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*Review Article*

# Research progress on the role of CaMKII in heart disease

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**Abstract:** In the heart, $Ca^{2+}$ participates in electrical activity and myocardial contraction, which is closely related to the generation of action potential and excitation contraction coupling (ECC) and plays an important role in various signal cascades and regulates different physiological processes. In the $Ca^{2+}$ related physiological activities, CaMKII is a key downstream regulator, involving autophosphorylation and post-translational modification, and plays an important role in the excitation contraction coupling and relaxation events of cardiomyocytes. This paper reviews the relationship between CaMKII and various substances in the pathological process of myocardial apoptosis and necrosis, myocardial hypertrophy and arrhythmia, and what roles it plays in the development of disease in complex networks. This paper also introduces the drugs targeting at CaMKII to treat heart disease.

**Keywords:** CaMKII, $Ca^{2+}$, cardiomyocyte, necrosis, hypertrophy, arrhythmology

## Introduction

Calcium ($Ca^{2+}$), one of the most common signal transducers, plays many important regulatory roles in cardiomyocytes [1]. It can mediate various biological functions, such as muscle contraction, extracellular swallowing, neuronal activity and triggering programmed cell death [2]. In the initial stage of action potential, $Ca^{2+}$ which flows into L-type $Ca^{2+}$ channel through myoplasma voltage gating triggers sarcoplasmic reticulum (SR) to release a large amount of $Ca^{2+}$. This process of myocardial contraction and blood drawing driven by $Ca^{2+}$ is called excitation contraction coupling (ECC) [3]. The transport mechanism of $Ca^{2+}$ in cardiomyocytes includes $Ca^{2+}$ cycling between cytoplasm and extracellular space and $Ca^{2+}$ cycling between cytoplasm and calcium pool, especially SR. In the place where the distance between T-tubules and SR is very close, dyad is very important for intracellular $Ca^{2+}$ cycle [4], Dyad is regarded as a signal link related to cardiac contraction, and it is composed of L-type $Ca^{2+}$ channel clusters on SR, which are closely distributed to form RyRs clusters. Cardiac dyad may help regulate the release of $Ca^{2+}$ in SR during systole [5].

In the initial depolarization phase of AP, the probability of LCC opening increases, which allows $Ca^{2+}$ to enter dyad. SR is the main intracellular $Ca^{2+}$ storage cell [6]. $Ca^{2+}$ release in SR is mediated by RyR2 which is a special $Ca^{2+}$ release channel [7]. With the increase of $Ca^{2+}$ concentration in dyad, $Ca^{2+}$ binds to RyR2s, which increase the probability of receptor opening. When calcium triggers the release of calcium, the large opening of RyR2 receptor results in $Ca^{2+}$ releasing from JSR. $Ca^{2+}$ is rapidly accumulated in dyad and diffuses to cytoplasm. $Ca^{2+}$ in the cytosol binds to and activates cardiac troponin C (TNC), and then initiates myofilament contraction [8]. The $Na^{+}$-$Ca^{2+}$ exchanger (NCX) excretes one $Ca^{2+}$ every three $Na^{+}$, which is the main way to excrete $Ca^{2+}$ in cardiomyocytes (**Figure 1**) [9]. During the diastolic phase, $Ca^{2+}$ enters SR from SERCA2a, or enters extracellular space from NCX, which causes myocardial relaxation. In addition, $Ca^{2+}$ released from SR enters the cytoplasm rapidly, and then enters SR or extrudes out of the cells, which

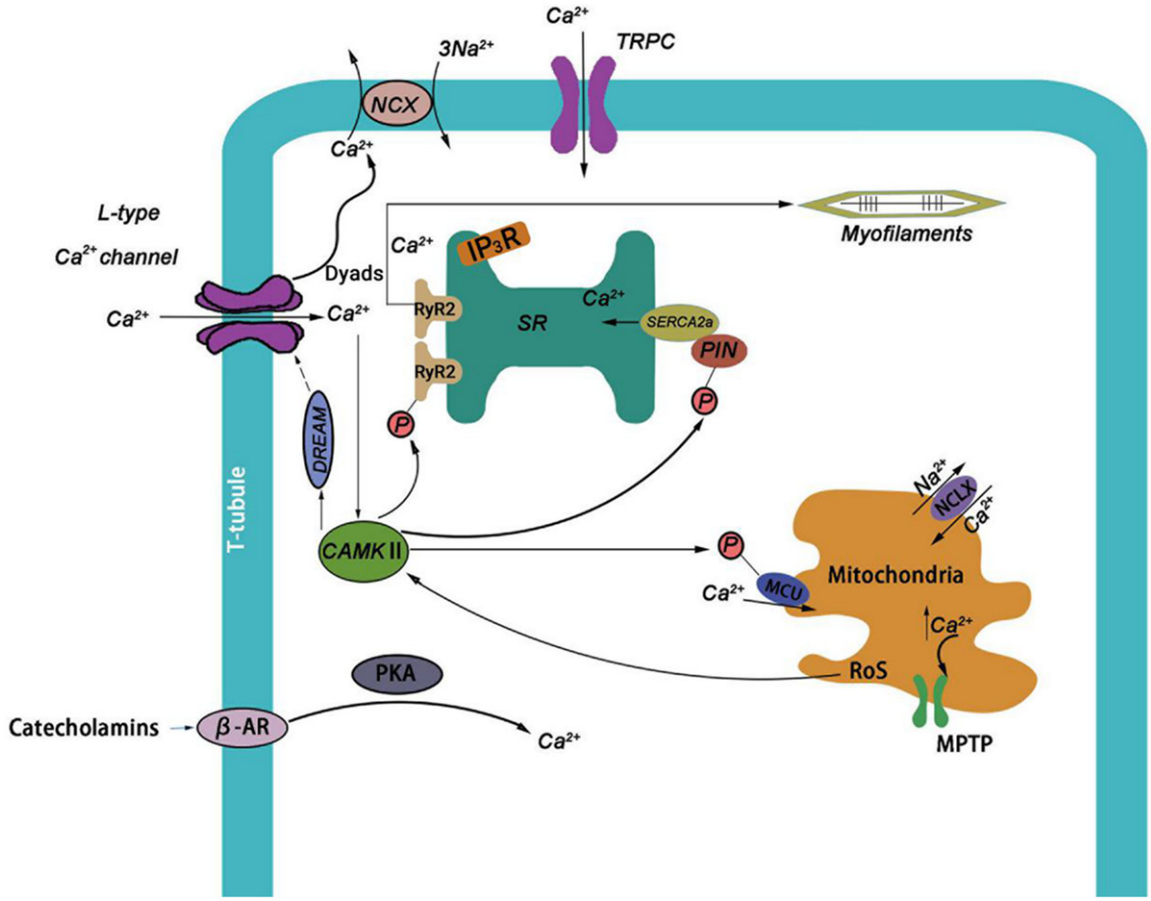


**Figure 1.** $Ca^{2+}$ and CaMKII in cardiomyocytes. $Ca^{2+}$ can enter cardiomyocytes through LTCC, TRPC and other channels, β-AR can also regulate the influx of $Ca^{2+}$. When $Ca^{2+}$ increases to a certain extent in dyads, it will combine with RyR2 and cause CICR. When a large amount of $Ca^{2+}$ influx into the cytoplasm, it can promote the contraction of cardiomyocytes. $Ca^{2+}$ can be transported out of cells by NCX. The increase of $Ca^{2+}$ concentration can activate CaMKII, which can phosphorylate $IP_3R$ and increase the opening of RyR, and also phosphorylate PLN and promote the absorption of SR $Ca^{2+}$. DREAM, a downstream factor stimulated by CaMKII, inhibited the opening of LTCC by negative feedback. Meanwhile, under the activation of CaMKII, MCU would be phosphorylated to promote $Ca^{2+}$ inflow into mitochondria, and a large increase in mitochondrial $Ca^{2+}$ concentration would cause the opening of MPTP channels and trigger cell apoptosis.

causes a transient wave of $Ca^{2+}$ throughout the cardiomyocytes.

The activity of $Ca^{2+}$ channel and exchanger involving EC coupling is regulated by various mechanisms and signal pathways. $IP_3$ (inositol 1, 4, 5-trisphosphate) is the substrate produced by phospholipase C (PLC), hydrolysis of ptdIns (4, 5) P2 (phosphatidylinositol-4, 5-bisphosphate), which acts as the second messenger to regulate $Ca^{2+}$ release by stimulating $IP_3$ receptors [10]. The increase of paracrine or autocrine of Endothelin-1 (ET-1) can promote the production of IP [11]. Protein kinase A (PKA) can phosphorylate $IP_3R$ (Inositol trisphosphate receptor) and enhance its $Ca^{2+}$ release at a lower concentration of $IP_3$ [12]. TRP channel plays an important role in regulating cell contraction, proliferation and death. The integrated stimulation is transmitted to the downstream signal pathway through $Ca^{2+}$. In cardiomyocytes, especially TRPC channel, it is an important regulatory factor of $Ca^{2+}$ cycle, which is related to calcineurin and other effectors to regulate and control the physiological and pathological processes of the heart [13, 14]. PKA and CaMKII play an important role in the regulation of cardiac $Ca^{2+}$ circulation. Activated β-adrenergic receptor (β-AR) stimulates aden-y late cyclase (AC) to activate PKA and regulate calcium uptake in SR. CaMKII has a similar function with PKA, and is also activated by sym-

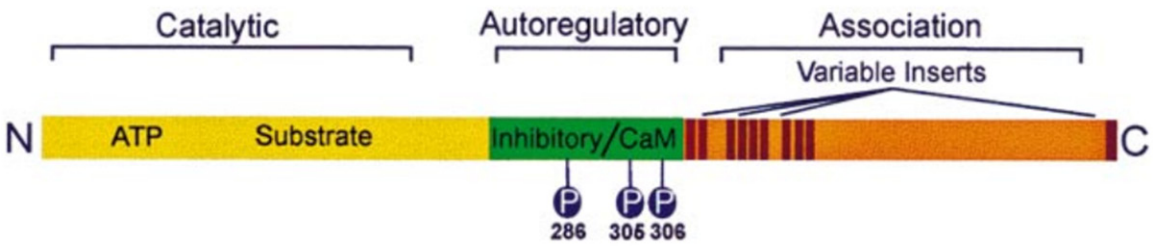


**Figure 2.** Linear diagram of a prototypical CaMKII subunit.

**Table 1.** Structure and function of CaMKII subunit

| Domain | Structure and function |
|---|---|
| N-terminal catalytic domain | The catalytic domain is autoinhibited by a pseudosubstrate autoregulatory sequence that is disinhibited following $Ca^{2+}$/CaM binding. |
| self regulatory domain | The association domain produces the native form of the enzyme, a multimeric holoenzyme composed of 12 subunits. |
| C-terminal association domain | Conserved sites of autophosphorylation are indicated in the autoregulatory region. |

pathetic nerve to play a role. CaMKII can also phosphorylate $Ca^{2+}$ and $Na^{+}$ channels, change $I_{Ca}$ and $I_{Na}$ gating, in order to prolong APD time and improve the possibility of early depolarization. CaMKII has a more important and long-term impact on $Ca^{2+}$ cycle [15].

### $Ca^{2+}$/calmodulin dependent protein kinase II

CaMKII is a polymer compound composed of 12 monomers [16]. Each CaMKII monomer has three main domains: N-terminal catalytic domain, self regulatory domain and C-terminal association domain (**Figure 2** and **Table 1**) [17, 18]. The catalytic activity of the self regulatory domain which has the binding site with $Ca^{2+}$/CaM is relatively low without stimulation, and regulates the activation state through binding $Ca^{2+}$/CaM and self phosphorylation [18]. When the intracellular $Ca^{2+}$ concentration increases, it can be keenly sensed by the regulatory domain, and thus $Ca^{2+}$/CaM is bound to liberate the catalytic domain and activate CaMKII [19, 20]. When the concentration of $Ca^{2+}$ increases, CaMKII will self phosphorylate at threonine 287 (T287), and destroy the interaction between self inhibition domain and catalytic site [21]. Autophosphorylation occurs between different subunits of CaMKII holoenzyme, and the polymerization structure of CaMKII hol enzyme increases the relative concentration of subunits when autophosphorylation occurs, which makes the built-in kinase cascade possible [18]. T287 autophosphorylation can significantly increase the affinity of CaMkinase to calmodulin [20]. Phosphorylation of substrate subunits at T287 depends on $Ca^{2+}$/CaM binding [22]. Self phosphorylation of T287 can produce CaM capture and maintain the activity of CaMKII [23]. The N-terminal of the binding domain of $Ca^{2+}$/CaM and CaM produce high affinity binding after self phosphorylation [24]. It has also been proved that with the help of CASK, when T305/T306 site is self phosphorylated, the sensitivity of CaM binding domain to CaM will be lost [25, 26].

In addition to autophosphorylation, there are several other post-translational modifications. The nitrosylation of Cys290 site promotes the NO-induced CaMKII to develop and live [27], and increases $Ca^{2+}$ spark frequency after activation [28]. The direct oxidation of M281/282 to CaMKII is mainly through the $H_2O_2$ activation pathway, and the direct oxidation at Met-281/282 site is possible to increase the coordination activities of CaMKII [29]. When the blood glucose rises sharply, O-GlcNAc covalently will modify CaMKII. CaMKII modified by O-GlcNAc at Ser279 can activate CaMKII autonomously, which can produce molecular memory even after calcium concentration decreases [30]. The inactivation of CaMKII also involves some complex mechanisms, one of which is to block the signal to inhibit CaMKII by expressing inhibitor protein. Besides, PEP-19 indi-

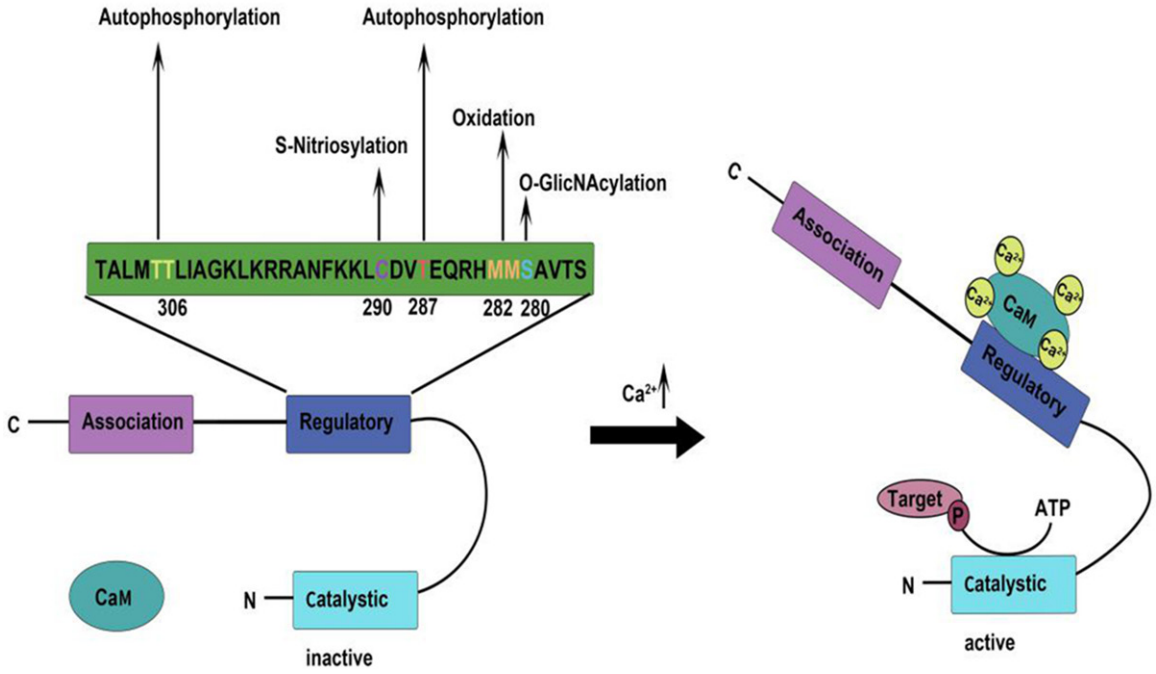


**Figure 3.** Structure, regulatory sites and activation mechanism of CaMKII. CaMKII includes catalytic, regulatory and association domains. Different stimuli can act on the corresponding sites at regulaory domain, directing CaMKII to undergo autophosphorylation or post-translational modification. When $Ca^{2+}$ concentration increases, the $Ca^{2+}$/CaM complex binds to the self-regulatory domain, which releases its inhibition of the catalytic domain, enabling it to phosphorylate the target.

rectly mobilizes intracellular $Ca^{2+}$ flow and antagonizes the activation of CaMKII [31]. PP2A belongs to heterotrimer, and multiple PP2A holoenzymes may contribute to the dephosphorylation of soluble CaMKII (**Figure 3**) [32].

CaMKII can regulate the intracellular calcium content. CaMKII is distributed in the high-density cardiomyocytes near the T-tube, and in the vicinity of mitochondria and nuclei, close to RyR2 channels of LTCC and SR, which can regulate calcium release triggered by calcium in cells [33]. It has been suggested that CaMKII can inhibit the expression of LTCC by activating downstream regulatory elements through combination with the transcription factor Dream, which forms a negative feedback mechanism and inhibits the inflow of $Ca^{2+}$ [34]. $IP_3R2$, the main subtype in cardiomyocytes, will be phosphorylated by CaMKII at specific sites, which will cause the release of nuclear $Ca^{2+}$ mediated by $IP_3R$ and enhance the opening of RyR [35, 36]. CaMKII can phosphorylate PLN, which promotes the reabsorption of SR $Ca^{2+}$ and the relaxation of muscle cells, and counteracts the enhanced release of $Ca^{2+}$ [37]. RyR in sarcoplasmic reticulum is the main target of phosphorylation of CaMKII. CaMKII can phosphorylate RyR2 at ser2815, change the probability of RyR opening, increase the leakage of SR calcium into the cytoplasm, and enhance the spontaneous release of SR $Ca^{2+}$ (**Figure 1**) [38].

CaMKII is also distinguished by its four isomers (α, β, γ, δ), with different expression rates in different types of tissue, α and β are mainly in neurons [39], δ and some γ are mainly located in cardiomyocytes [40]. At present, CaMKIIδ was studied most and fully. CaMKIIδ can induce cardiac hypertrophy after catecholamine stimulation [41]. It mediates histone deacetylase (HDAC) phosphorylation, regulation of transcription, and stress overload [42]. Other studies have shown that the activation of CaMKIIδ can mediate inflammation-driven remodeling [43]. The activated CaMKIIδ triggers inflammatory bodies in cardiomyocytes by NF-κB and ROS signals and induces the production of chemokines, thus promoting macrophage infiltration [44]. δA is mainly expressed in neonatal cardiomyocytes [45], and overexpressed in plasma membrane and T-tube [46]. The nuclear

localization sequence is mainly located in CaMKIIδB, while CaMKIIδC is mainly located in cytoplasm [47].

The Increasing expression of CaMKIIδA can enhance EC coupling [48]. CaMKIIδB plays an anti apoptotic role by binding the necessary transcription factor GATA4 and protein Bcl-2 to the premotor region, which can inhibit cardiomyocyte apoptosis after adriamycin treatment [49]. CaMKIIδC can improve diastolic function [50], and it can significantly enhance the apoptosis of cardiomyocytes induced by β1-adrenergic receptor (β1AR) [51]. It is significant to study the relationship between these splicing variants and different stages of heart development and disease.

## The role of CaMKII in heart disease

### *Myocardial apoptosis and necrosis*

In general physiological state, the uptake of $Ca^{2+}$ by mitochondria plays an important role in metabolic response, which is used to increase the activity of tricarboxylic acid cycle to increase the reduction equivalent, mainly in the form of NADPH, thus promoting oxidative phosphorylation and the production of ATP. If there are too much $Ca^{2+}$ in mitochondria, it will cause apoptosis or programmed necrosis through open MPTP. It is evidenced that activated CaMKII can induce harmful cardiac remodeling and cardiomyocyte apoptosis [52, 53]. Under the continuous stimulation of Angiotensin II (AngII), cardiomyocytes will produce ROS, and through PKA mediating activation of CaMKII, ROS can also increase the activity of CaMKII by oxidation of M281/282 site, aggravate heart injury, and even resulted in the increase of mortality after myocardial infarction [54, 55]. About 10% of CaMKII is located in mitochondria [56]. Compared with WT, there is no significant increase in the expression of CaMKII in Epac1$^{-/-}$ cardiac myocytes, and similar results are obtained by transfection of Epac1$^{\Delta 2\text{-}37}$ into WT cardiac myocytes and immunoprecipitation assay, and these results suggest that MITEpac1 (mitochondrial exchange protein directly activated by cAMP 1) is involved in the mitochondrial localization of CaMKII. Knockout of CaMKIIδ with specific siRNA can prevent IDH2 phosphorylation induced by 8-CPT-AM. Finally, some studies show that MITEpac1-CaMKII pathway inhibits the activity of isocitrate dehydrogenase (IDH2) and reduces ROS detoxification, so as to promote the death of cardiomyocytes in the process of I/R [57].

Inhibition of SR dependent phosphorylation of CaMKII can prevent I/R damage induced by CaMKII, which is closely related to RyR2, PLN, and two substrates of CaMKII at SR level [58]. Activated CaMKIIi is important for the activity of calcium-regulated/mediated [59]. In the model of cardiac arrest, after 30 minutes of cardiac arrest and the same time of extraporal membrane oxygenation (ECMO) reperfusion, the ratio of PCaMKII T287 to total CaMKII in the experimental group is almost twice that of the control group. After cardiac arrest/reperfusion in vivo, the phosphorylation state of RyR2 and PLN, which are the common targets of CaMKII and PKA, is also detected. The results clearly shows that the CaMKII rather than PKA pathway is activated after cardiac arrest, thus maintaining the increase of CICR triggered by the surge of catecholamine and reactive oxygen species [60]. The phosphorylation level of Thr-17-PLN and PThr17-PLN is used as the index of CaMKII activity. It is found that HMGB1 stimulates RAGE to enhance CaMKII activation, and CGP, a β1AR blocker, which could completely eliminate CaMKII induced by HMGB1. Under the influence of hormone and metabolism, RAGE and β1AR can form a protein complex, activate the common downstream signal molecule CaMKII, and result in the death and remodeling of cardiac myocytes [61].

Ox LDL is the key to heart injury. In the presence of ox LDL, the use of KN93 (CaMKII inhibitor) and Mn (III) TABP (ROS scavenger) significantly reduce the apoptosis rate, which suggests that ox LDL stimulates apoptosis through CaMKII and ROS pathways [62]. RIP3 binds directly to CaMKII and makes it phosphorylate at T287 and oxidize at M281/282, which can cause various heart diseases [63]. RIP3 can also bind to MLKL, and the T357 and S358 sites of MLKL are phosphorylated, which can cause cell necrosis [64]. In SNI, chronic pain is induced, and the phosphorylation of RIP3 reduces the expression of TNFα, which in turn inhibits the phosphorylation of MLKL and CaMKII, and significantly reduces the myocardial necrosis of SNI mice induced by myocardial ischemia-reperfusion (MI/R) [65]. It has been proved that CaMKII can regulate the expression of membrane surface and current density of

KATP channels in the heart [66]. In healthy hearts, CaMKII phosphorylates Kir6. 2 pore to form KATP channel subunit, which promotes the endocytosis of KATP channel [67]. Cardiac KATP pathway is closely linked with cellular metabolic signaling pathway, which plays an important role in the coordination of myocardial energy health [68], and can also reduce the injury caused by myocardial ischemia-reperfusion [69]. Under pathophysiological conditions, such as the non ischemic heart failure model induced by ligation of the transverse aorta, CaMKII will be continuously activated, the expression of KATP channel on the membrane surface will be significantly reduced, and the energy consumption of the heart will increase. Therefore, it is helpful for the development of myocardial injury, cell death and heart failure [70]. In vitro kinase test, CgA fragment catestatin (CST) strongly inhibits the activity of CaMKIIδ in a dose-dependent manner. In vivo, CST could alleviate the phosphorylation of RyR2 and PLB in CaMKIIδ dependent. In post infarction HF mice, chromogranin A(CGA)-CST conversion is impaired, and the inhibition of CaMKIIδ is reduced, which will increase the mortality of cardiomyocytes [71]. It is speculated that CaMKII plays a significant regulatory role by preventing uncontrolled necrosis in myocardial injury.

*Myocardial pressure overload and hypertrophy*

Cardiac hypertrophy is an adaptive cardiac response to cardiac stress. Recent evidence strongly suggests that CaMKII is a key regulator of cardiac pathological hypertrophy [72], and its mechanism is being explored by the further studies. The continuous increase of intracellular calcium concentration can activate calcineurin (PP2B), which combines with the activated nuclear factor of activated T cells (NFAT). The rapid transfer of NFAT to the nucleus can induce pathological cardiac hypertrophy [73, 74]. Cellular hypertrophy and fibrosis are important consequences of cardiac remodeling caused by obesity or hyperlipidemia. It is re ported that free fatty acids, such as palmitic acid, can induce cellular hypertrophy [75]. In a diabetic model, impaired intracellular $Ca^{2+}$ metabolism activates CaMKII, promotes ROS production and brings about cardiac remodeling [76]. RT-qPCR analysis shows that 12 hours after palmitate treatment, the proliferation markers (ANP and BNP) and fibrosis markers (TGF-β1, collagen1) significantly increase, while CaMKII inhibitor has a significant inhibitory effect on them. These results indicate that CaMKII plays an important role in mediating hypertrophy and fibrosis of H9c2 cells [77]. Previous studies indicate that overexpression of STAT3 can aggravate pathological cardiac hypertrophy [78]. Some studies suggest that CaMKII can promote the expression of STAT3, and IL-6 can activate the CaMKII-STAT3 pathway in cardiac hypertrophy [79, 80]. A mouse model of cardiac hypertrophy is established by TAC surgery. ANG-II treating mice shows higher heart/body weight and heart weight/length ratio. Echocardiography suggests that the left ventricular wall of ANG-II group is thinner than that of PBS group. But after the silence of CaMKII, EF and FS in the Silence Group are lower than those in the control group, which suggests that the silence of CaMKII can eliminate the myocardial hypertrophy induced by ANGII [81].

A previous report suggests that TRPC is a cation selective internal flow channel, overexpression can cause cardiac hypertrophy, and $Ca^{2+}$ can regulate gene transcription of TRPC through CaMKII and calinerin [82, 83]. It has been evidenced that TRPA1 expression increase in hypertrophic heart, and HC and TCS (TRPA1 blocker) can reduce myocardial hypertrophy in vivo, and can significantly reduce the pressure overload causing autophosphorylation of CaMKII, indicating that the activation of CaMKII may be necessary for TRPA1 mediating myocardial hypertrophy [84]. At the same time, the combination of calcineurin and CaMKII inhibitor can significantly reduce hypertrophic response induced by IGF-IIR [85]. It has been proved that the expression of cardiac hypertrophy gene induced by urotensin II (UII) requires the participation of CaMK kinase [86]. UII is used to stimulate the primary culture of neonatal rat cardiomyocytes for 48 h. The cell size, protein/DNA content and intracellular $Ca^{2+}$ increase, and the phosphorylation of CaMKII and its downstream targets PLN and SERCA2a increase. KN-93 treatment can reverse all of these effects of UII. The results show that UII could induce cardiomyocyte hypertrophy through the upregulation of the signaling pathway of the PLN Thr17-phosphorylation mediated by CaMKII [87].

In the heart samples of HCM patients, the phosphorylation of CaMKII and its downstream targets also increase [88]. In HCM, the increase of $I_{NaL}$ will cause the overload of $Na^+$ in cells, which will damage the NCX mediating $Ca^{2+}$ extrusion, give rise to $Ca^{2+}$ overload, and then enhance the activity of CaMKII through calmodulin binding [89]. The activated CaMKII can move to the nucleus and phosphorylate the hystone deacetylase (HDAC), thus relieving the inhibition of myocyte enhancer factor-2 (MEF2) - controlled genes and promoting cardiac hypertrophy [90]. In addition, recent evidence reveals the key role of mitochondrial dynamics in the pathogenesis of cardiac hypertrophy [91]. Drp1, a mitochondrial mission protein, is used to feed rats with high salt food to promote hypertension. Mdivi1 (an inhibitor of drp1) is used or not used at the same time, and then myocardial hypertrophy is evaluated. High salt fed rats show left ventricular hypertrophy (LVH), cardiomyocyte hypertrophy and myocardial fibrosis, while mdivi1 inhibited them by inhibiting calcineurin and CaMKII [92].

*Arrhythmia*

It is well known that late $I_{Na}$ elevation is closely related to the development of systolic dysfunction and arrhythmia [93]. The disorder of cardiac $Ca^{2+}$ circulation is closely related to the late $I_{Na}$. The results show that the late $I_{Na}$ dependent increase induced by $Ca^{2+}$ leakage of SR is also mediated by CaMKII in mouse cardiomyocytes [94]. The enhanced $I_{Na}$ of mouse cardiomyocytes results in the increase of $Ca^{2+}$ spark frequency and $Ca^{2+}$ transient amplitude. Inhibition of CaMKII or PKA attenuates the late $I_{Na}$ dependent induction of $Ca^{2+}$ leakage of SR. This study shows that the disturbance of phosphatase/kinase balance brings about the destruction of $Ca^{2+}$ circulation through CaMKII and PKA dependent pathways [95]. In HCM samples, CaMKII increases the $Na^+$ channel phosphorylation level by 2.5 times, which may lead to the increase of $I_{NaL}$ in HCM cardiomyocytes, thus resulting in AP prolongation and $Na^+$ overload [96]. Compared with normal myocardium, the rate of $I_{CAL}$ inactivation observed in HCM cardiomyocytes is slower [97]. CaMKII increases phosphorylation of β-subunit of L-type $Ca^{2+}$ channel, thus delaying repolarization [98].

The increase of ROS will cause the oxidation of RyR2, which will result in SR $Ca^{2+}$ leak and promote arrhythmia in mice [99, 100]. ROS can enhance the response of CaMKII to the increase of $Ca^{2+}$, and change the excitation contraction coupling of the heart [101]. Fluorescein staining shows that the increase of ROS production in MDX mouse ventricular myocytes is consistent with the increase of ox CaMKII in Western blotting. The results showed that inhibition of ROS or ox CaMKII can protect $Ca^{2+}$ in arrhythmogenic cells and prevent ventricular arrhythmia in DMD mice [102]. There are many factors that cause arrhythmia. Excessive drinking can easily induce arrhythmia [103]. The activation of JNK is helpful for liver toxicity and other organ damage induced by alcohol [104]. CaMKII of WT mice labeled by human influenza hemagglutinin is overexpressed in HEK293 cells after 24 hours of alcohol exposure. It is found that drinking alcohol significantly increases the activity of CaMKII, but when JNK2 inhibitors appeare, this will not happen. The pure active human JNK2 protein is incubated with the anti ha antibody immunoprecipitated CaMKII of WT mice or mutant CaMKIIT286A protein. It is found that activated JNK2 significantly increase the phosphorylation of HA labeled CaMKII protein. The results show that JNK2 is activated by alcohol, and then JNK2 phosphorylates CaMKII protein and enhances the activity of CaMKII in cells, which results in atrial arrhythmia [105].

Catecholaminergic pleomorphic ventricular tachycardia (CPVT) is an arrhythmia caused by RyR2 gene mutation [106]. CaMKII phosphorylated RYR2-S2814 can promote $Ca^{2+}$ leakage of RyR2 in diastolic period and promote arrhythmia [107]. A human engineering tissue model based on CPVT is constructed in a laboratory. In the model, when CPVT tissue is stimulated by rapid pacing and catecholamine, it is easy to have reversible rhythm. The $Ca^{2+}$ spark and depolarization rate in CPVT related tissues are significantly reduced by cell permeable AIP. RYR2-S2814 phosphorylation by CaMKII is found to be necessary for the cause arrhythmia potential in CPVT tissue. These studies indicate that CaMKII is a key signal molecule in the pathogenesis of CPVT [108]. Fibroblast growth factor (FGF)-23 can regulate the steady state of phosphorus and calcium [109]. It can promote the expression of PKC, increase $I_{NaL}$, bring about abnormal oxidation of CaMKII and calcium treatment, and induce atrial arrhythmia

[110, 111]. The central role of CaMKII in arrhythmia pathology makes it an attractive therapeutic target.

### Treatment methods for CaMKII

CaMKII is a downstream target with a variety of agonists and has been regarded as a conventional target for the treatment of heart disease. KN-93, a common CaMKII inhibitor, can affect many ion channels, including LTCC [112]. One study finds that the use of CaMKII inhibitor KN-93 in the experimental substance reduces the activity of CaMKII in AF with noradrenaline [113]. SMP-114 is an ATP competitive inhibitor of CaMKII, which has a significant inhibitory effect on VEGF production of macrophages in rheumatoid synovium fluid and can be used in the treatment of arthritis [114-116]. It has been proved that 10 mol/L SMP-114 can greatly inhibit the activity of CaMKII [117]. The reduction of VEGF production by smp-114 is due to its inhibition of CaMKII, similar with KN-93 [118]. It is found that SMP-114 strongly reduces the correlation of SR$Ca^{2+}$ leak and arrhythmia in cardiac myocytes, and improves post-rest potentiation of cardiomyocyte $Ca^{2+}$ transients and contractility. In addition, it can inhibit the late sodium current [119]. AS105 is also a high affinity ATP competitive CaMKII inhibitor [120]. Cardiomyocytes of heart failure mice overexpressing CaMKIIδC are isolated from the donor, and AS105 effectively reduced the leakage of SR$Ca^{2+}$ in diastolic phase. In addition, the ability of SR to accumulate $Ca^{2+}$ is enhanced in the presence of SR $Ca^{2+}$ [121].

All trans retinoic acid (RA) can alleviate the transition from adaptive cardiac hypertrophy to heart failure, and also can alleviate the ventricular remodeling after myocardial infarction [122, 123]. It has been shown that the absence of Cellular tretinoin binding protein 1 (Crabp1) leads to the over activation of CaMKII, which suggests that Crabp1 has a protective effect on the reduction of inadaptable cardiac remodeling [124]. Under the induction of isoproterenol (ISO), mice with Crabp1 knockout experiences more severe heart failure and remodeling. RA is used to pretreat induced mice. It is found that the ejection fraction recovered in the wild-type mice, but not in the CKO mice. Cell culture experiments confirms that RA inhibits the phosphorylation of CaMKII, in which crabp1 participate. The molecular data reveals that RA selectively enhances the interaction between Crabp1 and the regulatory domains of CaMKII. These data suggests that RA plays a protective role in β-adrenergic stimulation of cardiac remodeling, mainly due to its inhibition of CaMKII activity [125].

Researches show that Chicago Sky Blue 6B (CSB) has many biological targets, including VGLUT [126], and can reduce the conditional reward effect caused by methamphetamine (METH) and relieve pain [127, 128]. The proliferation of p8 cardiomyocytes is successfully induced by CSB, a VGLUT inhibitor. After 5 days of MI, CSB prevents the increase of phosphorylated CaMKII under the premise of keeping the total level of CaMKII. CSB treatment reduces the scar size, maintains the cardiac ejection fraction (EF) and fractional shortening (FS), and inhibition of CaMKII weakens the protective effect of CSB. The experimental data shows that the CSB in adult mice promotes the cardiac repair and improves the contractility of cardiomyocytes by inhibiting the CaMKII signal pathway [129]. Phenolic compounds have many medicinal and health care functions [130], and they can be anti-inflammatory, antioxidation, affect the metabolism of sugar and lipid, and prevent cardiovascular disease and its complications [131-134]. Three month old Wistar rats are selected and treated with phenol compounds (PC) for 14 months. Compared with the untreated control group, the PC group shows a decrease in ejection fraction, left ventricular hypertrophy, and AR ventricular diameter and posterior wall thickness. The analysis of cardiac tissue protein shows that PC could weaken many hypertrophic pathways, including calcineurin/activated T-cell nuclear factor (NFATc3) and CaMKII [135].

Chinese herbal medicine has a unique curative effect in the treatment of chronic and complex diseases. Ginseng can improve the general health condition and has been widely used in the treatment of cardiovascular diseases [136], which combined with other drugs can achieve better therapeutic effect [137]. The results show that ginseng combined with Fuzi Beimu can maintain the lung function improvement caused by FBC (Fuzi and Beimucompatibility), inhibit the cardiotoxicity, inhibit the activation of βAR-Gs-PKA/CaMKII and Epac1/ERK1/2 axis through the crosstalk of PKA and Epac signal pathways, and protect the cardiac function and

inhibit the myocardial apoptosis [138]. In addition, the YiQiFuMai powder injection (YQFM) is a traditional Chinese medicine prescription which has been used in the treatment of cardiovascular diseases. The research shows that YQFM can improve the mitochondrial function of heart failure (HF) by inhibiting the production of ROS and the CaMKII signal pathway, and provide another way for the clinical treatment of HF [139].

## Conclusions

Under normal conditions, CaMKII can stimulate energy production, glucose uptake, sarcolemma ion flux, SR $Ca^{2+}$ release/reuptake and myocyte contraction/relaxation, so as to promote cardiac adaptability. However, in the pathological state, various therapeutic factors will cause the continuous and chronic activation of CaMKII, which will cause mitochondrial dysfunction, remodeling of ion channels, intracellular $Ca^{2+}$ circulation disorder, inflammation and myocardial contraction dysfunction, and promote the progress of myocardial necrosis, hypertrophy, arrhythmia and other diseases. Therefore, inhibition of the activation of CaMKII is likely to have a good effect on inhibiting the progress of heart disease. This paper has introduced several new drugs targeting at CaMKII, and in the future more studies should be made to develop specific drugs targeting at the heart subtype of CaMKII, and focus on the clinical effect and possible side effects of the combination of new drugs for CaMKII and traditional drugs for heart disease.

## Disclosure of conflict of interest

None.

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