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Review

Bridging Role of Calcium/Calmodulin-Dependent Protein Kinase II (CaMKII) in the Pathogenesis of Diabetes and Cardiac Arrhythmias

Jianli Li[1], Yifei Zhang[1], Xu Zhang[1], Xuewen Li[1,*]

[1]Department of Cardiology, Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, 030032 Taiyuan, Shanxi, China
*Correspondence: lixuewen@sxbqeh.com.cn (Xuewen Li)
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Abstract

The incidence of cardiac arrhythmias is substantially elevated in patients with diabetes, posing a serious threat to patient survival. Calcium/calmodulin-dependent protein kinase II (CaMKII), a key intracellular signaling molecule in cardiomyocytes, plays a crucial role regulating calcium homeostasis and cardiac electrophysiological function. Growing evidence identifies CaMKII as a central contributor to the development of diabetes-associated arrhythmias. This review summarizes the mechanisms underlying CaMKII activation, with particular emphasis on abnormal activation mediated by oxidized CaMKII (ox-CaMKII) and O-linked β-N-acetylglucosamine (O-GlcNAcylation) under diabetic conditions. These post-translational modifications impair cardiomyocyte calcium handling and destabilize electrophysiological activity, thereby promoting arrhythmogenesis. Indeed, by integrating evidence from recent animal experiments and clinical studies, we further examine the complex interactions among hyperglycemic fluctuations, oxidative stress, inflammatory responses, and CaMKII activation in diabetes. In addition, this review discusses CaMKII-mediated pathological remodeling of ion channels and calcium-handling proteins, including the late sodium current ($I_{Na\text{-}L}$), potassium channels, and ryanodine receptor 2 (RyR2) calcium release channels. Finally, we highlight emerging therapeutic strategies targeting CaMKII signaling pathways and evaluate their potential clinical value in the prevention and treatment of diabetes-related cardiac arrhythmias. Overall, this review provides a comprehensive overview of the bridging role of CaMKII in the pathogenesis of diabetes and cardiac arrhythmias, thereby offering a theoretical basis for future mechanistic studies and therapeutic development.

Keywords: calcium/calmodulin-dependent protein kinase II; diabetes; cardiac arrhythmias; oxidative stress; O-linked β-N-acetylglucosamine; calcium signaling; late sodium current

1. Introduction

Diabetes mellitus (DM), particularly type 2 diabetes mellitus (T2DM), represents a major global metabolic health challenge, with its prevalence continuing to rise worldwide. This chronic metabolic disorder is characterized by persistent hyperglycemia resulting from insulin resistance and/or impaired insulin secretion. Beyond classical metabolic abnormalities, diabetes markedly increases the risk of cardiovascular complications, which remain the leading causes of morbidity and mortality among diabetic patients [1,2]. Among these complications, cardiac arrhythmias, defined as abnormalities in cardiac rhythm, are increasingly recognized as major contributors to adverse cardiovascular outcomes, including sudden cardiac death (SCD). The clinical burden is considerable. Epidemiological studies have demonstrated that individuals with type 2 diabetes are at an increased risk of developing atrial fibrillation (AF) compared to non-diabetic individuals, and diabetes contributes to a considerable proportion of the population-attributable risk for AF [3]. Moreover, diabetic patients exhibit a 2- to 3-fold greater risk of ventricular arrhythmias and SCD, with the risk further amplified in the presence of microvascular complications, poor glycemic control, or antecedent hypoglycemic episodes. Large registry studies have reported a higher prevalence of VT/VF in diabetic populations compared with non-diabetic controls [4]. Collectively, these findings underscore the substantial arrhythmic burden associated with diabetes, as reflected by significantly higher rates of arrhythmia-related hospitalization, cardiovascular events, and mortality among diabetic individuals compared with non-diabetic counterparts [5,6].

In addition to hyperglycemia, several comorbidities commonly associated with T2DM substantially modulate arrhythmia risk. Hypertension, which is present in approximately 60–80% of diabetic patients, promotes left ventricular hypertrophy and myocardial fibrosis, thereby facilitating the formation of a reentrant substrate [7]. Obesity independently activates Calcium/calmodulin-dependent protein kinase II (CaMKII) through adipokine-mediated inflammatory signaling and increases the risk of AF by nearly 50% [8]. Cardiovascular autonomic neuropathy, affecting approximately 20–40% of diabetic individuals, results in sympathovagal imbalance, QT interval prolongation, and reduced heart rate variability, all of which predispose patients to ventricular arrhythmias and SCD [9]. Chronic kidney disease, another frequent complication of diabetes, further

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contributes to arrhythmic susceptibility by disrupting electrolyte homeostasis and impairing drug clearance. Importantly, these comorbidities interact synergistically with diabetes induced CaMKII activation and should therefore be considered collectively when evaluating arrhythmic risk in diabetic patients.

The pathophysiological relationship between diabetes and arrhythmias is highly complex and multifactorial. Hyperglycemia, a hallmark feature of diabetes, initiates a cascade of molecular and cellular alterations that predispose the myocardium to electrical instability. These alterations include oxidative stress, chronic inflammation, autonomic dysfunction, and structural remodeling, including fibrosis and hypertrophy [7,10]. Importantly, disturbances in intracellular calcium (Ca^{2+}) handling and ion channel function have emerged as central mechanisms linking diabetic metabolic derangements to arrhythmogenesis. Impaired calcium homeostasis can induce delayed afterdepolarizations (DADs) and triggered activity, both of which are well-established substrates for arrhythmia initiation and maintenance [11,12]. Furthermore, diabetes associated electrical remodeling frequently manifests as prolonged ventricular repolarization, reflected by QT interval prolongation on electrocardiography, which is strongly associated with an elevated risk of life threatening ventricular tachyarrhythmias and SCD.

At the molecular level, CaMKII has emerged as a pivotal regulator of cardiac excitation-contraction coupling and electrical stability. CaMKII regulates the activity of several key ion channels and calcium-handling proteins, including the Ryanodine receptor type 2 (RyR2), L-type calcium channels, and sodium channels, thereby orchestrating intracellular Ca^{2+} dynamics and action potential properties [7,11]. Under diabetic conditions, CaMKII undergoes pathological activation through post-translational modifications, particularly oxidation and O-linked β-N-acetylglucosamine (O-GlcNAcylation), which enhance its autonomous activity independently of Ca^{2+}/calmodulin (CaM) binding [13,14,15]. This aberrant activation contributes to sarcoplasmic reticulum (SR) Ca^{2+} leak, impaired ion channel gating, and proarrhythmic electrophysiological remodeling [11,12,16].

The interaction between diabetes-induced metabolic stress and CaMKII activation establishes a feed-forward mechanism that further exacerbates myocardial electrical instability. Hyperglycemia-induced reactive oxygen species (ROS) production activates CaMKII through oxidative modification, whereas enhanced O-GlcNAcylation sustains its pathological activation [13,15]. Consequently, CaMKII-mediated phosphorylation of RyR2 at specific residues, such as Ser2814, promotes diastolic SR Ca^{2+} leak, DADs generation, and triggered arrhythmias [11,16]. In parallel, CaMKII-dependent modulation of sodium and potassium currents alters action potential duration (APD) and diminishes repolarization reserve, thereby further increasing susceptibility to arrhythmogenesis [17].

Clinically, these molecular abnormalities translate into an increased risk of both atrial and ventricular arrhythmias in diabetic patients. AF, the most common sustained cardiac arrhythmia, occurs more frequently in individuals with diabetes and is associated with substantial morbidity and mortality [18,19]. Ventricular arrhythmias, including VT and VF, are major contributors to SCD in diabetic populations. Importantly, the arrhythmic risk associated with diabetes is further influenced by comorbid conditions such as heart failure (HF), hypertension, and autonomic neuropathy, as well as by glycemic variability and hypoglycemic episodes, all of which may independently precipitate arrhythmogenic events [20,21,22].

Therapeutic strategies targeting the molecular pathways linking diabetes to arrhythmias are rapidly evolving. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, initially developed as glucose-lowering agents, have demonstrated substantial cardiovascular benefits, including reductions in arrhythmia incidence. These beneficial effects may be mediated through improvements in myocardial energy metabolism, stabilization of ion homeostasis, and attenuation of oxidative stress and CaMKII activity [23,24,25]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have also shown promise in reducing cardiovascular mortality without increasing arrhythmic risk, although their direct effects on arrhythmogenesis remain under active investigation [26,27,28]. In addition, experimental pharmacological agents that directly inhibit CaMKII activity or modulate its downstream signaling pathways have emerged as potential therapeutic approaches for mitigating diabetes-associated arrhythmias.

Despite these advances, substantial knowledge gaps remain regarding the precise molecular interplay between diabetes and arrhythmogenesis, particularly concerning the role of CaMKII in integrating metabolic, oxidative, and electrophysiological signals within the diabetic myocardium. A more comprehensive understanding of these mechanisms is essential for the development of targeted therapeutic interventions aimed at reducing arrhythmic burden and improving cardiovascular outcomes in the rapidly growing diabetic population.

In this context, CaMKII has emerged as a critical molecular mediator linking the diabetic metabolic environment to cardiac electrical dysfunction and arrhythmogenesis. This review aims to comprehensively summarize current evidence regarding the role of CaMKII in the pathophysiological mechanisms underlying diabetes-associated arrhythmias. Specifically, we discuss the molecular mechanisms responsible for CaMKII activation in diabetes, its effects on calcium handling and ion channel regulation, and its interactions with diabetes-related pathological processes, including hyperglycemia, oxidative stress, and inflammation. By integrating both clinical and experimental

findings, this review seeks to provide a comprehensive understanding of CaMKII as a central mediator of arrhythmogenesis in diabetes and to highlight its potential as a promising therapeutic target for reducing arrhythmic risk in diabetic patients.

2. Structure and Activation Mechanism of CaMKII

2.1 CaMKII Structural Features and Isoform Distribution

CaMKII is a multifunctional serine/threonine kinase that plays a pivotal role in decoding Ca^{2+} signals across diverse tissues, including the heart. Structurally, CaMKII is a multimeric holoenzyme composed of 12 subunits arranged in a ring-like assembly, with each subunit containing a kinase domain, a regulatory segment, a variable linker region, and an association domain that mediates oligomerization. This architecture enables cooperative interactions among subunits and allows for complex regulation through autophosphorylation and conformational changes that modulate enzymatic activity and substrate specificity [29,30]. Among the four mammalian CaMKII isoforms α, β, γ, and δ, the δ isoform is predominantly expressed in cardiac tissue, where it plays a central role in regulating myocardial Ca^{2+} signaling and electrophysiological properties [31]. The CaMKIIδ isoform exists in multiple splice variants, including δB and δ9, which are implicated in nuclear localization and transcriptional regulation, highlighting the enzyme's functional versatility beyond cytosolic signaling [32].

The δ isoform's prominence in cardiomyocytes is linked to its specialized ability to regulate excitation-contraction coupling by modulating key Ca^{2+}-handling proteins such as RyR2, phospholamban (PLN), and the SR Ca^{2+}-ATPase 2a (SERCA2a) [33]. This isoform-specific expression pattern allows CaMKIIδ to finely tune cardiac Ca^{2+} dynamics and electrical stability, which are essential for maintaining normal heart rhythm and contractility. Its regulatory influence extends to phosphorylation events that affect ion channel function and intracellular Ca^{2+} homeostasis, thereby linking CaMKIIδ activity to arrhythmogenesis in pathological states such as heart failure and diabetes [34,35].

Moreover, the δ isoform's interaction with anchoring proteins such as A-kinase anchor protein 18 (AKAP18δ) facilitates its spatial targeting to subcellular compartments like the sarcoplasmic reticulum, where it modulates PLN and RyR2 phosphorylation in response to local Ca^{2+} signals, thereby orchestrating Ca^{2+} uptake and release with high precision [31]. This compartmentalization underscores the isoform's role in integrating Ca^{2+} signaling with cardiac electrical function. In contrast, other isoforms such as α and β are more abundant in neuronal tissues, where they contribute to synaptic plasticity and cytoskeletal organization, respectively [36]. The β isoform, for instance, contains a longer linker region that biases it toward inhibitory autophosphorylation, in contrast to the α isoform's greater propensity for activation, reflecting isoform-specific tuning of kinase responsiveness to Ca^{2+} signals [37].

In summary, CaMKII's structural organization as a multimeric holoenzyme, together with its isoform-specific expression patterns and splice variants, enables it to function as a versatile Ca^{2+} signal transducer. The enrichment of the δ isoform in the heart and its unique regulatory properties underscore its critical role in modulating cardiac Ca^{2+} signaling and electrophysiology. Understanding these structural and isoform-specific characteristics is essential for elucidating CaMKII's contribution to cardiac physiology and pathophysiology, including its involvement in diabetes-associated arrhythmogenesis.

2.2 Unified Activation Mechanisms of CaMKII

2.2.1 Classical Ca^{2+}/CaM -Dependent Activation Mechanism

The classical activation mechanism of CaMKII is fundamentally driven by elevations in intracellular calcium concentration ($[Ca^{2+}]i$), which enable the formation of the Ca^{2+}/CaM complex. Upon binding Ca^{2+} ions, CaM undergoes conformational changes that allow it to interact with the regulatory domain of CaMKII, thereby relieving autoinhibition and activating the kinase. This activation triggers autophosphorylation at Thr286 in the α isoform, which confers Ca^{2+}-independent autonomous activity, allowing CaMKII to sustain signaling beyond transient calcium spikes [38,39]. The Ca^{2+}/CaM complex thus functions as a molecular switch that converts transient calcium signals into prolonged kinase activity, a process critical for diverse cellular functions, including synaptic plasticity and cardiac excitation-contraction coupling.

At the molecular level, CaMKII holoenzymes consist of 12 subunits arranged in a dodecameric assembly, where inter-subunit interactions facilitate trans-autophosphorylation. Structural studies indicate that CaM binding neutralizes basic residues within the regulatory and linker domains, promoting conformational opening and kinase activation [40,41]. High affinity binding partners further stabilize the active state by competitively displacing autoinhibitory segments, thereby sustaining kinase activity [38]. This intricate regulatory architecture enables CaMKII to decode the frequency and amplitude of Ca^{2+} transients, functioning as a leaky integrator that modulates downstream signaling pathways in a stimulus-dependent manner [42].

Functionally, activated CaMKII phosphorylates a variety of ion channels and calcium-handling proteins, thereby modulating their activity to maintain cellular calcium homeostasis and electrical stability. In cardiomyocytes, CaMKII phosphorylates RyR2 and PLN, which are key regulators of SR calcium release and reuptake, respectively. Anchoring proteins such as AKAP18δ spatially organize CaMKII near these targets, enabling precise regu-

lation of calcium cycling [31]. CaMKII-mediated phosphorylation of RyR2 increases channel open probability, contributing to calcium-induced calcium release (CICR), whereas phosphorylation of PLN relieves its inhibitory effect on SERCA2a, thereby promoting calcium reuptake into the SR and facilitating myocardial relaxation [31,43]. Dysregulation of this pathway, often resulting from excessive CaMKII activation, leads to aberrant calcium leak and promotes arrhythmogenic events [44].

Moreover, CaMKII influences voltage-gated sodium channels such as Voltage-gated sodium channel subunit alpha Nav1.6 (Nav1.6), enhancing neuronal excitability by increasing channel currents and shifting the voltage dependence of activation [45]. In the sinoatrial node, oxidative stress activates CaMKII, which in turn potentiates the slow delayed rectifier potassium current (I_{Ks}), thereby affecting pacemaker activity [46]. These examples underscore CaMKII's central role as a calcium signal transducer that integrates intracellular calcium fluctuations to regulate ion channel function and maintain cellular excitability.

Beyond ion channel regulation, CaMKII activity is also modulated by post-translational modifications such as O-GlcNAcylation, which influences its autophosphorylation and functional output in cardiomyocytes [47]. Additionally, CaMKII undergoes activity-dependent degradation via ubiquitination, ensuring turnover of persistently active kinase and preventing pathological accumulation [48]. The kinase also participates in higher-order protein assemblies at synapses, where it undergoes liquid-liquid phase separation with postsynaptic density proteins, facilitating synaptic reorganization and plasticity [49].

In summary, the classical Ca^{2+}/CaM-dependent activation of CaMKII involves a finely tuned molecular mechanism in which Ca^{2+}/CaM binding relieves autoinhibition, promotes autophosphorylation, and sustains kinase activity. This activation enables CaMKII to regulate a broad spectrum of ion channels and calcium-handling proteins, thereby critically modulating cellular calcium dynamics and electrical signaling. The spatial and temporal precision of this process is essential for physiological functions such as memory formation, cardiac excitation-contraction coupling, and rhythm regulation, whereas its dysregulation contributes to pathological states including arrhythmias and diabetic cardiomyopathy [50,51].

2.2.2 Non-Classical Activation Mechanisms: Oxidative Modification and O-GlcNAcylation

Autophosphorylation is the classical mechanism conferring Ca^{2+}-independent autonomous activity to CaMKII. Upon Ca^{2+}/CaM binding, the regulatory domain moves away from the catalytic domain, exposing Thr286 in the α isoform (Thr287 in the δ isoform) for autophosphorylation by an adjacent subunit within the holoenzyme. This phosphorylation locks the kinase in an active conformation, allowing it to remain active long after Ca^{2+} levels return to baseline, thereby functioning as a form of molecular memory [52]. In diabetic conditions, however, pathological oxidative and O-GlcNAcylation described below can similarly induce autonomous activity, bypassing or synergizing with autophosphorylation to sustain maladaptive signaling.

DM, characterized by chronic hyperglycemia, induces a pathological milieu that promotes oxidative stress and aberrant protein modifications, both of which critically affect cardiac signaling pathways. Among these, CaMKII emerges as a central mediator linking diabetic metabolic disturbances to cardiac dysfunction and arrhythmogenesis through non-classical activation mechanisms, particularly oxidized CaMKII (ox-CaMKII) and O-GlcNAcylation.

Hyperglycemic conditions in diabetes increase ROS production, which oxidizes methionine residues in the regulatory domain of CaMKII, notably Met281/282, leading to the formation of ox-CaMKII. This modification induces sustained autonomous activation of CaMKII independent of Ca^{2+}/CaM binding. Oxidation-induced CaMKII activation has been demonstrated in patients with sleep-disordered breathing and atrial arrhythmias, where elevated ox-CaMKII levels correlate with enhanced SR Ca^{2+} leak and increased arrhythmogenic Ca^{2+} sparks [53]. Similarly, oxidative stress-driven CaMKII activation exacerbates AF by promoting Early afterdepolarizations (EADs) through disrupted calcium cycling and prolonged APD, as shown in computational and experimental studies [54].

Mechanistically, oxidation of CaMKII involves formation of disulfide bonds within its regulatory domain, particularly between cysteine residues Cys273 and Cys290, which stabilizes its autonomous activity. This disulfide bond formation is facilitated by the relatively low pKa of Cys273, enabling formation of a sulfenic acid intermediate followed by disulfide linkage, as demonstrated in biochemical studies [55]. Notably, this oxidative activation pathway is distinct from autophosphorylation-mediated autonomous activity and contributes to maladaptive cardiac remodeling and arrhythmogenesis. Experimental models using oxidation-resistant CaMKII mutations such as MM281/282VV (MMVV) substitution at Met281/282 exhibit protection against oxidative stress-induced cardiac dysfunction and arrhythmias, underscoring the pathological significance of ox-CaMKII in disease states [56,57].

Parallel to oxidative modification, O-GlcNAcylation represents another critical post-translational modification regulating CaMKII activity in diabetes. Elevated glucose flux through the hexosamine biosynthetic pathway increases O-GlcNAc transferase activity, leading to the attachment of O-GlcNAc moieties to serine and threonine residues on target proteins. CaMKII is directly modified at Ser280 by O-GlcNAcylation, which enhances its autonomous activity independent of Ca^{2+} levels. This modification has been implicated in diabetic arrhythmias, where O-GlcNAcylation of CaMKII increases ROS production via NADPH oxidase 2 (NOX2), creating a feed-forward

loop that sustains CaMKII activation and promotes SR Ca^{2+} leak [13,58]. Genetic ablation of the O-GlcNAcylation site, S280A mutation, in CaMKIIδ prevents hyperglycemia-induced ROS generation and arrhythmogenic Ca^{2+} disturbances, highlighting the functional importance of this modification [13].

Moreover, O-GlcNAcylation also directly modifies RyR2 at S280, enhancing its Ca^{2+} leak propensity independent of CaMKII, further contributing to arrhythmogenesis in diabetes [15]. This indicates that both CaMKII and RyR2 are targets of O-GlcNAcylation, synergistically exacerbating calcium mishandling in the diabetic heart.

Importantly, these non-classical activation mechanisms confer persistent CaMKII activity that is uncoupled from transient Ca^{2+} signals, thereby sustaining pathological signaling cascades. Oxidation and O-GlcNAcylation prolong CaMKIIδ activity by slowing CaM dissociation kinetics, enabling a form of molecular memory that integrates cellular stress signals over time [59]. This persistent activation underlies maladaptive cardiac remodeling, including apoptosis, fibrosis, and electrophysiological disturbances observed in diabetic cardiomyopathy and arrhythmias.

From a therapeutic perspective, targeting these modifications offers promising avenues. Pharmacological inhibition of CaMKII oxidation or O-GlcNAcylation reduces ROS production, normalizes Ca^{2+} handling, and mitigates arrhythmia susceptibility in diabetic models [60,61]. In addition, natural compounds and traditional formulations that attenuate CaMKII oxidation have shown cardioprotective effects by restoring calcium homeostasis and reducing oxidative stress [62]. Furthermore, modulation of upstream regulators such as NADPH oxidases and enzymes controlling O-GlcNAcylation may indirectly suppress pathological CaMKII activation.

In summary, hyperglycemia-induced oxidative stress and enhanced O-GlcNAcylation converge on CaMKII, promoting its autonomous and sustained activation independent of Ca^{2+} signaling. These modifications form a pathological nexus linking diabetic metabolic derangements to cardiac electrical and structural remodeling, thereby bridging diabetes and arrhythmogenesis. Understanding these non-classical activation pathways of CaMKII provides critical insights into the molecular pathogenesis of diabetic cardiac complications and highlights potential therapeutic targets. The structural basis for these mechanisms, including key regulatory residues Met281/282 and Ser280, is illustrated in Fig. 1A, while their impact on cardiomyocyte Ca^{2+} handling and downstream effectors is summarized in Fig. 1B.

2.3 Hyperglycemia, Glycemic Fluctuations, and ROS Generation

Hyperglycemia and glycemic fluctuations, hallmark features of DM, exert profound effects on CaMKII activity, a critical mediator linking metabolic disturbances to cardiac arrhythmogenesis. Notably, glycemic variability appears to provoke a higher propensity for arrhythmias than sustained hyperglycemia, a phenomenon mechanistically associated with enhanced ROS generation and subsequent CaMKII activation. Experimental studies using streptozotocin (STZ)-induced diabetic rat models have demonstrated that glucose fluctuations significantly increase ventricular arrhythmia susceptibility, as evidenced by higher incidence rates in fluctuating glucose (GF-STZ) groups compared with controlled (C-STZ) or sustained hyperglycemia (U-STZ) groups. This heightened arrhythmogenicity correlates with increased ROS production and ox-CaMKII, which in turn exacerbates electrophysiological abnormalities such as prolonged APD at 90% repolarization (APD90), increased late sodium current ($I_{Na\text{-}L}$), and the emergence of EADs and DADs. Pharmacological inhibition of ROS or CaMKII effectively reverses these electrophysiological disturbances, underscoring the pivotal role of the ROS/-CaMKII axis in mediating arrhythmogenic effects induced by glycemic fluctuations [12].

At the molecular level, hyperglycemia induces CaMKII activation through post-translational modifications, notably O-GlcNAcylation at the Ser280 residue of the CaMKIIδ isoform. This modification facilitates autonomous CaMKII activation independent of Ca^{2+}/CaM binding, promoting pathological disturbances in cardiomyocyte calcium handling. *In vitro* studies using adult mouse ventricular myocytes exposed to high glucose (30 mmol/L) have demonstrated a significant increase in ROS generation, which is abrogated by CaMKII inhibition or genetic deletion of CaMKIIδ, indicating that CaMKII activation is required for hyperglycemia-induced oxidative stress. Moreover, pharmacological modulation of O-GlcNAcylation pathways confirms that O-GlcNAcylation at CaMKIIδ-S280 is essential for high glucose-induced ROS production, with NOX2 identified as the primary ROS source in this context. These findings elucidate a feed-forward loop in which hyperglycemia triggers O-GlcNAcylation-dependent CaMKII activation, which in turn stimulates NOX2-mediated ROS generation, further sustaining CaMKII activation and calcium mishandling, thereby increasing arrhythmia susceptibility [13]. In the nucleus, activated CaMKII phosphorylates class II histone deacetylases (HDACs), triggering their nuclear export and relieving transcriptional repression of hypertrophic and pro-arrhythmic genes. This process contributes to pathological cardiac remodeling and electrophysiological instability in diabetic hearts [63].

Chronic diabetic models also exhibit elevated CaMKII activity accompanied by derangements in cardiac calcium handling. In metabolic syndrome rats with obesity, autonomous CaMKII activation enhances diastolic calcium leak via increased phosphorylation of RyR2 at Ser2814, a CaMKII-specific site, leading to spontaneous calcium waves and increased arrhythmogenic risk, particularly un-

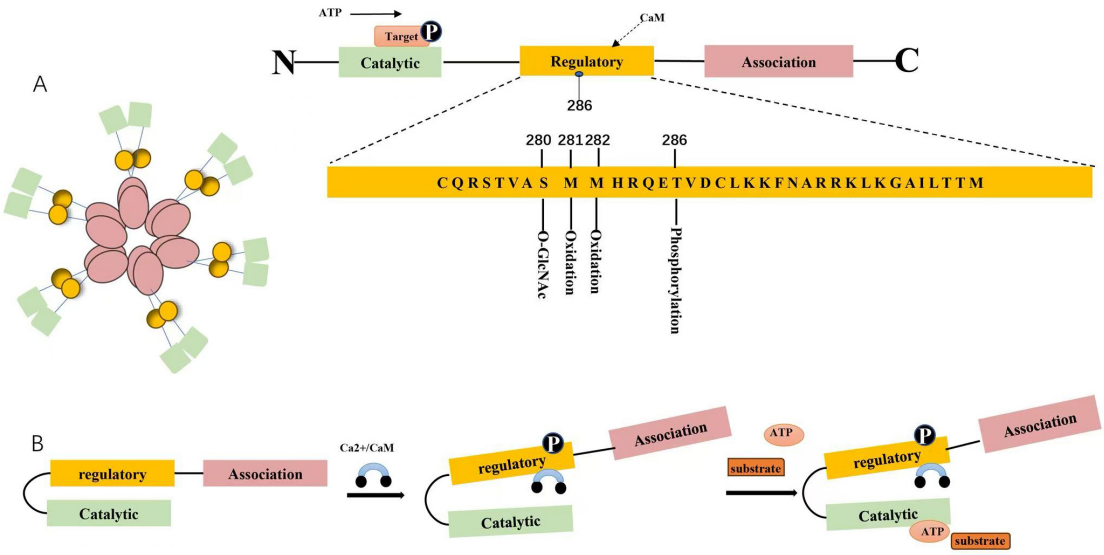


Fig. 1. Calcium/calmodulin-dependent protein kinase II (CaMKII) structure and function. (A) CaMKII is a multi-subunit complex, with each holoenzyme consisting of 12 subunits. Each subunit contains the following domains: kinase domain; regulatory domain; oligomerization domain. Oxidation of Met281/282 pair and O-GlcNAcylation of Ser280 have been identified in the regulatory hub region of CaMKII, and both promote autonomous, pathologically sustained kinase activity. (B) CaMKII activation in cardiomyocytes is triggered by a propagating action potential that drives calcium (Ca^{2+}) influx. Intracellular Ca^{2+} binds to calmodulin (CaM), and the complex interacts with CaMKII's regulatory domain to induce a conformational change, this relieves the catalytic domain from inhibition, enabling phosphate transfer to substrates. The shift also exposes Thr286, whose phosphorylation is mediated by a preactivated CaM-bound monomeric subunit of the same holoenzyme. ATP, adenosine triphosphate. N, C, and P denote the N-terminus, C-terminus, and phosphate group, respectively. Solid arrows indicate activation, promotion, or the transfer of phosphate groups. Dashed lines indicate structural magnification or binding orientation.

der β-adrenergic stimulation. This pathological calcium leak is prevented by CaMKII inhibition, highlighting the kinase's central role in calcium dysregulation in diabetic cardiomyopathy [64]. Additionally, chronic hyperglycemia modulates cardiac potassium channels through CaMKIIδ O-GlcNAcylation and ROS-protein kinase C (PKC) signaling pathways, resulting in altered repolarization and further predisposing to arrhythmias [17].

Notably, transient elevations in glucose, even in non-diabetic hearts, can enhance CaMKII activity via O-GlcNAcylation, thereby increasing the velocity of calcium waves and arrhythmia susceptibility. This finding underscores the sensitivity of CaMKII to acute glycemic changes [65]. Furthermore, endothelial cells and vascular smooth muscle cells also exhibit increased CaMKII activation under hyperglycemic conditions, contributing to vascular dysfunction and remodeling, which may indirectly influence cardiac electrophysiology [66].

In summary, both sustained hyperglycemia and glycemic fluctuations potentiate CaMKII activation through mechanisms involving O-GlcNAcylation and ROS generation, primarily mediated by NOX2. This activation disrupts calcium homeostasis in cardiomyocytes, promoting arrhythmogenic calcium leak, electrophysiological remodeling, and increased vulnerability to ventricular arrhythmias. Collectively, these findings underscore the central bridging role of CaMKII in linking diabetic metabolic disturbances to cardiac arrhythmogenesis and highlight potential therapeutic targets for mitigating arrhythmic risk in diabetic patients.

2.4 Inflammatory Response and Mutual Promotion With CaMKII Signaling Pathway

Chronic low-grade inflammation is a hallmark of DM and plays a pivotal role in the pathogenesis of diabetic cardiomyopathy and associated arrhythmias. In this context, CaMKII emerges as a critical mediator linking inflammatory signaling to myocardial structural and electrical remodeling. Diabetes-induced persistent inflammation leads to the activation of multiple pro-inflammatory cytokines and increased oxidative stress, which in turn activate CaMKII through mechanisms such as oxidation and phosphorylation. For instance, the CaMKIIδ9 isoform, predominant in the human heart, has been shown to directly interact with components of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, including inhibitor of nuclear factor κB alpha (IκBα), enhancing its phosphorylation and promoting NF-κB activation. This amplifies the inflammatory response within cardiomyocytes [67]. Such CaMKII-driven inflammatory sig-

naling fosters myocardial fibrosis by stimulating extracellular matrix production and fibroblast proliferation, contributing to adverse structural remodeling that predisposes the heart to arrhythmogenesis.

Moreover, CaMKII activation exacerbates cardiomyocyte apoptosis, a key event in the formation of a pathological substrate for arrhythmias. In viral myocarditis, for example, CaMKII inhibition by compounds such as dihydrotanshinone I markedly reduces cardiomyocyte death and inflammation, underscoring the kinase's role in mediating cell death pathways, including apoptosis, necroptosis, and pyroptosis [68]. Similarly, in diabetic cardiomyopathy models, CaMKII activation is associated with mitochondrial dysfunction and oxidative stress, which further promote cardiomyocyte apoptosis and fibrosis [69]. The interplay between CaMKII and inflammatory signaling cascades such as NF-κB is further supported by studies showing that CaMKII activation aggravates the senescence-associated secretory phenotype in cardiomyocytes via NF-κB signaling. This process perpetuates chronic sterile inflammation and contributes to cardiac aging and functional decline [70].

The mutual reinforcement between inflammation and CaMKII signaling is also evident in endothelial dysfunction and vascular inflammation in diabetes. CaMKII activation enhances endothelial cell proliferation and migration but also contributes to maladaptive vascular remodeling through increased production of inflammatory mediators and extracellular matrix components, thereby exacerbating vascular injury under diabetic conditions [66]. In obesity-related vascular dysfunction, CaMKII antagonism improves endothelium-dependent vasodilation and reduces oxidative stress and pro-inflammatory gene expression, highlighting the kinase's role in modulating inflammatory responses in metabolic disease contexts [71].

At the molecular level, ROS generated during chronic inflammation serve as potent activators of CaMKII via oxidation, creating a feed-forward loop that sustains kinase activity and inflammatory signaling. This has been demonstrated in airway inflammation models, where allergen-induced ROS activates ox-CaMKII, promoting mitophagy and cytokine production [61]. In immune cells such as macrophages, CaMKII is essential for the inflammatory response to viral components, acting downstream of Toll-like receptor 3 (TLR3)-mediated Ca^{2+} influx to regulate pannexin 1 hemichannel activity and cytokine release [72]. These findings suggest that CaMKII functions as a nodal integrator of calcium signaling, oxidative stress, and inflammatory responses.

In the diabetic heart, pathological activation of CaMKII contributes to electrical remodeling by promoting arrhythmogenic substrates through fibrosis and apoptosis. The kinase's role in mediating inflammation-induced structural changes and cell death underscores its potential as a therapeutic target. Pharmacological inhibition of CaMKII has been shown to attenuate inflammation, reduce myocardial fibrosis, and improve cardiac function in various disease models, including ischemia/reperfusion injury and diabetic cardiomyopathy [73,74]. Furthermore, natural compounds such as tilianin and perillaldehyde exert cardioprotective effects partly by inhibiting CaMKII-dependent inflammatory and apoptotic pathways [69]. The integration of glucose metabolism, ROS production, CaMKII activation, and downstream transcriptional regulation, such as via HDACs, is schematically represented in Fig. 2.

In summary, chronic inflammation in diabetes activates CaMKII through oxidative stress- and cytokine-mediated mechanisms, which in turn amplifies inflammatory signaling, promotes myocardial fibrosis, and exacerbates cardiomyocyte apoptosis. This self-perpetuating cycle establishes a pathological substrate that is highly conducive to arrhythmogenesis. Targeting the CaMKII signaling pathway therefore represents a promising strategy to interrupt the reciprocal reinforcement between inflammation and CaMKII activation, with the potential to mitigate diabetic cardiac remodeling and reduce arrhythmic risk.

3. CaMKII-Mediated Calcium Handling Abnormalities in Diabetic Cardiomyocytes

3.1 Fundamentals of Cardiomyocyte Calcium Signaling

Intracellular Ca^{2+} is the central second messenger coupling electrical excitation to mechanical contraction in cardiomyocytes. During each cardiac cycle, an action potential opens L-type Ca^{2+} channels (LTCCs) on the plasma membrane and transverse tubules, allowing a small Ca^{2+} influx. This influx triggers a much larger release of Ca^{2+} from the SR through RyR2, a process termed CICR [75].

The released Ca^{2+} binds to troponin C, initiating myofilament contraction. Relaxation requires rapid Ca^{2+} removal from the cytosol via two main pathways, SERCA2a, which pumps Ca^{2+} back into the SR and is regulated by PLN, and the sodium-calcium exchanger (NCX), which extrudes Ca^{2+} in exchange for Na^{+} [75].

Normal Ca^{2+} cycling is essential for electrical stability. Diastolic Ca^{2+} must remain low to prevent spontaneous RyR2 opening. When this homeostasis is disrupted, due to SR Ca^{2+} overload, RyR2 hyperphosphorylation, or reduced SERCA2a function, spontaneous Ca^{2+} release events (Ca^{2+} sparks) can summate into Ca^{2+} waves. These waves activate NCX-generated transient inward current (Iti), which depolarizes the membrane and triggers DADs [76]. CaMKII is positioned at the center of this regulatory network, phosphorylating RyR2 to increase its open probability, PLN to relieve SERCA2a inhibition, LTCCs, and other key proteins, thereby tightly regulating intracellular Ca^{2+} handling and electrical stability.

3.2 CaMKII-Mediated RyR2 Channel Abnormal Activation and Calcium Leak

The RyR2 is a pivotal SR calcium release channel in cardiomyocytes, and its dysregulation is a critical con-

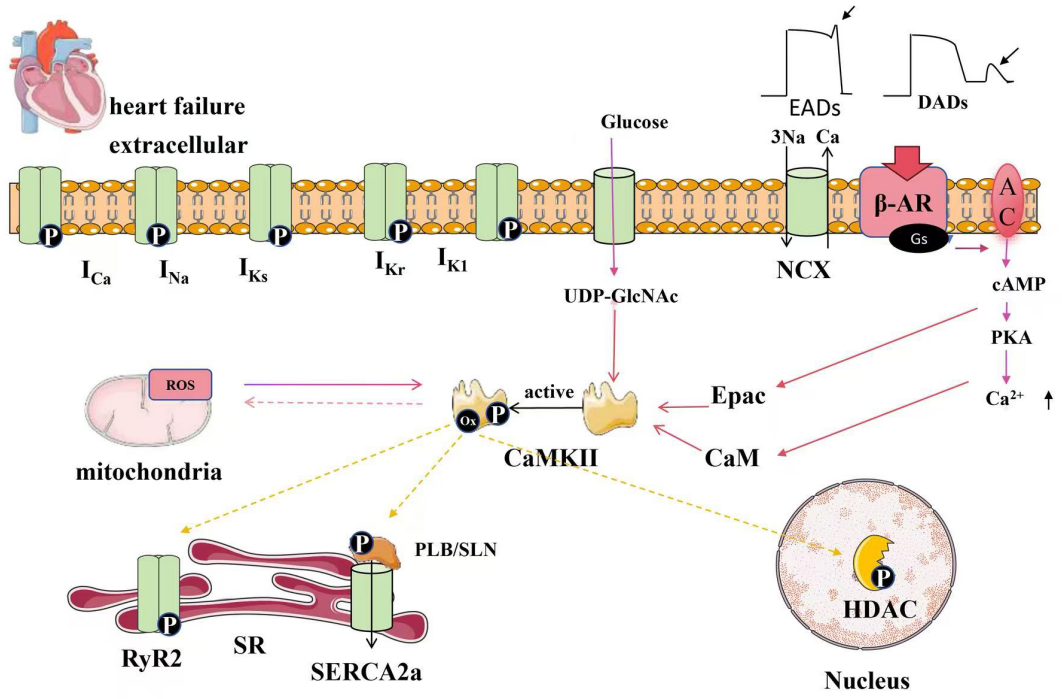


Fig. 2. Glucose metabolism in CaMKII-mediated cardiac dysfunction. In diabetes glucose enters cells via membrane transporters and activates CaMKII through O-GlcNAcylation, which synergizes with β-AR pathway activation and increased mitochondrial ROS production. Activated CaMKII induces EADs/DADs and calcium homeostasis disorder, and regulates gene expression by phosphorylating membrane ion channels, SR calcium regulatory proteins and nuclear HDACs, ultimately promoting myocardial electrophysiological disorders and the progression of heart failure. Abbreviations: $I_{Ca\text{-}L}$, L-type calcium current; $I_{Na\text{-}L}$, late sodium current; IKs, slow delayed rectifier potassium current; IKr, rapid delayed rectifier potassium current; IK1, inward rectifier potassium current; NCX, sodium-calcium exchanger; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; Epac, exchange protein directly activated by cAMP; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CaM, calmodulin; RyR2, ryanodine receptor 2; PLB/SLN, phospholamban/sarcolipin; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a; HDACs, histone deacetylases; P, phosphate group; Ox, oxidation; Gs, stimulatory G protein. Arrow types: solid arrows indicate direct activation or promotion; dashed arrows indicate indirect or proposed effects; directional arrows indicate the direction of signal transduction or ion flow.

tributor to cardiac arrhythmogenesis and contractile dysfunction. CaMKII mediates phosphorylation of RyR2 at the Ser2814 (S2814) site, which increases RyR2 channel open probability, leading to abnormal diastolic calcium leak from the SR. This pathological calcium leak can promote DADs and triggered arrhythmias, as well as impair excitation-contraction coupling. Several clinical and experimental studies have demonstrated that increased CaMKII-dependent phosphorylation of RyR2 at S2814 is associated with various cardiac diseases, including postoperative AF (POAF), HF and diabetic cardiomyopathy. For example, in atrial cardiomyocytes from patients who develop POAF, CaMKII expression and RyR2 phosphorylation at S2814 are significantly elevated, resulting in increased spontaneous SR calcium release events despite unchanged SR calcium content, thereby creating a substrate for arrhythmia [77]. Similarly, in a mouse model of heart failure induced by CaMKIIδC overexpression, phosphorylation of RyR2 at S2814 is essential for the observed diastolic SR calcium leak, although this modification alone does not fully account for the heart failure phenotype [78]. Pharmacological stabilization of RyR2 channels, such as with dantrolene, can reduce spontaneous calcium release events and improve cardiac function in CaMKIIδC transgenic mice, underscoring the pathogenic role of CaMKII-mediated RyR2 hyperphosphorylation [79].

In addition to phosphorylation, RyR2 function is modulated by post-translational modifications such as O-GlcNAcylation, which is elevated in diabetes and contributes to calcium mishandling. Empagliflozin, a selective SGLT2 inhibitor, attenuates ventricular arrhythmias in diabetic cardiomyopathy by normalizing intracellular calcium handling, partly through inhibition of O-GlcNAcylation and reduction of CaMKII-dependent RyR2 phosphorylation at Ser2814. Moreover, direct O-GlcNAcylation of RyR2 has been shown to enhance calcium leak, further promoting arrhythmogenesis in diabetic hearts [25]. This dual regulation by CaMKII-dependent phosphorylation and O-GlcNAcylation highlights the complexity of RyR2 channel modulation in pathological states.

Inflammation also plays a critical role in RyR2 dysfunction via CaMKII activation. In heart failure with preserved ejection fraction (HFpEF) and AF models, activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome leads to increased CaMKII-dependent phosphorylation of RyR2 at Ser2814, resulting in augmented diastolic calcium leak and increased arrhythmia susceptibility [77]. Pharmacological inhibition of NLRP3 with dapansutrile reduces atrial fibrosis, inflammation, and CaMKII-mediated RyR2 hyperphosphorylation, thereby decreasing AF vulnerability [80]. Similarly, recombinant Klotho administration after myocardial infarction reduces ventricular arrhythmias by suppressing CaMKII activation and subsequent RyR2 hyperphosphorylation, demonstrating the therapeutic potential of targeting this pathway [81].

The role of CaMKII-mediated RyR2 phosphorylation in arrhythmogenesis is further supported by genetic models. Knock-in mice carrying a phosphoresistant RyR2 S2814A mutation are protected from CaMKII-induced SR calcium leak and AF susceptibility, confirming the causal role of Ser2814 phosphorylation in RyR2 dysfunction [82]. Conversely, gain-of-function mutations or conditions that enhance CaMKII activation exacerbate RyR2-mediated calcium leak and arrhythmic events [64]. Notably, the interplay between CaMKII activation and other signaling pathways, such as c-Jun N-terminal kinase 2 (JNK2)-mediated modulation of SERCA2a activity, can further disturb calcium handling and aggravate arrhythmogenic calcium leak-load relationships [83].

In summary, CaMKII-dependent phosphorylation of RyR2 at Ser2814 is a central mechanism driving abnormal SR calcium leak and arrhythmogenesis across multiple cardiac pathologies, including diabetes, HF and POAF. This process is often exacerbated by additional RyR2 modifications such as O-GlcNAcylation and is further modulated by inflammatory signaling pathways. Therapeutic strategies aimed at inhibiting CaMKII activity, stabilizing RyR2 channels, or modulating RyR2 post-translational modifications hold promise for reducing calcium leak and preventing arrhythmias in these conditions [81].

3.3 Overactivation of CaMKII Under β-Adrenergic Receptor (β-AR) Stimulation

In the diabetic milieu, β-AR signaling is notably enhanced, leading to excessive activation of CaMKII and thereby exacerbating Ca^{2+} handling dysregulation in cardiomyocytes. This pathological cascade is a key contributor to the progression of diabetic cardiomyopathy and the increased susceptibility to arrhythmias. Under diabetic conditions, chronic β-AR stimulation, often modeled experimentally using isoproterenol (ISO), induces maladaptive cardiac remodeling characterized by impaired calcium handling and contractile dysfunction. For instance, ISO-treated rat models exhibit deteriorated cardiomyocyte contraction-relaxation kinetics, elevated diastolic intracellular Ca^{2+} levels, and altered Ca^{2+} transient dynamics, including prolonged decay time and reduced SR Ca^{2+} content. These changes are accompanied by increased phosphorylation of CaMKII and its downstream targets such as RyR2, which promotes SR Ca^{2+} leak, a well-established arrhythmogenic substrate [84]. In metabolic syndrome models with obesity, autonomous CaMKII activation is markedly increased, leading to enhanced spontaneous diastolic Ca^{2+} leak manifested as Ca^{2+} waves. This leak is further exacerbated by β-AR stimulation, highlighting the synergistic deleterious effects of β-AR signaling and CaMKII overactivation in diabetic hearts [64].

Mechanistically, β-AR stimulation activates CaMKII through multiple pathways, including direct phosphorylation and signaling intermediates such as exchange proteins directly activated by cAMP (Epac). The involvement of Epac1 in β-AR-induced Ca^{2+} handling abnormalities has been demonstrated, with the transmembrane receptor CD44 acting as a critical regulator of Epac1-mediated CaMKII activation. In mouse models, the β-AR agonist ISO increases CD44 and Epac1 expression as well as their interaction, leading to enhanced phosphorylation of CaMKII and RyR2, thereby promoting arrhythmogenic Ca^{2+} sparks. Genetic deletion or pharmacological inhibition of CD44 attenuates these effects, reducing ventricular arrhythmia susceptibility, which underscores the pathological role of β-AR-induced CaMKII activation mediated through CD44-Epac1 signaling [85]. Furthermore, β-AR stimulation promotes phosphorylation of RyR2 at Ser2814, a CaMKII-specific site, which increases RyR2 open probability and diastolic Ca^{2+} leak, contributing to triggered arrhythmias in diabetic and hypertensive models [86].

From an electrophysiological perspective, β-AR activation enhances the inward rectifier K^+ current (I_{K1}) via CaMKII-dependent pathways, thereby modulating APD and repolarization and influencing arrhythmia susceptibility. In canine ventricular myocytes, β-AR stimulation increases I_{K1} during the action potential plateau phase through CaMKII activation, whereas protein kinase A (PKA) does not mediate this effect, indicating a specific role for CaMKII in β-AR-driven electrophysiological remodeling [87]. Similarly, the I_{Ks} is augmented by β-AR stimulation, with CaMKII playing a pivotal role downstream of Epac activation, independent of changes in intracellular Ca^{2+} concentration. This complex regulation of K^+ currents by β-AR-CaMKII signaling contributes to fine-tuning of cardiac excitability and arrhythmogenesis [88].

Importantly, the spatial organization of β-AR subtypes and their coupling to CaMKII also influences pathological outcomes. β2-adrenergic receptors (β2-AR), but not β1-AR, form functional complexes with LTCCs in cardiomyocyte microdomains such as transverse tubules. This coupling requires caveolin-3 and CaMKII activation and is disrupted in HF, leading to impaired β2-AR-LTCC regulation and calcium-handling abnormalities. Loss of

this microdomain-specific β2-AR-CaMKII signaling axis may further exacerbate Ca^{2+} dysregulation and increase arrhythmia risk in diabetic hearts [89]. Conversely, β1-AR signaling predominantly activates PKA pathways but can also engage CaMKII through scaffolding proteins such as Synapse-associated protein 97 (SAP97) and G protein-coupled receptor kinase 5 (GRK5), which modulate receptor complex integrity and downstream CaMKII activity. Disruption of these interactions enhances CaMKII activation, promoting maladaptive cardiac remodeling and arrhythmogenesis [90].

The pathological consequences of β-AR-induced CaMKII overactivation are further evidenced by increased frequencies of spontaneous Ca^{2+} sparks and waves, which serve as triggers for arrhythmic events. Pharmacological inhibition of CaMKII using agents such as N-[2-[[[(E)-3-(4-chlorophenyl)prop-2-enyl]-methylamino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxybenzenesulfonamide (KN-93) or Autocamtide-2-related inhibitory peptide (AIP) effectively reduces diastolic Ca^{2+} leak and arrhythmia incidence in experimental models, highlighting CaMKII as a potential therapeutic target to mitigate β-AR-mediated arrhythmogenic remodeling in diabetes [64,86]. Moreover, the interplay between nitric oxide (NO) signaling and CaMKII S-nitrosylation modulates β-AR-induced arrhythmias, with specific cysteine residues on CaMKII influencing the balance between protective and deleterious effects during β-AR stimulation [91].

In summary, in the diabetic context, enhanced β-AR signaling leads to excessive CaMKII activation, which disrupts intracellular Ca^{2+} homeostasis by promoting RyR2 phosphorylation and diastolic Ca^{2+} leak, alters K^+ currents, and impairs excitation-contraction coupling. These molecular and electrophysiological alterations increase the propensity for spontaneous Ca^{2+} waves and triggered activity, thereby elevating the risk of cardiac arrhythmias. Understanding the intricate β-AR-CaMKII signaling axis in diabetes provides critical insights into arrhythmia mechanisms and identifies potential molecular targets for therapeutic intervention.

3.4 Regulation of Sodium-Calcium Exchanger Expression and CaMKII Action

The NCX plays a pivotal role in cardiac calcium homeostasis by extruding intracellular Ca^{2+} in exchange for extracellular Na^+, thereby influencing cardiac electrophysiology and contractility. In the context of DM, aberrant NCX expression and function have been implicated in atrial electrical remodeling, contributing to increased susceptibility to AF. Emerging evidence highlights CaMKII activation as a key upstream regulator that promotes NCX upregulation, facilitating maladaptive electrical remodeling in diabetic atria. For instance, a study using diabetic rat models demonstrated that enhanced CaMKII phosphorylation correlates with increased NCX protein expression, disorganized atrial myocyte architecture, and fibrosis, culminating in conduction abnormalities and heightened AF inducibility. Importantly, pharmacological attenuation of oxidative stress with allopurinol, a xanthine oxidase inhibitor, reduced CaMKII oxidation, reduced NCX expression, and ameliorated electrophysiological disturbances, underscoring the pathological CaMKII-NCX axis in diabetic atrial remodeling [92].

Mechanistically, CaMKII activation can be triggered by elevated intracellular Ca^{2+} and oxidative stress, both of which are prevalent in diabetic cardiomyopathy. Activated CaMKII phosphorylates key calcium-handling proteins, thereby enhancing NCX activity and expression. This upregulation of NCX may exacerbate calcium extrusion during diastole, leading to intracellular Na^+ accumulation and altered calcium cycling, which predisposes to DADs and triggered arrhythmias. Additionally, studies in neonatal rat cardiomyocytes exposed to tachycardia have shown CaMKII phosphorylation occurring downstream of NCX activation, suggesting a bidirectional regulatory loop that amplifies pathological remodeling signals [93]. This interplay indicates that NCX functions not only as a downstream effector but also participates in feedback mechanisms that sustain CaMKII activity and arrhythmogenic remodeling.

Furthermore, oxidative stress is a critical modulator of the CaMKII-NCX axis. ROS can oxidize CaMKII, leading to sustained activation independent of Ca^{2+}/CaM binding. ox-CaMKII then promotes NCX upregulation and disruption of calcium homeostasis, as observed in diabetic atrial tissue and other cardiac pathologies. Interventions targeting oxidative stress, such as xanthine oxidase inhibition with allopurinol, have been shown to reduce CaMKII oxidation, decrease NCX expression, and improve atrial conduction properties, thereby lowering AF risk [92]. Similarly, histone deacetylase inhibitors such as suberoylanilide hydroxamic acid have demonstrated cardioprotective effects in ischemia-reperfusion models by inhibiting NCX expression and CaMKII activation, further supporting the therapeutic potential of modulating this pathway [94].

In addition to diabetes, other pathological stimuli such as sympathetic nervous system activation and adipocyte-derived factors can modulate the NCX-CaMKII axis. For example, leptin released from epicardial adipose tissue activates sympathetic neurons, which in turn increase NCX activity and CaMKII phosphorylation in cardiomyocytes, promoting arrhythmogenesis [95]. This highlights the multifactorial regulation of NCX expression by CaMKII across diverse disease contexts.

Overall, CaMKII-mediated upregulation of NCX constitutes a central mechanism in atrial electrical remodeling, particularly in diabetic cardiomyopathy. The resulting calcium-handling abnormalities and conduction heterogeneity increase susceptibility to AF. Therapeutic strategies aimed at inhibiting CaMKII activity and reducing oxidative stress effectively downregulate NCX expression and im-

prove electrophysiological stability, representing promising avenues to mitigate arrhythmia risk in diabetes and related cardiac disorders [94,95].

4. Ion Channel Abnormalities and Electrophysiological Remodeling Regulated by CaMKII

4.1 Fundamental Mechanisms of Cardiac Arrhythmias in Diabetes

Cardiac arrhythmias arise from three principal mechanisms: enhanced automaticity, triggered activity, and reentry. In the diabetic heart, triggered activity resulting from abnormal calcium handling is particularly prominent. Triggered activity arises from afterdepolarizations that reach threshold and generate premature action potentials. Two main types are recognized. EADs occur during the plateau or repolarization phase, phases 2 to 3 of the action potential, and are typically caused by reactivation of LTCCs or an enhanced $I_{Na\text{-}L}$. If an EAD reaches threshold, it can trigger a premature action potential, leading to extrasystoles and reentrant arrhythmias such as torsade de pointes [96]. DADs occur after complete repolarization, phase 4, and are caused by diastolic Ca^{2+} overload and spontaneous Ca^{2+} release from the SR via RyR2. The released Ca^{2+} is extruded by the NCX, generating I_{ti} that depolarizes the membrane. When sufficiently large, DADs can trigger new action potentials, leading to arrhythmias, as observed in conditions such as digitalis toxicity or catecholaminergic polymorphic VT [97].

Reentry, the third principal mechanism, occurs when conduction is slowed in one region while remaining relatively normal in adjacent tissue, creating a self-sustaining electrical circuit. Diabetes promotes reentrant mechanisms through myocardial fibrosis, gap junction remodeling, and increased heterogeneity of APD [10]. In diabetic patients, ventricular arrhythmias manifest as premature ventricular contractions, non-sustained VT, sustained monomorphic VT, polymorphic VT, and VF. These arrhythmias arise from distinct substrates. Non-sustained VT is often driven by triggered activity, whereas sustained VT and VF typically require a reentrant substrate maintained by structural remodeling such as fibrosis [98].

4.2 Enhancement of $I_{Na\text{-}L}$ and Its Association With CaMKII

The $I_{Na\text{-}L}$ plays a pivotal role in cardiac electrophysiology by influencing APD and cellular excitability, and its enhancement represents a key arrhythmogenic mechanism. CaMKII has been identified as a major modulator of $I_{Na\text{-}L}$ through phosphorylation of the cardiac sodium channel Nav1.5, which increases persistent sodium influx during the plateau phase of the action potential. This modification prolongs APD, thereby facilitating EADs and DADs, both of which are recognized triggers of arrhythmias. Experimental studies across various cardiac pathologies, including diabetes and metabolic disorders, have demonstrated that CaMKII-mediated phosphorylation of Nav1.5 significantly augments $I_{Na\text{-}L}$, contributing to electrical instability. For example, in diabetic models characterized by glycemic fluctuations, elevated ROS activate CaMKII, which in turn phosphorylates Nav1.5, enhancing $I_{Na\text{-}L}$ and increasing susceptibility to ventricular arrhythmias. Pharmacological inhibition of CaMKII or direct blockade of $I_{Na\text{-}L}$ reverses these electrophysiological abnormalities, underscoring the mechanistic link between CaMKII activity and late sodium current enhancement in diabetic arrhythmogenesis [99].

A similar mechanism has been observed in obesity-related AF, where CaMKII-dependent phosphorylation of Nav1.5 increases $I_{Na\text{-}L}$, thereby promoting arrhythmia susceptibility. Genetic ablation of the phosphorylation site on Nav1.5 (S571A mutation) in mice prevents $I_{Na\text{-}L}$ augmentation and confers protection against AF induced by a high-fat diet, highlighting the critical role of CaMKII-mediated Nav1.5 modification in metabolic disease-associated arrhythmias. Furthermore, β-adrenergic stimulation, a common proarrhythmic trigger, synergizes with CaMKII activation to potentiate $I_{Na\text{-}L}$ and promote AF. In isolated rabbit atrial preparations, ISO-induced phosphorylation of Nav1.5 and CaMKII increases $I_{Na\text{-}L}$, leading to triggered activity and AF episodes. These effects are attenuated by combined inhibition of CaMKII and $I_{Na\text{-}L}$ blockers, indicating a cooperative interaction between these pathways in arrhythmogenesis [100].

Mechanistically, the dependence of $I_{Na\text{-}L}$ on $[Ca^{2+}]i$ has been demonstrated in canine ventricular myocytes, where reduction of $[Ca^{2+}]i$ decreases $I_{Na\text{-}L}$ amplitude. This calcium sensitivity is mediated by CaMKII, as pharmacological inhibition of CaMKII reduces $I_{Na\text{-}L}$ amplitude and shortens APD, confirming that basal CaMKII activity sustains $I_{Na\text{-}L}$ enhancement [101]. Additionally, the neuronal sodium channel isoform Nav1.8 has been implicated in $I_{Na\text{-}L}$ augmentation and arrhythmogenic calcium handling via CaMKII-dependent mechanisms, suggesting that multiple sodium channel isoforms contribute to the CaMKII-$I_{Na\text{-}L}$ axis [35].

In diabetic cardiomyopathy, increased $I_{Na\text{-}L}$ is accompanied by elevated CaMKII phosphorylation and oxidative stress, leading to prolonged QTc intervals and impaired calcium homeostasis. Interventions such as ketogenic diets have been reported to mitigate these alterations by normalizing CaMKII activity and reducing $I_{Na\text{-}L}$, thereby improving electrophysiological stability. Moreover, pharmacological agents such as moricizine inhibit angiotensin II-induced $I_{Na\text{-}L}$ enhancement by suppressing CaMKII activation, further supporting the therapeutic potential of targeting the CaMKII- $I_{Na\text{-}L}$ pathway in diabetes-related arrhythmias [99].

In human HFpEF, increased late sodium current and Na^+ influx have been observed in atrial cardiomyocytes, linked to elevated CaMKII expression and enhanced Nav1.5 phosphorylation. The SGLT2 inhibitor em-

pagliflozin reduces $I_{Na\text{-}L}$ and Na^+ influx, suggesting that modulation of CaMKII-dependent sodium channel phosphorylation represents a viable antiarrhythmic strategy in metabolic heart disease [102]. Similarly, traditional formulations such as Shenlian-Fumai have demonstrated antiarrhythmic effects by modulating sodium channel function and CaMKII signaling in heart failure models [103].

Collectively, these findings establish a robust mechanistic link between CaMKII-mediated phosphorylation of Nav1.5 and enhancement of the late sodium current, which plays a central role in the pathogenesis of arrhythmias in diabetes and related metabolic disorders. Increased $I_{Na\text{-}L}$ prolongs the action potential, promotes afterdepolarizations, and disrupts calcium homeostasis, thereby creating a substrate for arrhythmogenesis. Importantly, both CaMKII inhibition and direct $I_{Na\text{-}L}$ blockade have demonstrated efficacy in reversing these electrophysiological disturbances, highlighting the CaMKII-$I_{Na\text{-}L}$ axis as a critical therapeutic target for preventing arrhythmias in diabetic patients.

4.3 Potassium Channel Dysfunction and CaMKII-Mediated Regulation - Expanded With I_{to} and I_{K1}

Potassium (K^+) channels are critical determinants of cardiac repolarization and electrical stability, and their dysfunction represents a well-established substrate for arrhythmogenesis, particularly in the context of DM. Hyperglycemia, a hallmark of diabetes, exerts complex regulatory effects on potassium channel expression and function through multiple signaling cascades, notably involving O-GlcNAcylation of CaMKII and the NOX2-ROS-PKC pathway. Elevated glucose levels enhance O-GlcNAcylation of CaMKII, leading to its autonomous activation independent of Ca^{2+}/CaM binding. This post-translational modification promotes aberrant phosphorylation of downstream targets, including potassium channels, thereby altering their gating properties and surface expression. Concurrently, hyperglycemia stimulates NOX2-dependent ROS production, which activates PKC, further modulating potassium channel function and expression.

Specific potassium channel remodeling in diabetes involves several key currents. The transient outward potassium current (I_{to}) is primarily conducted by Kv4.2/Kv4.3 channels and is critical for early repolarization during phase 1. Diabetes consistently downregulates I_{to} density and expression, contributing to APD prolongation and increased arrhythmic risk. CaMKII plays a key role in this remodeling. Chronic hyperglycemia enhances CaMKII-dependent phosphorylation of Kv4.2 at Ser438, accelerating channel internalization and degradation. In diabetic mouse ventricles, the reduction in I_{to} is prevented by CaMKII inhibition or by mutation of the CaMKII phosphorylation site on Kv4.2. Loss of I_{to} also flattens APD rate dependence and facilitates EADs, a key mechanism underlying VT in diabetic patients [104].

I_{K1} establishes the resting membrane potential and contributes to terminal repolarization. This current, primarily mediated by Kir2.1 subunits and downregulated in pathological states such as cardiac hypertrophy and HF, conditions frequently exacerbated by diabetes. This downregulation is associated with increased CaMKII activity and oxidative stress. Notably, I_{K1} agonists such as zacopride have been shown to attenuate cardiac remodeling and restore I_{K1} function by suppressing CaMKII hyperactivation and related signaling pathways [105,106].

ATP-sensitive potassium (K_{ATP}) channels couple cellular metabolic status to membrane excitability. In diabetic and atherogenic conditions, these channels are inhibited by L5 low-density lipoprotein via CaMKII activation and NOX2-mediated oxidative stress. This inhibition leads to prolonged APD and increased arrhythmogenic risk [107]. Collectively, these findings underscore the pivotal role of CaMKII as a nodal integrator of metabolic and oxidative signals that drive potassium channel remodeling in diabetes.

Potassium channel remodeling leads to repolarization abnormalities that increase susceptibility to arrhythmias. Reductions in I_{K1} and K_{ATP} currents impair the terminal phase of repolarization and destabilize the resting membrane potential, thereby prolonging APD and facilitating EADs and DADs, which act as triggers for ventricular arrhythmias. CaMKII-mediated phosphorylation of potassium channels and associated proteins, such as PLN, further disrupts calcium handling and electrical stability, creating a substrate for arrhythmogenesis [106]. In addition, oxidative activation of CaMKII exacerbates these effects by promoting channel dysfunction and amplifying proarrhythmic signaling cascades. The interplay between CaMKII and potassium channels extends beyond the heart; for example, in hippocampal neurons, CaMKII regulates the expression and phosphorylation of Kv4.2 channels, thereby influencing neuronal excitability and synaptic plasticity [108]. This cross-talk underscores the broad regulatory role of CaMKII in modulating potassium channel function under pathological conditions.

In diabetes, the combined effects of hyperglycemia-induced O-GlcNAc-mediated CaMKII activation and NOX2-ROS-PKC signaling lead to potassium channel downregulation and dysfunction, culminating in repolarization abnormalities and an increased risk of arrhythmias. Therapeutic strategies targeting CaMKII activity, oxidative stress, or potassium channel modulation have shown promise in preclinical models. For example, CaMKII inhibitors protect cardiomyocytes from mitochondrial dysfunction and metabolic stress-induced arrhythmias [109], while I_{K1} agonists restore channel expression and reduce reperfusion arrhythmias by suppressing CaMKII activity [106]. Furthermore, vasodilatory agents that activate endothelial CaMKII/eNOS signaling may indirectly influence potassium channel function and vascular tone, suggesting

a broader role for CaMKII in cardiovascular homeostasis [110]. Collectively, these findings delineate a mechanistic bridge whereby hyperglycemia-driven CaMKII activation orchestrates potassium channel remodeling, leading to repolarization abnormalities and increased arrhythmogenic susceptibility in diabetes. Understanding this axis provides a foundation for developing targeted interventions to mitigate cardiac electrical instability in diabetic patients.

4.4 L-Type Calcium Channel (Cav1.2 / $I_{Ca\text{-}L}$) Remodeling by CaMKII

In addition to sodium, potassium, and NCX remodeling, CaMKII directly modulates calcium influx through L-type calcium channels. Specifically, CaMKII phosphorylates the cardiac L-type calcium channel (Cav1.2) at multiple sites including Ser1512 and Ser1570, increasing channel open probability and enhancing Ca^{2+} influx during the action potential plateau. Under diabetic conditions, hyperglycemia-induced oxidative stress ox-CaMKII and O-GlcNAcylation further potentiate this effect, leading to excessive intracellular Ca^{2+} loading. This calcium overload contributes to DADs, triggered activity, and SR Ca^{2+} overload, all of which are strongly proarrhythmic. In STZ-induced diabetic models, increased CaMKII-dependent Cav1.2 phosphorylation correlates with prolonged APD and the occurrence of EADs; these abnormalities are attenuated by CaMKII inhibition (e.g., KN-93) [111]. Thus, CaMKII hyperactivation in diabetes promotes arrhythmogenesis in part through enhancement of the $I_{Ca\text{-}L}$. This mechanism acts synergistically with increased $I_{Na\text{-}L}$ and NCX dysregulation to generate a proarrhythmic state characterized by intracellular calcium overload [112].

4.5 CaMKII as a Driver of Myocardial Fibrosis and Structural Remodeling

Beyond its immediate electrophysiological effects, sustained CaMKII activation in the diabetic heart critically contributes to structural remodeling, thereby establishing a stable arrhythmogenic substrate. Hyperglycemia-induced CaMKII activation promotes cardiac fibroblast proliferation and differentiation into myofibroblasts, the primary effector cells responsible for extracellular matrix deposition. In fibroblasts, activated CaMKII enhances the expression of profibrotic proteins/markers including collagen I/III and fibronectin through phosphorylation of transcription factors such as cAMP response element-binding protein and via the HDAC/MEF2 signaling pathway [113].

This progressive fibrosis increases myocardial stiffness, promotes conduction heterogeneity, and facilitates anisotropic reentry, all of which are independent risk factors for VT and AF. Moreover, fibrotic scar tissue creates regions of slow conduction that further favor reentrant arrhythmias. In diabetic animal models, pharmacological inhibition of CaMKII with KN-93 not only normalizes calcium handling but also attenuates collagen deposition and interstitial fibrosis, thereby improving both electrical and structural integrity [114]. Thus, targeting CaMKII addresses both the functional electrophysiological and structural fibrotic components of arrhythmogenesis in diabetic cardiomyopathy. The convergence of diabetic metabolic stressors on CaMKII and the downstream pathological cascades leading to cardiac arrhythmias are comprehensively illustrated in Fig. 3.

5. Pharmacological Modulation of CaMKII Signaling by Current and Experimental Agents

5.1 Antioxidant and Direct CaMKII Inhibitor Strategies

Antioxidant therapies and CaMKII inhibition have emerged as promising strategies to mitigate diabetes-associated arrhythmogenesis, primarily through their ability to attenuate oxidative stress and modulate aberrant CaMKII signaling. In animal models of diabetes and related cardiac disorders, antioxidants such as Tempol have been shown to reduce the incidence of ventricular arrhythmias by scavenging ROS and thereby limiting oxidative activation of CaMKII. For example, in a STZ -induced diabetic rat model, glycemic fluctuations markedly increased susceptibility to ventricular arrhythmias via ROS-mediated CaMKII activation; Tempol administration significantly reduced ROS levels and CaMKII oxidation, effectively lowering arrhythmia inducibility [12]. Similarly, the CaMKII inhibitor KN-93 has been demonstrated to suppress CaMKII phosphorylation and activity, leading to a reduction in arrhythmic events across various experimental models. In diabetic and oxidative stress settings, KN-93 inhibits CaMKII-dependent phosphorylation of downstream targets such as PLN and RyR2, resulting in improved calcium handling and fewer arrhythmogenic triggers [12,115].

While KN-93 has been widely used in experimental studies, it has notable limitations, including off-target effects on other kinases and suboptimal selectivity. Consequently, more potent and selective CaMKII inhibitors have been developed. AIP is a highly selective peptide inhibitor that competes with substrate binding, exhibiting nanomolar potency with minimal off-target effects. In diabetic mouse models, AIP reduces RyR2 phosphorylation at Ser2814 and suppresses arrhythmia inducibility without affecting baseline contractility [116]. GSK-650394, a small-molecule ATP-competitive inhibitor of SGK1/SGK2, has also demonstrated efficacy in reducing AF burden in diet-induced obese mice. This effect is associated with decreased $I_{Na\text{-}L}$ and normalization of APD [117].

Novel approaches targeting CaMKII post-translational modifications are also emerging. Genetic knock-in of oxidation-resistant CaMKII with MMVV mutation protects against oxidative stress-induced arrhythmias without affecting physiological Ca^{2+}/CaM-dependent activation [118]. Similarly, mutation of the O-GlcNAcylation site with S280A in CaMKIIδ prevents hyperglycemia-

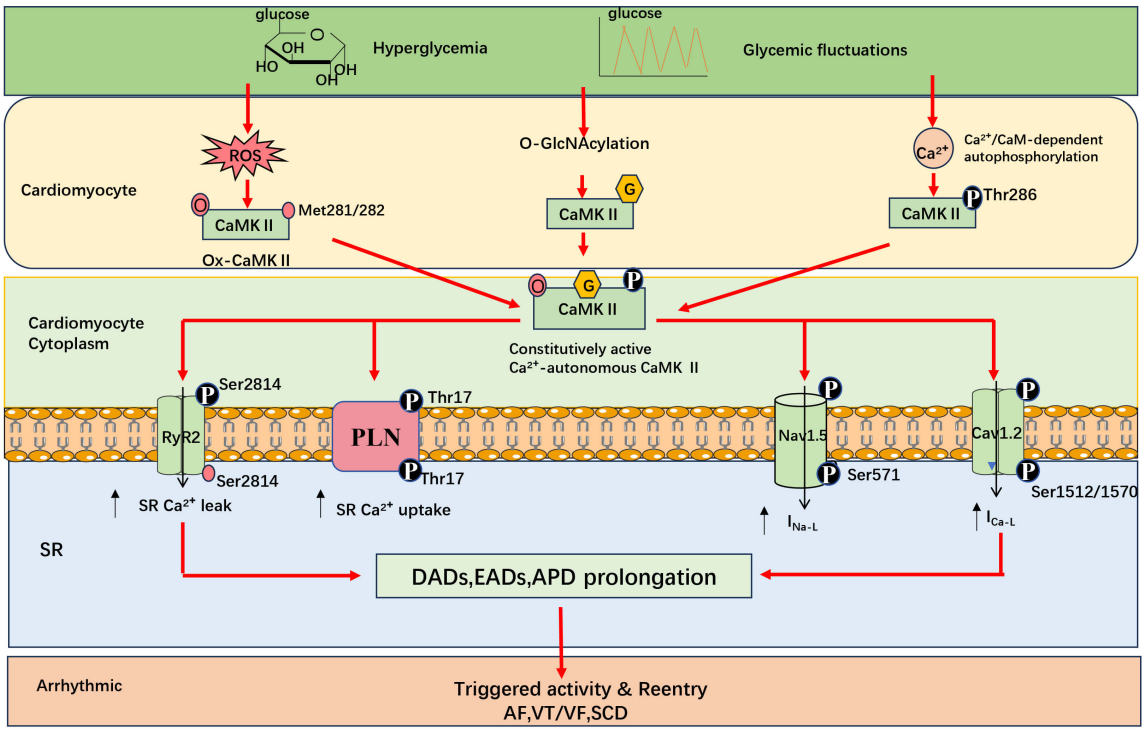


Fig. 3. Integrated schematic of CaMKII-mediated signaling pathways in diabetic cardiomyocytes. This figure summarizes the convergence of diabetic metabolic stressors on CaMKII and the downstream pathological cascades leading to cardiac arrhythmias. Left panel: Three interdependent mechanisms drive CaMKII activation under diabetic conditions: (1) classical Ca^{2+}/CaM-dependent autophosphorylation at Thr286; (2) O-GlcNAcylation at Ser280; and (3) oxidative modification at Met281/282. These post-translational modifications confer Ca^{2+}-independent autonomous activity, sustaining maladaptive signaling. Center: constitutively active CaMKII serves as a nodal hub. Right panel: Activated CaMKII phosphorylates multiple downstream effectors: Ryanodine receptor type 2 (RyR2) at Ser2814, phospholamban (PLN) at Thr17, cardiac sodium channel (Nav1.5 at Ser571), and L-type calcium channel (Cav1.2 at Ser1512/1570). These events promote SR Ca^{2+} leak, late sodium current ($I_{Na\text{-}L}$) enhancement, and L-type calcium current ($I_{Ca\text{-}L}$) increase, collectively leading to DADs, EADs, and action potential prolongation. Bottom panel: these cellular abnormalities converge to increase susceptibility to atrial fibrillation (AF), ventricular tachycardia/ventricular fibrillation (VT/VF), and sudden cardiac death (SCD). Symbols and abbreviations: P, phosphate group; G, O-GlcNAcylation; O, oxidation; ↑, increased expression or activity. Solid arrows indicate activation or promotion; directional arrows indicate the direction of signal transduction or ion flow. Ca^{2+} is presented as a superscript throughout.

induced ROS generation and associated Ca^{2+} handling disturbances that contribute to arrhythmogenesis. In addition, several clinically approved drugs with indirect or secondary CaMKII-modulating effects are gaining attention. Empagliflozin, a SGLT2 inhibitor, reduces CaMKII-dependent RyR2 phosphorylation and $I_{Na\text{-}L}$ in diabetic models. Ranolazine, a selective $I_{Na\text{-}L}$ blocker, also exerts antiarrhythmic effects partly through indirect suppression of CaMKII-driven downstream signaling [119]. These agents therefore hold translational promise for diabetic patients at high arrhythmic risk. Overall, combination strategies targeting oxidative stress, inflammation, and CaMKII signaling simultaneously may provide the most effective therapeutic benefit, as discussed below.

Moreover, combined antioxidant and CaMKII-inhibitory approaches appear to synergistically improve cardiac electrophysiological stability. For example, cinnamaldehyde, which possesses antioxidant properties, and KN-93 both inhibited CaMKII pathway activation in lipopolysaccharide-induced alveolar epithelial injury, thereby reducing oxidative stress and inflammation [115]. This suggests that antioxidant and CaMKII-targeted therapies may act in concert to alleviate pathological remodeling and arrhythmogenesis in diabetic hearts. Beyond oxidative stress and CaMKII inhibition, incorporating anti-inflammatory strategies further enhances therapeutic efficacy. In diabetic cardiomyopathy models, inhibition of Toll-like receptor 4 signaling reduced inflammation, oxidative stress, and CaMKII phosphorylation, collectively attenuating pyroptosis and cardiac dysfunction [120]. These findings underscore the importance of addressing inflammation alongside oxidative stress and CaMKII dysregulation to comprehensively target diabetic arrhythmias. Additionally, receptor-interacting protein

kinase 3 inhibitors such as GSK872 have been shown to downregulate CaMKII activation and oxidative stress, thereby reducing necroptosis and myocardial injury under hyperglycemic conditions [121,122]. This highlights the therapeutic potential of targeting upstream regulators of CaMKII in diabetes-associated cardiac pathology.

Collectively, these preclinical studies provide compelling evidence that antioxidant agents such as Tempol, combined with CaMKII inhibitors such as KN-93, can effectively reduce oxidative stress-induced CaMKII activation, improve calcium homeostasis, and decrease arrhythmic events in diabetic models. The addition of anti-inflammatory interventions further enhances these effects, suggesting that a multifaceted therapeutic strategy may be optimal for managing diabetes-related arrhythmias. Future clinical investigations are warranted to translate these findings into effective therapies that reduce arrhythmia risk and improve cardiovascular outcomes in patients with diabetes.

5.2 Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

SGLT2 inhibitors including empagliflozin and dapagliflozin reduce major adverse cardiovascular events and arrhythmic endpoints, including AF and ventricular arrhythmias [23,24]. Preclinical studies have implicated CaMKII as a key downstream target. In diabetic mice, empagliflozin attenuated ventricular arrhythmia susceptibility by reducing O-GlcNAcylation and suppressing CaMKII-dependent RyR2 phosphorylation at Ser2814 [25]. In human atrial cardiomyocytes from patients with HFpEF, empagliflozin reduced the pathological increase in $I_{Na\text{-}L}$, an abnormality driven in part by CaMKII-mediated Nav1.5 phosphorylation [102].

However, the relationship between SGLT2 inhibitors and CaMKII may be largely indirect. Using a CaMKII activity reporter in neonatal rat ventricular myocytes, a recent study found that neither empagliflozin nor dapagliflozin directly inhibited CaMKII at therapeutic concentrations of 1 μM. Although empagliflozin reduced AF inducibility in diabetic mice, this effect did not correlate with direct CaMKII inhibition [123]. These findings suggest that SGLT2 inhibitors exert their beneficial effects primarily through indirect mechanisms, including improvement of metabolic status, reduction of oxidative stress, and attenuation of O-GlcNAcylation, rather than direct kinase inhibition. Interestingly, contrasting evidence from endothelial cells indicates that dapagliflozin may normalize CaMKII-dependent signaling pathways in a cell type-specific manner [124], warranting further investigation into tissue-specific and context-dependent effects.

5.3 GLP-1 RAs

GLP-1 receptor agonists including liraglutide and semaglutide reduce major adverse cardiovascular events, with emerging evidence suggesting beneficial effects on AF and ventricular arrhythmias [27,28]. By attenuating oxidative stress and inflammation, key upstream drivers of pathological CaMKII activation, GLP-1 RAs are expected to reduce ox-CaMKII levels [26].

Direct evidence linking GLP-1 receptor activation to CaMKII-dependent antiarrhythmic mechanisms has been reported in pulmonary vein cardiomyocytes. GLP-1 (7-36) amide reduces spontaneous electrical activity, L-type Ca^{2+} current, NCX current, and late Na^{+} current in a concentration-dependent manner. Notably, pretreatment with the CaMKII inhibitor KN-93 abolishes these protective effects, indicating that CaMKII signaling is required for GLP-1-mediated electrophysiological modulation [125]. A more recent study using the GLP-1 RA supaglutide further suggests activation of a GLP-1R/cAMP/PKA/CaMKII/SIRT3 axis, associated with reduced ox-CaMKII and attenuation of atrial fibrosis, as presented at AHA 2025 [126].

5.4 Metformin and Conventional Agents

Metformin possesses antioxidant and anti-inflammatory properties that are expected to reduce ox-CaMKII levels, although direct evidence in cardiomyocytes remains limited. In contrast, insulin therapy and sulfonylureas warrant caution in the context of arrhythmia risk. Severe hypoglycemia triggers a catecholamine surge and β-adrenergic receptor-mediated CaMKII activation, promoting RyR2 hyperphosphorylation and diastolic SR Ca^{2+} leak [20,21]. Thus, hypoglycemia-induced CaMKII activation provides a mechanistic link between intensive glucose-lowering therapy and increased susceptibility to cardiac arrhythmias.

5.5 Summary and Clinical Perspective

Current evidence supports that SGLT2 inhibitors and GLP-1 receptor agonists exert antiarrhythmic effects that are partially mediated through modulation of CaMKII signaling. SGLT2 inhibitors appear to act indirectly by improving metabolic status and redox balance rather than through direct kinase inhibition [123]. In contrast, GLP-1 receptor agonists may require intact CaMKII signaling for their antiarrhythmic efficacy, as suggested by experimental studies [125]. Key clinical implications include a preference for SGLT2 inhibitors or GLP-1 receptor agonists over sulfonylureas or intensive insulin regimens in patients at high risk of arrhythmias, as well as minimizing iatrogenic hypoglycemia. Importantly, no currently approved antidiabetic agent directly inhibits cardiac CaMKII at therapeutic concentrations [51,123]. Direct CaMKII inhibitors therefore remain an experimental strategy requiring further development. Overall, combination approaches targeting oxidative stress, inflammation, and CaMKII signaling may offer the most effective strategy for reducing arrhythmia risk in diabetes. Table 1 summarizes the CaMKII-mediated mechanisms, targets, and therapeutic strategies in diabetes-associated cardiac disorders.

Table 1. Summary table of CaMKII-mediated mechanisms, targets and therapeutics in diabetes-associated cardiac disorders.

Category	Core mechanism	Key targets	Core disease
CaMKII Activation	Classical	Ca^{2+}/CaM, CaMKIIδ	Diabetes (early)
	Oxidative modification	CaMKII (Met281/282), NOX2	Diabetes
	O-GlcNAcylation	CaMKIIδ (Ser280), UDP-GlcNAc	Hyperglycemia, diabetes
Calcium Signaling Abnormality	RyR2 regulation	RyR2 (Ser2814)	Diabetic cardiomyopathy, AF
	PLN/ SERCA2a regulation	PLN (Thr17), SERCA2a	Diabetes, HF
	β-AR mediated	β-AR, Epac1	Diabetes
Ion Channel Abnormality	I_{Na-L} regulation	Nav1.5, CaMKIIδ	Diabetes, AF
	K^+ channel regulation	I_{K1}/I_{Ks}/I_{Kr}	Diabetes, cardiac hypertrophy
	NCX regulation	NCX	Diabetic AF
Oxidative Stress-Inflammation	ROS-CaMKII feedback	NOX2, ROS	Diabetes
	Inflammation-CaMKII crosstalk	NF-κB, NLRP3	Diabetic cardiomyopathy
Therapeutic Strategy	CaMKII inhibition	KN-93, AIP	Diabetes-associated arrhythmias
	Antioxidation	Tempol, Allopurinol	Diabetes
	SGLT2 inhibition	Empagliflozin	T2DM, diabetic cardiomyopathy
	GLP-1 RA	Liraglutide, Semaglutide	T2DM
	Ion channel modulation	Ranolazine, Dantrolene	Diabetic AF, ventricular arrhythmias
	Anti-inflammation	Dapansutrile, TAK-242	Diabetic cardiomyopathy

SERCA2a, Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a; NCX, Sodium-calcium exchanger; SGLT2, Sodium-glucose cotransporter 2; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; NOX2, NADPH oxidase 2; Epac, Exchange protein directly activated by cAMP; I_{Kr}, Rapid delayed rectifier potassium current; I_{Ks}, Slow delayed rectifier potassium current; I_{K1}, Inward rectifier potassium current; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; AIP, Autocamtide-2-related inhibitory peptide; AF, Atrial fibrillation; T2DM, Type 2 diabetes mellitus; TAK-242, ethyl (6R)-6-[(2-chloro-4-fluorophenyl)sulfamoyl]cyclohex-1-ene-1-carboxylate; UDP, uridine diphosphate; KN-93, N-[2-[[[(E)-3-(4-chlorophenyl)prop-2-enyl]-methylamino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxybenzenesulfonamide.

6. Conclusion

In conclusion, CaMKII serves as a pivotal molecular nexus linking diabetic metabolic disturbances to cardiac arrhythmogenesis, representing a significant advance in our understanding of diabetic cardiomyopathy. From a mechanistic perspective, the multifaceted activation of CaMKII, including oxidative modifications and O-GlcNAcylation, highlights the complexity of its dysregulation in diabetic cardiomyocytes. These post-translational modifications not only aberrantly enhance CaMKII activity but also drive a cascade of downstream effects, including disruption of calcium signaling, ion channel dysfunction, and electrophysiological remodeling. Collectively, these alterations contribute to the increased susceptibility to cardiac arrhythmias observed in patients with diabetes.

Balancing the diverse research perspectives, it is evident that while CaMKII's central role in arrhythmogenesis is well supported, the heterogeneity of its activation mechanisms and the context-dependent consequences require a more nuanced interpretation. Some studies emphasize oxidative stress as the predominant driver of CaMKII hyperactivation, whereas others highlight the importance of O-GlcNAcylation, particularly under hyperglycemic conditions. This divergence underscores the need for integrative research approaches that account for the interplay among multiple post-translational modification pathways and their temporal dynamics within the diabetic milieu.

From a therapeutic standpoint, targeting CaMKII and its upstream regulators offers promising avenues for mitigating arrhythmia risk in diabetes. Preclinical studies have shown that modulation of CaMKII activity can restore calcium homeostasis and stabilize electrophysiological function, thereby reducing arrhythmic events. However, translation of these findings into clinical practice requires careful evaluation of the safety profile and long-term effects of CaMKII-targeted interventions, given the kinase's broad physiological roles across multiple organ systems. In addition, the development of isoform-specific or modification-specific inhibitors may improve therapeutic precision and reduce off-target effects.

Looking forward, future research should prioritize delineating the distinct functional roles of different CaMKII post-translational modifications in the diabetic heart. Advanced molecular, genetic, and electrophysiological approaches will be essential to resolve these mechanisms with higher resolution. At the clinical level, trials of CaMKII-targeted therapies should incorporate robust biomarkers of kinase activity and downstream signaling to enable better

stratification of patient response and support more personalized treatment strategies.

In summary, the current body of evidence positions CaMKII as a central mediator linking metabolic dysregulation in diabetes to cardiac electrophysiological instability and arrhythmias. A balanced synthesis of existing findings supports continued investigation into its complex regulation and therapeutic targeting, with the goal of improving cardiovascular outcomes in diabetic populations.

Abbreviations

AF, Atrial fibrillation; APD, Action potential duration; APD90, Action potential duration at 90% repolarization; CaM, Calmodulin; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; DADs, Delayed afterdepolarizations; EADs, Early afterdepolarizations; Epac, Exchange protein directly activated by cAMP; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; HFpEF, Heart failure with preserved ejection fraction; I_{Kr}, Rapid delayed rectifier potassium current; I_{Ks}, Slow delayed rectifier potassium current; I_{K1}, Inward rectifier potassium current; $I_{Na\text{-}L}$, Late sodium current; NCX, Sodium-calcium exchanger; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NOX2, NADPH oxidase 2; O-GlcNAc, O-linked β-N-acetylglucosamine; ox-CaMKII, Oxidized CaMKII; PKC, Protein kinase C; PLN, Phospholamban; POAF, Postoperative atrial fibrillation; ROS, Reactive oxygen species; RyR2, Ryanodine receptor type 2; SCD, Sudden cardiac death; SERCA2a, Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a; SGLT2, Sodium-glucose cotransporter 2; SR, Sarcoplasmic reticulum; T2DM, Type 2 diabetes mellitus. LTCCs, L-type Ca^{2+} channels; CICR, calcium-induced calcium release; STZ, streptozotocin; ISO, isoproterenol; AIP, autocamtide-2-related inhibitory peptide; NO, nitric oxide; PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; Iti, transient inward current; $I_{Ca\text{-}L}$, L-type calcium current.

Author Contributions

JL, and XL made substantial contributions to the study conception and critical revisions. JL drafted the original manuscript. YZ and XZ prepared and edited the figures. XL reviewed and edited the manuscript. XL acquired the funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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