is featured by fibrillation and sudden death [113]. Cav1.2 mutations in Timothy syndrome cause impaired Cav1.2 inactivation and inapt Ca^{2+} entry, which subsequently activates CaMKII activation. This activation prolongs the action potential and cardiac arrhythmias [114]. According to the anticipated relation between increased Ca^{2+} input, CaMKII stimulation, and arrhythmogenesis, CaMKII inhibition stabilized the duration of the action potential, the Ca^{2+} content of the sarcoplasmic reticulum, and avoided arrhythmogenic post-depolarizations in heart muscles that have the timothy syndrome mutant CaV1.2 [115]. These observations back the view of CaMKII being capable of becoming a therapeutic target for the treatment of arrhythmias linked to Timothy syndrome, similar to CPVT. Also, it is fascinating to reflect on whether hereditary arrhythmias associated with faulty Ca^{2+} cycling would respond well to CaMKII suppression.

7.2. Atrial Fibrillation (Animal and Human Studies)

New evidence indicates that CaMKII can exercise a vital role in regulating the signaling pathways resulting in atrial fibrillation. This rhythm is especially familiar to heart failure patients [116] and sinoatrial node dysfunction patients [117]. CaMKII is stimulated via upstream signal transduction pathways, such as monoamine catecholamines [118] blood pressure that regulates the renin-angiotensin-aldosterone system [119] and oxidative stress [120] [121], which are vital to remodeling in congestive heart failure [122], and mostly atrial fibrillation [123].

Atrial muscle cells in patients with atrial fibrillation have enhanced levels of CaMKII [47] and exhibit intensified RyR2 phosphorylation [124] and PLB [125]. Intriguingly, atrial muscle cell atrial fibrillation patients also exhibit enhanced Ca^{2+} spark frequency stabilized by CaMKII inhibition [101].

7.3. Cardiac Hypertrophy (Animal Studies)

Cardiac hypertrophy is a significant risk component for unexpected cardiac death [126]. Like atrial fibrillation, the association of left ventricular hypertrophy with paroxysmal supraventricular tachycardia is also well established. CaMKII is significant in hypertrophy caused by ischemia and excess pressure, mainly through transcriptional control of hypertrophic genes. The addition to the class II histone deacetylase 4 (HDAC4) and HDAC5 by CaMKII activates the expression of myocyte enhancer factor-2-controlled genes. CaMKII phosphorylates HDAC4 more likely than HDAC5, causing hypertrophic gene activation. CaMKIIδ knockout mice, having excessive pressure due to invasive aortic banding, had suppressed ventricular hypertrophy and reduced phosphorylation of HDAC4 compared to controls [9].

Calcineurin acts as a robust prohypertrophic signal through the nuclear factor dephosphorylation of the transcriptional protein for activated T-cells (NFAT), resulting in enhanced NFAT containment NFAT and hypertrophic gene transcription [127]. CaMKII reduces the transcription of calcineurin. Calcineurin is concerned with cardiomyocyte hypertrophy [128]. Calcineurin induces overstimulation of CaMKII expression. CaMKII suppression in transgenic mice that overexpressed calcineurin was revealed to induce a decrease in cardiac arrhythmias, improved myocardial operation, and a lower mortality rate without any significant impact on hypertrophy [129]. Taken together, we deduce these results to indicate a complicated relationship between hypertrophic and inflammatory pathways, as stimulated directly or indirectly by CaMKII.

8. CaMKII and Diabetes

8.1. CaMKII Activation in the Diabetic Heart (Animal and Human Studies)

A new mechanism has been identified that affects CaMKII functions during diabetes by introducing an Oxygen-linked β-N-acetylglucosamine (O-GlcNAc) modification [28] [130]. The latter is an evolving discipline that has significant

regulatory consequences in pathological conditions explained by altered glucose signaling, for instance, in heart attack and type 2 diabetes [131]. This post-translational modification may change protein operation [132], and such a setting is instrumental in the heart [133]. The O-GlcNAcylation reaction occurs under the catalytic activity of the O-GlcNAc transferase enzyme under the influence of the uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) formed during the hexosamine biosynthesis pathway under circumstances of elevated glucose levels [131].

Once CaMKII is stimulated via Ca^{2+}/calmodulin binding under high glucose, O-GlcNAcylation is executed in the regulatory domain at Serine-280 residue to autonomous kinase activation [135]. The degree of O-GlcNAcylation, along with CaMKII stimulation, alters the accessibility of glucose sugar levels and is reversible through the O-GlcNAcase action. These observations indicate a possible regulatory function for CaMKII's O-GlcNAcylation, in harmony with the ratio of results that the O-GlcNAcylated CaMKII to total CaMKII in people with diabetes is significantly improved in the heart. Furthermore, glucose-stimulated Ca^{2+} leakage from the sarcoplasm reticulum depends on the availability of CaMKII and O-GlcNAc, indicating a relationship between CaMKII function facilitated by O-GlcNAc and the onset of arrhythmia in diabetic patients. Furthermore, suppression of the hexosamine pathway and, therefore, the formation of precursors O-GlcNAc did not allow the development of ventricular tachycardia in diabetic hearts injected with dobutamine diabetic rats [135]. These outcomes indicate that post-translational O-GlcNAcylation of CaMKII could have a pivotal role in the electrical remodeling of the heart in diabetic patients.

8.2. CaMKII Inhibition as a Potential Antiarrhythmic Therapeutic Strategy in the Diabetic Heart (Animal Studies)

Many experimental studies suggest that CaMKII is triggered in diabetes and is aware of its downstream signaling and activation results that mimic remodeling in diabetic hearts. We may hypothesize CaMKII as a possible pharmacological focus for type 2 diabetes.

Animals ingested with a diet rich in fructose have poor glucose tolerance, increased oxidative stress, increased expression of CaMKII and oxidized CaMKII, and increased reliant RyR2 CaMKII at Serine-2814 causing spontaneous sarcoplasm reticulum's Ca^{2+} release events connected with involuntary contractions, depolarization of the inner membrane of mitochondria, cell death, and most significantly, in-vivo arrhythmic events [134] [135]. Supplementation of the hydrophilic CaMKII inhibitor KN-93 or the Tempol antioxidant in the diet may avert increased Ca^{2+} release events in the sarcoplasm reticulum [136]. Likewise, mice administered with the CaMKII inhibitor AIP of the sarcoplasm reticulum targeted were resistant to fructose-rich diet caused Ca^{2+} leakage of the sarcoplasm reticulum's Ca^{2+} leakage, voluntary contractions, poor mitochondrial functioning, and arrhythmic events, regardless of continuous increase in the generation of reactive

oxygen species generation [134] [135].

9. Challenges and Limitations

9.1. Potential Off-Target Effects

The extensive involvement of CaMKII in various cardiac signaling pathways and its contribution to the pathogenesis of cardiovascular diseases underscores its potential as a therapeutic target [136]. However, the successful translation of CaMKII inhibition into clinical practice faces several challenges [137]. The ubiquitous expression of CaMKII and its diverse roles in various physiological processes raise concerns about potential off-target effects in non-cardiac tissues [138]. For instance, CaMKII is also involved in neuronal signaling, immune responses, and other critical cellular functions. Inhibiting CaMKII could inadvertently affect these processes, leading to unintended side effects. The widespread presence of CaMKII and its diverse functions in various physiological processes raise concerns about potential unintended effects in non-cardiac tissues. Thus, it is essential to devise approaches that can precisely target CaMKII in the heart while minimizing any adverse effects on other systems.

9.2. Isoform Specificity

The presence of various CaMKII isoforms, each with unique roles, highlights the need for creating inhibitors that specifically target individual isoforms. This targeted approach aims to enhance the effectiveness of treatment while reducing the risk of unwanted side effects [139]. CaMKIIδ and CaMKIIγ are the predominant isoforms in the heart, but other isoforms like CaMKIIα and CaMKIIβ are more prevalent in the brain. Isoform-specific inhibitors could help in selectively targeting the cardiac isoforms without affecting the neuronal isoforms. The significant structural resemblance between the various CaMKII isoforms poses a considerable challenge in developing inhibitors that can differentiate between them. Advanced techniques in drug design and molecular biology are needed to achieve this specificity.

9.3. Drug Delivery and Bioavailability

The effective delivery of CaMKII inhibitors to the heart and ensuring their bioavailability at the target site also present significant hurdles that need to be overcome [140]. The heart's active nature and extensive blood flow pose challenges in delivering and sustaining effective drug levels. Additionally, the blood-brain barrier and other physiological barriers can limit the distribution of the drug to the heart. Innovative drug delivery systems, such as nanoparticle-based delivery, targeted drug carriers, and controlled-release formulations, could enhance the delivery and bioavailability of CaMKII inhibitors in cardiac tissues.

9.4. Transition from Preclinical to Clinical Trials

Finally, the transition from promising preclinical findings to successful clinical

trials requires careful consideration of patient selection, trial design, and regulatory requirements [139]. Preclinical studies often use animal models that may not fully replicate human disease conditions. Therefore, selecting appropriate patient populations that closely match the preclinical models is essential. Additionally, designing clinical trials that can effectively evaluate the safety and efficacy of CaMKII inhibitors is crucial. This includes determining the optimal dosing regimen, identifying relevant biomarkers for monitoring treatment response, and ensuring compliance with regulatory standards. Collaboration between researchers, clinicians, and regulatory agencies is vital to address these challenges and facilitate the successful translation of CaMKII inhibitors into clinical practice.

10. Conclusions

Calcium/calmodulin-dependent protein kinase II (CaMKII) is crucial in cardiac signaling, affecting calcium cycling, excitability, and various cellular functions. This review underscores the complex nature of CaMKII, highlighting its roles in both normal and diseased heart states. CaMKII exists in multiple isoforms (α, β, δ, and γ), with CaMKIIδ and CaMKIIγ being predominant in the heart. Its activation involves intricate mechanisms, including autophosphorylation, oxidation, and other post-translational modifications.

CaMKII regulates several key ion channels and proteins, such as the ryanodine receptor (RyR2), potassium channels, L-type calcium channels (Cav1.2), and phospholamban (PLB), which are essential for cardiac excitation-contraction coupling and electrophysiology. Elevated CaMKII activity is associated with various cardiac disorders, including heart failure, atrial fibrillation, ventricular arrhythmias, and myocardial infarction, contributing to adverse cardiac remodeling, apoptosis, and inflammation. In diabetic hearts, CaMKII is activated through O-GlcNAcylation, leading to arrhythmias and defective calcium homeostasis. Inhibition of CaMKII shows promise as an antiarrhythmic strategy in diabetic cardiomyopathy.

Developing CaMKII inhibitors presents challenges such as potential off-target effects, isoform specificity, drug delivery, and bioavailability. Transitioning from preclinical to clinical trials requires careful consideration of these factors. To address these challenges and leverage the therapeutic potential of CaMKII, several strategies can be pursued. Advances in molecular biology and drug design can help create inhibitors that selectively target cardiac-specific CaMKII isoforms, such as CaMKIIδ and CaMKIIγ, while sparing other isoforms prevalent in non-cardiac tissues.

Innovative drug delivery systems, such as nanoparticle-based delivery, targeted drug carriers, and controlled-release formulations, can enhance the delivery and bioavailability of CaMKII inhibitors specifically to cardiac tissues, minimizing systemic exposure and potential off-target effects. Combining CaMKII inhibitors with other therapeutic agents may enhance efficacy and reduce the required dosage, thereby minimizing side effects. For example, combining CaMKII inhibitors

with antioxidants could mitigate oxidative stress-related activation of CaMKII.

Tailoring treatments based on individual patient profiles, including genetic, molecular, and clinical characteristics, can improve the efficacy and safety of CaMKII-targeted therapies. Identifying biomarkers that predict response to CaMKII inhibition will be essential for this approach. Developing more sophisticated preclinical models that better mimic human cardiovascular diseases can improve the translation of preclinical findings to clinical trials. This includes using genetically engineered animal models and human-induced pluripotent stem cell-derived cardiomyocytes.

Encouraging collaboration between researchers, clinicians, and regulatory agencies can streamline the development and evaluation of CaMKII-targeted therapies. The open exchange of information and collaborative efforts can expedite the discovery of effective therapies and streamline the regulatory process. Although obstacles remain, the continued investigation into CaMKII's role in the body and the creation of novel treatment approaches hold promise for enhancing the well-being of individuals with cardiovascular diseases. A deeper understanding of this complex mechanism will undoubtedly contribute to the creation of novel and more effective treatments for cardiac arrhythmias and ventricular hypertrophy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations and Acronyms

CaMKII:	Calcium/calmodulin-dependent protein kinase II
SR:	Sarcoplasmic Reticulum
RyR2:	Ryanodine receptor 2
DADs:	Delayed afterdepolarizations
NCX:	Sodium-calcium exchanger
I/R:	Ischemia/reperfusion
ROS:	Reactive oxygen species
ItKo:	Transient outward potassium current
IK1:	Inward rectifier potassium current
IKATP:	ATP-sensitive inward rectifier potassium current
Cav1.2:	L-type voltage-gated calcium channel
ICaL:	L-type calcium current
EADs:	Early afterdepolarizations
PLB:	Phospholamban
SERCA:	Sarco/endoplasmic reticulum Ca2+-ATPase
MyBP-C:	Myosin-binding protein C
RLC:	Regulatory light chain of myosin
AIP:	Automotive-2 linked inhibitor peptide
LTCCs:	L-type calcium channels
ER:	Endoplasmic Reticulum
JNK:	c-Jun N-terminal kinase
TAK1:	Transforming growth factor β-stimulated kinase 1
ASK1:	Apoptosis signal-regulating kinase 1
GJA1:	Gap junction alpha-1 protein
CPVT:	Catecholaminergic polymorphic ventricular tachycardia
Ang II:	Angiotensin II
TAC:	Transverse aortic constriction
HDAC:	Histone deacetylase
NFAT:	Nuclear factor of activated T-cells
O-GlcNAc:	Oxygen-linked β-N-acetylglucosamine
UDP-GlcNAc:	Uridine diphosphate N-acetylglucosamine