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REVIEW

CaMK II in Cardiovascular Diseases, Especially CaMK II-δ: Friends or Enemies

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Abstract: Cardiovascular diseases (CVDs) tend to affect the young population and are associated with a significant economic burden and psychological distress to the society and families. The physiological and pathological processes underlying CVDs are complex. Ca^{2+}/calmodulin-dependent kinase II (CaMK II), a protein kinase, has multiple biological functions. It participates in multiple pathological processes and plays a central role in the development of CVDs. Based on this, this paper analyzes the structural characteristics and distribution of CaMK II, the mechanism of action of CaMK II, and the relationship between CaMK II and CVDs, including ion channels, ischemia-reperfusion injury, arrhythmias, myocardial hypertrophy, cardiotoxicity, hypertension, and dilated cardiomyopathy. Given the different regulatory mechanisms of different isoforms of CaMK II, the clinical use of specific targeted inhibitors or novel compounds should be evaluated in future research to provide new directions.

Keywords: CaMK II, cardiovascular diseases, ischemia-reperfusion injury, arrhythmias, myocardial hypertrophy

Introduction

Cardiovascular diseases (CVDs) are chronic diseases caused by genetic and environmental factors. This entity encompasses coronary heart disease, cerebrovascular disease, rheumatic heart disease, heart failure, and cardiomyopathy. According to the data from NHANES 2017–2020, the prevalence of CVDs in adults aged >20 years was 48.6%, and age was positively correlated with CVD prevalence.[1] According to data from the World Health Organization, 17.9 million people die of CVDs annually. More than four-fifths of CVD-related deaths occur due to heart attacks and strokes, whereas one-third of deaths affect individuals aged <9 years. In 2019, 38% of non-infectious premature deaths were caused by CVDs.[2] CVDs tend to occur in the young population, which may lead to death, disability, substantial economic burden, and psychological distress for patients and their families.

The physiological and pathological processes of CVDs are complex, and multiple diseases are associated with comorbidities because of similar pathogenesis. Protein kinases are key regulators of multiple signaling molecules. They link upstream pathological stress signals with downstream regulatory procedures, coordinate the structure and function of cardiomyocytes, and regulate contractility, metabolism, transcription, and cell death.[3] Ca^{2+}/calmodulin-dependent kinase II (CaMK II) is a multifunctional serine/threonine protein kinase, which regulates a variety of biological functions, including Ca^{2+} stability, cell cycle, membrane excitability, excitation-contraction coupling, gene transcription, and apoptosis. It plays a central role in the pathogenesis of ischemia-reperfusion (I/R) injury, ventricular remodeling, hypertension, dilated cardiomyopathy (DCM), and other heart diseases. With increasing research, the role and regulatory mechanism of different CaMK II subtypes in various CVD models have gradually become a research hotspot. Different subtypes of protein kinases are involved in disease development.[4,5] Therefore, targeted regulation of highly specific CaMK II subtypes may be a new direction for disease research. Based on this, the present article reviews

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the structure of CaMK II and the mechanism of its role in CVDs to further explore the pathogenesis of CVDs and provide a reference for future drug research and development.

Structure, Distribution and Activation of CaMK II

The primary structure of CaMK II contains an N-terminal kinase domain, a catalytic domain, a middle regulatory region, and a tail C-terminal association domain, which can bind ATP and substrates to provide catalytically activated proteins. In the resting state, the self-inhibition sequence interacts with the catalytic domain, which competes with peptide substrates rather than the ATP. The CaMK II holoenzyme is formed by 12 subunits through its C-terminal association domain, and the N-terminal kinase domain radiates outward. The holoenzyme complex enables CaMK II to target a variety of cell substrates with diverse functions. CaMK II has multiple subunits. Mammalian CaMK II is encoded by four genes: CaMK II-α, CaMK II-β, CaMK II-γ, and CaMK II-δ, which have molecular weights of 50, 60, 59, and 60 kDa, respectively. Each gene is alternatively spliced to produce a variety of independent subtypes, and more than 40 subtypes have been reported so far, making its function more diverse.[6–8]

The four subunits are highly homologous in sequence, but their distribution is different. The four subtypes are expressed in the brain. CaMK II-α and CaMK II-β are mainly distributed in the central nervous system, with the highest expression levels in the neocortex and hippocampal formation. CaMK II-β and CaMK II-δ are mainly distributed in the cerebellum. CaMK II-γ and CaMK II-δ are distributed throughout the body, and CaMK II-δ is the main phenotype in the heart. CaMK II-δ is divided into δB and δC subtypes. The δB subtype is mainly distributed in the cytoplasm and participates in excitatory contraction coupling processes, such as voltage-gated ion channels and Ca^{2+} dynamic regulation. The δC subtype contains nuclear localization sequences and is mainly involved in excitatory transcriptional coupling. The two splice variants are not completely exclusive in terms of their nucleocytoplasmic distribution. The relative abundance of different subtypes is conducive to nucleocytoplasmic localization.[6,9] The domain structure of CaMK II is shown in Figure 1.

The premise of the activation of CaMK II is the complex formed by Ca^{2+}/CaM. The degree of activation is related to the structure and Ca^{2+} concentration. The activation methods can be divided into classical Ca^{2+}/CaM-dependent activation and non-Ca^{2+}/CaM-dependent activation.[10] In the Ca^{2+}/CaM-dependent activation mechanism, the intracellular Ca^{2+} concentration increases, and the Ca^{2+}/CaM complex binds to the carboxyl terminus of CaMK II to activate CaMK II. In the Ca^{2+}/CaM-independent activation pathway, once CaMK II is activated by Ca^{2+}, even after Ca^{2+}/CaM dissociation, regulating the T286 site, the enzyme activity of the substrate still exists, which is called " CaMK II memory function". The autophosphorylation of T286 can significantly increase the affinity of kinase to Ca^{2+}/CaM, which is called "CaM capture effect".[11]

Mechanism of Involvement of CaMK II in CVDs

CaMK II is regulated by the Ca^{2+}/calmodulin (CaM) complex, reactive oxygen species (ROS), and exchange protein, which is directly activated by cAMP. The elevation of Ca^{2+} in cardiomyocytes and vascular smooth muscle cells is perceived by CaM. As an intermediate target of the secondary messenger Ca^{2+}, CaM ensures the activation of downstream CaMK.[12] CaMK II is an important mediator of neurohumoral stimulation in the heart. Its activity is elevated in the early stages of cardiac disease, while its expression is significantly upregulated in patients with advanced or end-stage heart failure.[13] CaMK II upregulation has effects on signal transduction, cardiac remodeling, and arrhythmias, which can

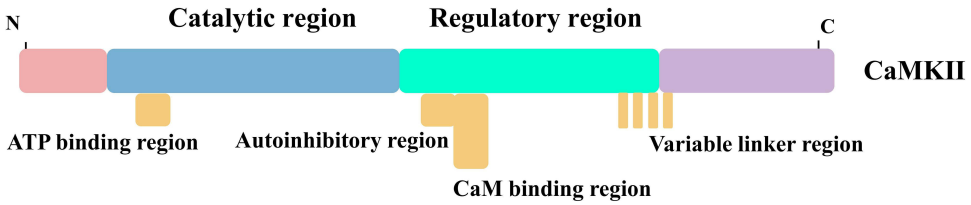

Figure 1 Domain structures of CaMK II. CaMK II, Ca^{2+}/calmodulin-dependent kinase II. The primary structure of CaMK II contains an N-terminal kinase domain, a catalytic domain, a middle regulatory region, and a tail C-terminal association domain.

lead to adverse cardiovascular events. Therefore, specific targeting of CaMK II is expected to be an effective treatment strategy for patients with heart disease or heart failure.[14]

CaMK II and Ion Channels

CaMK II is an important kinase that regulates Na^+, K^+, and Ca^{2+} ion channel activities and calcium transport in cardiomyocytes.

Sodium Channel

NaV1.5 is the main sodium channel in the myocardium. The inward flow of late sodium current (INa L) in cardiomyocytes is the basis of cell membrane excitation in atrial and ventricular myocytes and is an important trigger for arrhythmias in CVDs. CaMK II can phosphorylate NaV1.5 channels, increase INa L, cause sodium overload, prolong the action potential duration (APD), and produce early afterdepolarization (EAD).[15] Activation of the Na^+-Ca^{2+} exchanger (NCX) causes calcium overload and induces arrhythmias. INa L can also increase mitochondrial ROS production and CaMK II oxidation.[16,17] Macrophage migration inhibitory factor is activated by CaMK II signal transduction of ROS, resulting in Na^+ and Ca^{2+} dysregulation, leading to the occurrence of atrial fibrillation (AF) during inflammation.

Studies have shown that the main enzyme sources of ROS in the cardiovascular system are NADPH oxidase (NOX), uncoupled endothelial nitric oxide synthase (eNOS; also known as NOS3), mitochondria and xanthine oxidase (XO). NOX is different from other enzyme sources because its main function is to produce ROS. Low levels of ROS produced by some NOX isomers (such as NOX2) are associated with physiological processes such as cell proliferation, migration, differentiation, and cytoskeleton organization. NOX-derived ROS, such as superoxide and hydrogen peroxide (H_2O_2), can trigger ROS production by activating other enzyme systems. For example, ROS produced by NOX can induce the oxidative inactivation of tetrahydrobiopterin (H4B), which is an important cofactor of eNOS, leading to eNOS uncoupling and the production of superoxide rather than nitric oxide (NO). In addition, ROS can stimulate the conversion of xanthine dehydrogenase (XDH) to XO through the oxidation of thiol residues. ROS produced by NOX can also lead to mitochondrial DNA damage, oxidation of membrane permeability transition pore components, and opening of redox-sensitive mitochondrial ATP-sensitive K^+ channels (mitoKATP), all of which contribute to mitochondrial uncoupling and ROS production.[18] Many studies have shown that NO and ROS can be produced by different enzymes, or by the same enzyme through alternating reduction and oxidation processes. The latter oxidoreductase system includes NO synthase, molybdate and hemoglobin, which can form superoxide through the reduction of molecular oxygen or NO through the reduction of inorganic nitrite. Enzymatic coupling, changes in oxygen tension, and the concentration of coenzymes and reducing agents can regulate the NO/ROS produced by these oxidoreductases and determine the redox balance in health and disease.[19] Therefore, CaMK II inhibition provides a feasible target for the treatment of AF.[20]

Selective inhibitors, such as ranolazine, eleclazine, and KN-93, can inhibit INa L and reduce Ca^{2+} overload. Previous studies have found that ranolazine can improve Na^+ overload and restore Na^+-induced Ca^{2+} overload in an NCX-dependent manner in a mouse model of chronic pressure overload induced by aortic arch constriction. Ranolazine inhibits Ca^{2+}-dependent CaM/CaMK II/myocyte enhancer factor-2 and CaM/CaMK II/calmodulin/nuclear factor. In addition, inhibition of INa L and NCX resulted in the alleviation of endoplasmic reticulum stress-induced cardiomyocyte apoptosis, thereby improving cardiac hypertrophy and heart failure.[21] The synergistic mechanisms of ranolazine, elorazine, and KN-93 can improve isoproterenol (ISO)-induced AF, attenuate the phosphorylation of NaV1.5 and CaMK II, and reduce INa L ($P < 0.05$), thereby exerting anti-arrhythmic effects.[22] The key components of the vicious cycle of arrhythmias induced by targeting Na^+-Ca^{2+}-CaMK II-ROS-Ina L exhibit in-target and cross-target effects.[23] It is known that abnormal ryanodine receptor 2 (RyR2)-mediated sarcoplasmic reticulum Ca^{2+} release and NCX activity may lead to premature ventricular contractions.[24] Selective activation of protein phosphatase 1 (PP1) can significantly reduce INa L-induced sarcoplasmic reticulum (SR) Ca^{2+} leakage, without affecting the Ca^{2+} release during systole. Therefore, PP1 activation on RyR2 provides a new target for treatment.[17] Figure 2 shows the mechanism of CAMK II-mediated arrhythmias by acting on sodium channel.

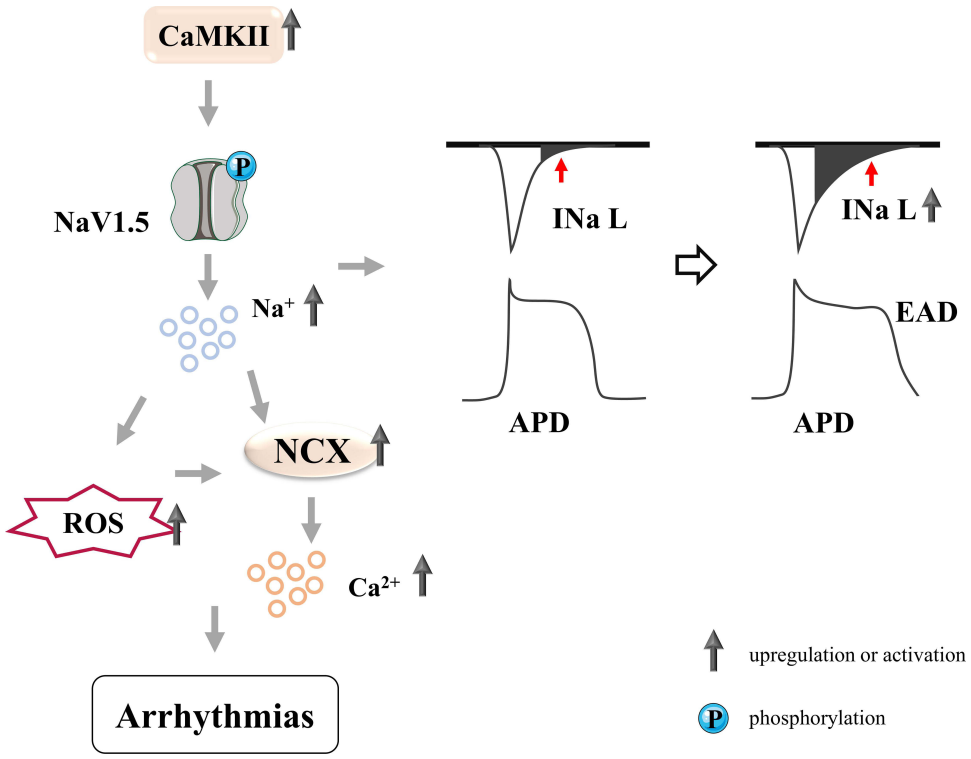

Figure 2 CAMK II-mediated arrhythmias by acting on sodium channel. CaMK II can phosphorylate NaV1.5 channels, increase INa L, cause sodium overload, prolong the APD, and produce EAD. Activation of the NCX causes calcium overload and induces arrhythmias.
Abbreviations: CaMK II, Ca^{2+}/calmodulin-dependent kinase II; INa L, late sodium current; APD, action potential duration; EAD, early afterdepolarization; NCX, Na^{+}-Ca^{2+} exchanger; ROS, reactive oxygen species.

Potassium Channel

There are multiple potassium channels in the myocardium, and the effect of CaMK II on the potassium current is complex. Functional ATP-sensitive potassium [K(ATP)] channels are essential for cardiac protection during ischemia. L5 is a highly electronegative and atherogenic abnormal form of LDL. Patch clamp analysis showed that L5 reduced the Kir6.2 expression by more than 50%, reduced the K(ATP) current density induced by the L5 K(ATP) opener, and increased the CaMK II activity, CaMK II-δ phosphorylation, and NOX2/gp91(phox) expression. The addition of the CaMK II inhibitor KN-93 can inhibit L5-induced apoptosis.[25] The occurrence of arrhythmias in myocardial infarction is related to action potential prolongation, a decrease in inward rectifier potassium channel [I(K1), Kir], and excessive CaMK II activation.

Kir2.1 is the dominant subunit of I (K1). The inward rectifier K^{+} current is dominated by Kir2.1, which may be targeted by the CaMK II-dependent intracellular signaling system.[26] After myocardial infarction, the Kir2.1 expression was significantly downregulated, and the p-CaMK II expression was upregulated. The use of I (K1) agonists can improve Kir2.1 and p-CaMK II; reduce the occurrence of atrioventricular block, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation; and control fatal arrhythmias.[27] In cardiomyocytes, CaMK II inhibition increased fast repolarization potassium current (Ito, f) and inward rectifier potassium current (IK1). A study using a model of combined inhibition of CaMK II and IK1 found that combined inhibition eliminated the IK1 upregulation in CaMK II–inhibited mice and had no effect on the cardiac structure or function or arrhythmias.[28] CaMK II also regulates KCNQ1. Under β-adrenergic receptor stimulation, the phosphorylation of the carboxyl-terminal site of KCNQ1 was enhanced, and the S484 peptide showed the strongest CaMK II-δ phosphorylation. CaMK II regulates the S484 site of KCNQ1 during continuous β-adrenergic receptor stimulation, thereby inhibiting I(Ks), which was involved in the arrhythmogenic effect of heart failure.[29]

In addition, vascular endothelial growth factor (VEGF) has been found to upregulate Ca^{2+} influx by increasing the nonselective cation current [I (NSC)] of transient receptor potential (TRP) channels and the potassium current of medium-conductance calcium-activated potassium channels [K(Ca)3.1]. VEGF increased the expression of phosphorylated ERK, fibroblast migration, myofibroblast differentiation, and production of type I procollagen and type III procollagen. Ethylene glycol tetraacetic acid can attenuate the CaMK II upregulation caused by VEGF, and KN-93 reduces the increased production of type I procollagen and type II procollagen caused by VEGF, which provides a new strategy for arrhythmias and myocardial fibrosis.[30]

Calcium Channel

CaMK II can activate the expression of the L-type calcium channel (CaV1.2) in the heart. Oxidative stress stimulation can increase Ca^{2+} influx, trigger SR Ca^{2+} release through calcium channels, and increase intracellular Ca^{2+} and CaMK II activity, which is called facilitation. It can induce mitochondrial calcium overload and provide positive feedback to further increase CaMK II activity.[31] Under pathological conditions, the CaMK II activity increases, thereby inducing EAD and causing arrhythmias. In addition, mitochondrial calcium uniporter and CaMK II are therapeutic targets for arrhythmias caused by metabolic abnormalities.[32]

The CaV1.2/CaM/CaMK II signaling pathway plays an important role in maintaining intracellular Ca^{2+} balance. In the rat model of myocardial ischemia, there is a dynamic change in CaV1.2/CaM/CaMK II signal at different time points. Targeted intervention at different periods can improve the curative effect.[33] Proline hydroxylase domain containing enzymes act as a cellular oxygen sensor, which can activate CaMK II through the transient receptor potential ankyrin 1 ion channel. RyR2 induces calcium release from the sarcoplasmic reticulum, activates AMP-activated protein kinase, and initiates the protective effect against myocardial hypoxia.[34] ISO administration induced cardiac hypertrophy in rats. Studies have shown that after the withdrawal of ISO, hypertrophy does not improve. Furthermore, it is accompanied by a continuous increase in p-CaMK II levels and increased expression of histone deacetylase 4 (HDAC4) and CaV1.2 channels. On the contrary, CaMK II inhibitors can improve these changes. The use of inhibitors to interfere with CaMK II and its complex with CaV1.2 can improve myocardial hypertrophy and reverse ventricular remodeling.[35] KN-93 can reduce the L-type calcium current density, increase the half-activation voltage, prolong the recovery time constant, and effectively improve ISO-induced calcium homeostasis imbalance in cardiomyocytes.[36] Therefore, KN-93 plays a vital role in regulating ISO-induced calcium homeostasis.

Calcium channel blockers are effective drugs that improve cardiomyocyte hypertrophy. Lercanidipine can also improve cardiomyocyte hypertrophy by regulating calcineurin-activated T cell nuclear factor 3 (NFAT3) and CaMK II - HDAC4 signaling pathways.[37] Nifedipine can affect the calcium concentration and apoptosis of hypertrophic cardiomyocytes through the CaMK II-SERCA2a signaling pathway, thereby exerting an anti-cardiomyocyte hypertrophy effect.[38] Figure 3 shows the mechanism of CAMK II-mediated arrhythmias by acting on calcium channel.

CaMK II and I/R Injury

CaMK II is a substrate of substrate receptor-interacting protein 3 (RIP3), which is activated by phosphorylation, oxidation, or both. Excessive Ca^{2+} influx into mitochondria during mitochondrial reactivation during I/R triggers mitochondrial permeability transition pore (mPTP) opening and programmed myocardial necroptosis, which can mediate myocardial injury and heart failure induced by ischemia and oxidative stress.[39,40] Submicron particles composed of poly (lactic-co-glycolic acid) and surface-modified particles loaded with CaMK II inhibitors can reduce ROS, reduce mitochondrial membrane potential, and improve I/R injury.[40] At the beginning of I/R, the phosphorylation of S2814, the main CaMK II site on cardiac RyR2, was significantly increased. In I/R, CaMK II-dependent cardiac RyR phosphorylation regulates cell death.[41] Receptor-interacting protein kinase 3 (RIPK3) is one of the indicators of necrosis, which mediates myocardial necrosis in I/R injury and heart failure by activating CaMK II. RIPK3 downregulation can improve the splicing disorder of CaMK II-δ, inhibit CaMK II activation, reduce oxidative stress, and improve cardiomyocyte necrosis.[42]

CaMK II-δ is also the main phenotype in the heart. Myocardial death and dysfunction after I/R require CaMK II-δ oxidation. Ox-CaMK II-δ and ATP-sensitive potassium channels promote ROS and aggravate I/R injury.[43] CaMK II-δ is

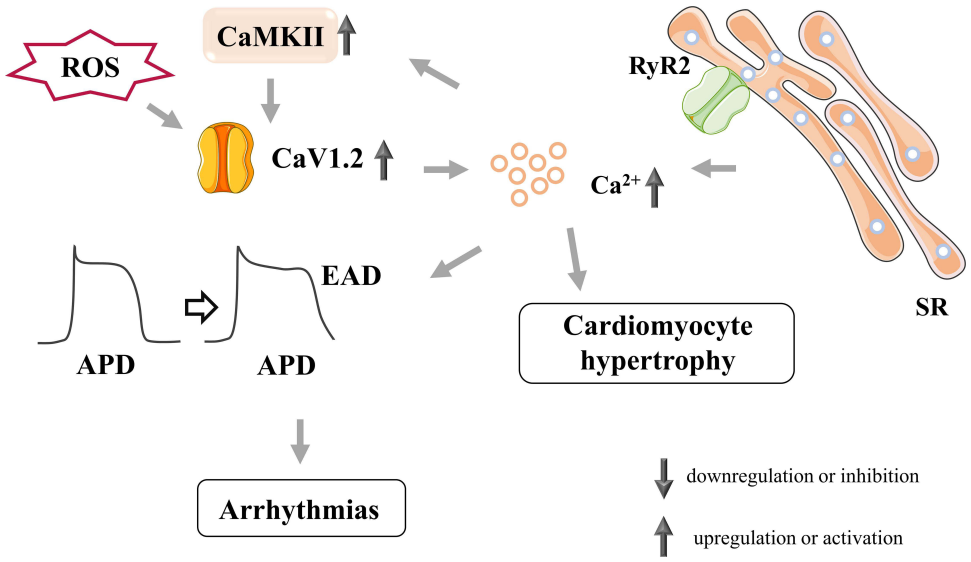

Figure 3 CAMK II-mediated arrhythmias by acting on calcium channel. CaMK II can activate the expression of the CaV1.2 in the heart. ROS can increase Ca^{2+} influx, trigger SR Ca^{2+} release through calcium channels, and increase intracellular Ca^{2+} and CaMK II activity. It can increase CaMK II activity, thereby inducing EAD and causing arrhythmias.

Abbreviations: CaMK II, Ca^{2+}/calmodulin-dependent kinase II; APD, action potential duration; EAD, early afterdepolarization; ROS, reactive oxygen species; SR, sarcoplasmic reticulum; RyR2, ryanodine receptor 2.

a direct downstream target of microRNA-145, which improves apoptosis by inhibiting ROS-induced Ca^{2+} overload in cardiomyocytes via targeting CaMK II-δ.[44] CaMK II inhibition can alleviate the mitochondrial oxidative stress, reduce the phosphorylation of Beclin-1 at the Ser90 site, improve autophagy dysfunction, and reduce myocardial I/R injury.[45,46] CaMK II-δ9 is the most abundant splicing variant of CaMK II-δ in the heart. Studies have shown that CaMK II-δ9 inhibition can improve cardiac inflammation and inhibit I/R-induced NF-κB activation. The CaMK II-δ9-IKK/IkB-NF-κB signaling pathway can regulate cardiomyocyte inflammation, thereby improving ventricular remodeling and heart failure.[47] Different CaMK II-δ subtypes play different roles in I/R. CaMK II-δC aggravates myocardial injury after I/R, whereas CaMK II-δB has a protective effect on the myocardium, and its differential effect can be achieved through its action on NF-κB or TNF-α.[48]

Hesperadin has been found to bind directly to CaMK II-δ and block its activation in an ATP-competitive manner. It can be used as a specific small molecule inhibitor of CaMK II-δ to exert I/R protection.[49] Inhibitor 1 of protein phosphatase 1 (I1PP1) can regulate CaMK II. I1PP1 overexpression can improve cardiac pathological structure, reduce myocardial infarction area, inhibit CaMK II oxidation, and increase CaMK II-δA and the number of mitochondria.[50] In addition, some compounds have similar effects. Through the CaMK II pathway, rhynchophylline reduces LDH and ROS levels, regulates mitochondrial dynamics, and ameliorates I/R injury.[51] S-limonene may play a protective role by acting on the CaMK II and regulating Ca^{2+} pathways to reduce oxidative stress.[52] Sulforaphane protects the myocardium from I/R injury by regulating CaMK II-δ and CaMK II inhibitors.[53] Tilianin interacted with CaMK II-δ with high binding performance to inhibit p-CaMK II and ox-CaMK II expression. Tilianin may play a protective role by inhibiting apoptosis and the JNK/NF-κB inflammatory pathways.[54] The mechanism of CaMK II in I/R injury are shown in Figure 4.

CaMK II and Arrhythmias

CaMK II is an important mechanism of arrhythmia induced by myocardial electrical signal disorder caused by the imbalance of Na^+, K^+, Ca^{2+}, and other ion channels. With the development of patch clamp technology, the anti-arrhythmia mechanism of multi-ion channel blockade has been explored in detail. Cardiac autonomic nerve disorder, oxidative stress, inflammatory response, and ventricular remodeling are also important mechanisms of arrhythmia, and such non-ionic channel regulation is equally important. CaMK II can lead to arrhythmias through multi-ion channel blockade and non-ion channel-mediated mechanisms.

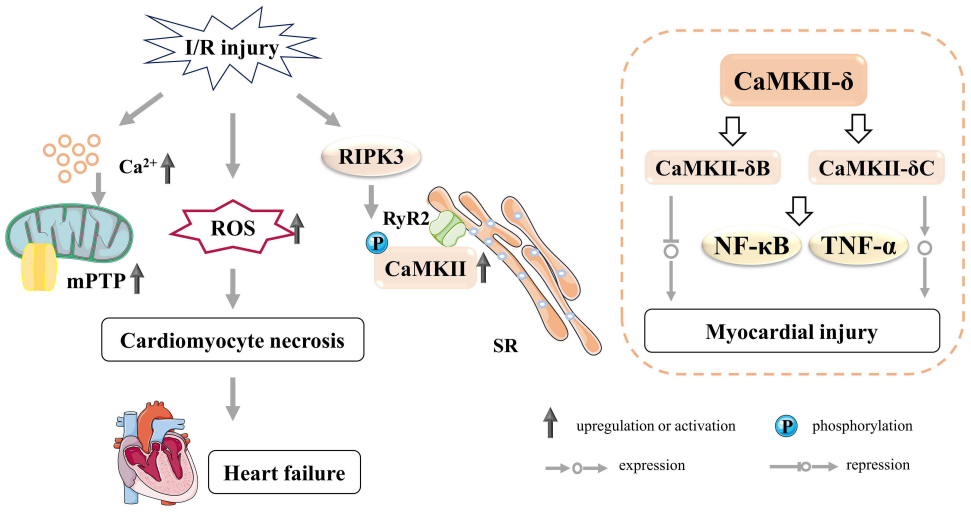

Figure 4 The mechanism of CaMK II in I/R injury. I/R injury, Ca^{2+} influx, trigger the opening of mPTP, and promote oxidative stress injury. RIPK3 leads to cardiomyocyte necrosis by activating CaMKII. CaMKII-δC aggravates myocardial injury after I/R, whereas CaMK II-δB has a protective effect on the myocardium, and its differential effect can be achieved through its action on NF-κB or TNF-α.

Abbreviations: CaMK II, Ca^{2+}/calmodulin-dependent kinase II; I/R, ischemia-reperfusion; RIPK3, receptor-interacting protein kinase 3; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; SR, sarcoplasmic reticulum; RyR2, ryanodine receptor 2.

CaMK II enhances small-conductance Ca^{2+}-activated K^+ currents in AF patients.[55] CaMK II also phosphorylates Nav1.5 and further increases INa L, whereas CaMK II inhibitors synergistically attenuate INa L-induced arrhythmias and CaMK II activation.[22,56] INa L has a significant effect on atrial Ca^{2+} homeostasis by activating CaMK II and protein kinase A (PKA). Inhibition of INa L, CaMK II, and PKA can reduce SR-Ca^{2+} leakage and regulate the cAMP/PKA pathway.[57] C-Jun N-terminal kinase isoform 2, a newly identified SERCA2 enhancer, plays a dual role in SR Ca^{2+} dynamics, which can maintain normal Ca^{2+} transient and aggravate atrial arrhythmias.[58]

In patients with AF, the inflammatory cytokine-macrophage migration inhibitory factor is highly expressed, which can activate the CaMK II signaling pathway through ROS. The resulting imbalance of Na^+ and Ca^{2+} promotes AF occurrence.[20] Studies have suggested that NLRP3/CaMK II is a possible mechanism of postoperative AF. It has been found that postoperative CaMK II protein expression, RyR2 single channel opening, NLRP3-inflammasome system activation, and inflammatory mediators are involved in postoperative AF. Molecular substrate polarization is sensitive and prone to postoperative AF.[59] Anti-β1-adrenergic receptor autoantibodies (β1-AAb) are closely related to the occurrence of cardiomyopathy and arrhythmias; can prolong the action potential duration, Ca^{2+} transient duration, and conduction heterogeneity; and can aggravate electrical instability and fibrosis. The underlying mechanism is related to the activation of myocardial cells and fibroblasts by CaMK II /RyR2. Inhibition of β1-AAb can interfere with autoimmune AF.[60] Intestinal microflora disorders are also related to AF. Phenylacetylglutamine, a derivative metabolite, can increase apoptosis and ROS, which may be involved in AF development through oxidative stress response and apoptosis.[61]

CaMK II and Cardiac Hypertrophy

Cardiac hypertrophy often occurs in progressive heart disease, which is related to calcium overload, oxidative stress, autophagy, and inflammatory response. In phenylephrine (PE) -induced hypertrophic cardiomyocytes, the expression of CaMK II-δ is enhanced, which activates the calcium pool-operated Ca^{2+} influx, whereas the Ca^{2+} current through the activated Ca^{2+} channel is increased due to Ca^{2+} release, thereby inducing cardiomyocyte hypertrophy.[62] The decrease in Kv4.3 protein is one of the characteristics of cardiac hypertrophy. Kv4.3 expression can reduce CaMK II autophosphorylation and inhibit norepinephrine-induced cardiac hypertrophy.[63] In an in vitro Ang II–induced cardiomyocyte hypertrophy model, the Ca^{2+} concentration is increased, and transient receptor potential vanilloid receptor 3 (TRPV3) is activated, which promotes the expression of calcineurin and pCaMK II, as well as enhances the nuclear translocation of

calcineurin-activated T cell nuclear factor 3 (NFAT3). Blocking TRPV3 can inhibit the expression of the three proteins and thus plays a therapeutic role in cardiac hypertrophy.[64] TRPV4 can upregulate Ca^{2+}/CaMK II-mediated NF-κB-NLRP3 activation and participate in pressure overload-induced cardiac hypertrophy and dysfunction. TRPV4 can also play a therapeutic role in cardiac hypertrophy.[65] In addition, the expression levels of CaMK II mRNA and protein and the levels of LC3 II/I and Beclin-1 protein were significantly increased after Ang II treatment, indicating that CaMK II may not only participate in Ang II–induced cardiac hypertrophy but also participate in autophagy.[66] RIPK3 can not only interfere with I/R injury but also target RIPK3 inhibition, which can effectively reduce -induced ROS accumulation, stabilize mitochondrial membrane potential, inhibit CaMK II activation, and improve necroptosis and oxidative stress, thereby reducing myocardial hypertrophy.[67]

Some inhibitors and compounds also play an active role in regulating CaMK II–involved cardiac hypertrophy. Ranolazine is a selective inhibitor of INa L, which can regulate the levels of Na^{+} and Ca^{2+} and inhibit downstream pathways and endoplasmic reticulum stress to improve cardiac hypertrophy and cardiac dysfunction caused by pressure overload.[21] Crocus sativus extract can induce cardiac hypertrophy by participating in the calcineurin-NFAT3 and CaMK II-HDAC4 signaling pathways: Leu (27) and IGF-II.[68] Trans-cinnamaldehyde, one of the main components of cinnamon, can inhibit PE-induced cardiac hypertrophy and phosphorylation and nuclear localization of CaMK II and ERK, prevent hyperphosphorylation of RyR2 and PLN, and play an anti-cardiomyocyte hypertrophy role through the CaMK II/ERK pathway.[69] It is interesting to find that pretreatment with KN-93 decreased the microvessel density, vascular endothelial cell apoptosis, cardiomyocyte apoptosis, cardiac collagen deposition, and deterioration of cardiac function in rats. KN-93 can impair angiogenesis and aggravate cardiac remodeling and heart failure by inhibiting the NOX2/mtROS/p-VEGFR2 and STAT3 pathways.[70] Figure 5 shows the mechanism of CaMK II in cardiac hypertrophy.

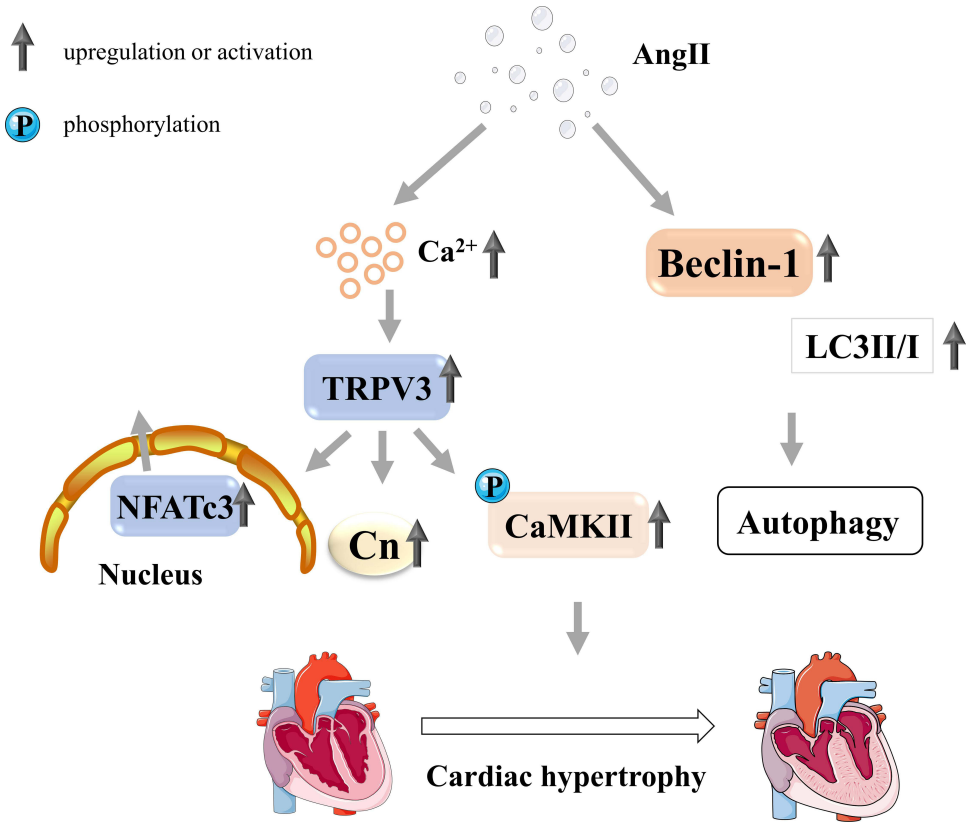

Figure 5 The mechanism of CaMK II in cardiac hypertrophy. After Ang II treatment, the Ca^{2+} concentration is increased, and TRPV3 is activated, which promotes the expression of calcineurin and pCaMK II, enhances the NFAT3, thereby reducing myocardial hypertrophy.
Abbreviations: CaMK II, Ca^{2+}/calmodulin-dependent kinase II; TRPV3, transient receptor potential vanilloid receptor 3; Ang II, angiotensin II; NFATc3, activated T cell nuclear factor 3.

CaMK II and Cardiotoxicity

Cardiotoxicity is a common clinical drug-induced cardiotoxicity, which is one of the adverse drug reactions. The mechanism is relatively complex and is limited by the effects of the drug itself and the intervention in patients. Long-term or excessive use of drugs will lead to accumulation in the body and aggravate cardiac injury. Heroin is the most commonly abused opioid, which can increase the phosphorylation of myocardial CaMK II Thr287 site, leading to CaMK II autophosphorylation, altering the expression levels of myocardial contraction proteins TPM1 and MYOM2, and predisposing to arrhythmias.[71] Doxorubicin (Dox) is an anthracycline antibiotic with strong anti-tumor effects. It can increase serum cardiac toxicity indicators; lead to Ca^{2+} overload; activate calpain 1 and the mitochondrial-mediated apoptosis cascade; upregulate CaMK II-δ, Bax, and calpain I; downregulate Bcl-2; consume ATP; reduce the ATP/ADP ratio; lead to mitochondrial energy disorder; and increase the NF-κB and IL-6 levels. NAM and 1α(OH)D(3) can regulate ion homeostasis, reduce apoptosis, improve the inflammatory response, and regulate energy metabolism disorders to protect against the heart damage caused by Dox. The effect of NAM is particularly prominent.[72] CaMK II can regulate the inositol-requiring enzyme 1α (IRE1α)/splicing X-box binding protein 1 (XBP1s) pathway, promote endoplasmic reticulum stress and apoptosis, and aggravate Dox-induced cardiotoxicity.[73] RGS7 inhibition can protect against Dox-induced heart damage and improve heart function. RGS7 is significantly upregulated in human and mouse myocardium after chemotherapy exposure. In ventricular myocytes, RGS7 can promote CaMK II oxidation and phosphorylation, form a complex with CaMK II, and induce oxidative stress, mitochondrial dysfunction, and apoptosis.[74]

CaMK II and Hypertension

Ang-II is an important mediator of vascular remodeling. In vivo experiments have shown that CaMK II inhibition aggravates vascular remodeling and vasoconstriction after Ang-II treatment. CaMK II is an important regulator of Ang-II -mediated hypertension.[75] Four CaMK II isoforms (α, β, γ, and δ) are expressed in the vascular system. CaMK II-γ can inhibit TMEM16A, regulate the activity of Ca^{2+}-activated chloride channels, guide the proliferation of basilar artery smooth muscle cells, and improve hypertensive cerebral vascular remodeling.[76] Alamandine is a vasoactive peptide, which is a component of the renin-angiotensin system. It can activate CaMK II in a nitric oxide-dependent manner to mediate cardiomyocyte contractility, thereby interfering with hypertension.[77]

CaMK II and DCM

Cardiac and mitochondrial CaMK II-overexpressing mice have severe DCM and decreased ATP, resulting in increased Ca^{2+} concentration and decreased mechanical properties. The lack of any specific treatment for cardiac dilatation can be overcome by targeted replacement of mitochondrial creatine kinase or mitochondria-targeted inhibition of CaMK II. Mitochondrial CaMK II causes adverse metabolic reprogramming and DCM.[78] CaMK II-δ is activated downstream of Gαq transgene (Gq). Overexpression of Gq and CaMK II-δ causes cardiac hypertrophy, and the continuous activation of the Gq signal during pressure overload induces DCM.[79] Baicalin, a monomer of traditional Chinese medicine, has good effects in the treatment of Dox-induced DCM. It can improve ventricular remodeling, reduce serum NT-proBNP and ST2 levels, reduce cardiomyocyte apoptosis, and decrease the expression levels of β1-AR, PKA, and CaMK II, which may play a protective role by inhibiting the β1-AR/PKA/CaMK II signaling pathway.[80]

CaMK II and Blood Vessels

A large number of studies have suggested that the process of coronary atherosclerosis is closely related to the inflammation of the vascular wall. Similarly, CaMK II is also important for blood vessels. Blood vessels are mainly composed of endothelial cells and parietal cells (vascular smooth muscle cells and pericytes). Mitochondrial CaMK II is present in the mitochondria of vascular smooth muscle cells and is activated by platelet-derived growth factor, and its mechanism depends on mitochondrial Ca^{2+} one-way transport protein. CaMK II is a key regulator of mitochondrial calcium uptake by mitochondrial Ca^{2+} one-way transporter, which can control mitochondrial translocation and vascular smooth muscle cell migration after vascular injury.[81] In addition, in smooth muscle cells, there is a dynamic interaction between CaMK II-δ2 and Src family tyrosine kinase (Fyn), which can coordinate the movement of vascular smooth

muscle cells, and the increase of vascular smooth muscle cell movement can lead to the formation of new intima.[82] The increase of intracellular Ca^{2+} concentration can activate CaMK and promote gene transcription. This signaling pathway is called excitation-transcription (E-T) coupling, and vascular muscle cells can show E-T coupling. After depolarization stimulation, Ca^{2+} influx activates CaMKK2 and CaMK1a through Cav1.2 voltage-dependent Ca^{2+} channel. In the caveolae, Cav1.2/CaMKK2/CaMK1a complex formation is promoted in vascular myocytes. Thereby activating the space-restricted enzyme cascade, leading to the transcription of genes related to chemotaxis and inflammation, and then inducing macrophage migration and vascular remodeling.[83] Studies have shown that allicin, the main active ingredient in garlic, can reduce aortic vascular thickening and protect blood vessels in spontaneously hypertensive rats by inhibiting CaMK II/NF-κb activation.[84]

In different diseases, the mechanism of CaMK II on blood vessels is different. The main pathological feature of acute respiratory distress syndrome/acute lung injury is increased pulmonary vascular permeability caused by endothelial cell barrier dysfunction. The activation of NOX induces endothelial cell dysfunction by producing ROS. NOX 4 knockdown attenuated the redox-sensitive activation of the CaMK II/ERK1/2/MLCK pathway to maintain the integrity of the endothelial cell barrier.[85] Studies have found that dapagliflozin can inhibit CaMK II activation by inhibiting the XO-SERCA2-CaMK II-cofilin pathway, maintain cytoskeleton integrity and endothelial cell viability, and reduce cardiac microvascular injury and endothelial dysfunction caused by myocardial I/R injury.[86] In aortic-derived large vascular endothelial cells, CaMK II can mediate redox-sensitive upregulation of endothelial nitric oxide synthase (eNOS) gene expression. In endothelial cells derived from pulmonary microvessels, CaMK II mediates barrier dysfunction. In brain capillary endothelial cells, CaMK II is located upstream of voltage-gated potassium channels and hypoxia-induced cell swelling. In macrovascular and microvascular endothelial cells, CaMK II can mediate actin cytoskeleton reorganization.[87] It is worth mentioning that Panax notoginseng total saponins (PNS) has a protective effect on acute myocardial infarction (AMI). PNS and its main components Rg1 and R1 significantly enhance the migration and angiogenesis of endothelial cells to reduce myocardial infarction injury.[88]

Drug Development About CaMK II

In recent years, CaMK II has gradually become the main target of heart failure, arrhythmia and other cardiovascular diseases. Various types of CaMK II inhibitors have been used in preclinical studies, such as Ca^{2+}/CaM competitive CaMK II inhibitors (KN-62, KN-93), peptide inhibitors (AC3-I, AIP) and so on. The above inhibitors are essential for the study of CaMK II in the treatment of cardiovascular diseases, but are not selective and inhibit other ion channels, so they are not suitable for clinical treatment.[89,90] ATP-competitive CaMK II inhibitors have the advantages of high affinity and clear site of action, and are gradually attracting the attention of the pharmaceutical industry. For example, Rimacalib (SMP-114) is expected to be a candidate drug for the treatment of human arrhythmia and heart failure.[91] GS-680 and AS105 have good antiarrhythmic activity, but are still in preclinical research,[92,93] the natural derivative 3′,4′-dihydroxyflavonol (DiOHF) has made it to a human trial.[94]

Recent studies have tested the effects of 4475 FDA-approved drugs on human cardiomyocytes cultured in vitro, and found five previously unknown CaMK II inhibitors: ruxolitinib, baricitinib, silmitasertib, crenolanib, and abemaciclib. Among these five drugs, ruxolitinib is most effective in inhibiting CaMK II activity in CaMK II-driven arrhythmia cells and mouse models. Most importantly, mice treated with ruxolitinib did not show any adverse cognitive effects when subjected to memory and learning task tests. Patients with catecholaminergic polymorphic ventricular tachycardia are usually resistant to standard treatment, and the treatment method based on ruxolitinib may provide another choice.[95]

Discussion

CaMK II, an important regulatory molecule, plays an essential role in CVD. In recent years, studies on CaMK II have gradually increased, and the mechanism of action of CaMK II subtypes has become clearer. Due to the different signaling pathways mediated by different CaMK II subtypes, different types of inhibitors are essential for the mediation of the various effects of CaMK II. CaMK II has different effects on ion channels, I/R injury, arrhythmia, cardiac hypertrophy, cardiotoxicity, hypertension, and DCM.

We reviewed the literature on CaMK II and cardiovascular related functions in the past five years on NCBI and other websites. The researchers summarized the mechanism of CaMK II in cardiovascular diseases from different perspectives. Zhang et al summarized the regulation and function of CaMK II in a variety of cell types during I/R, including cardiomyocytes, endothelial cells, and macrophages. It is believed that CaMK II mediates inflammation in the myocardial microenvironment, leading to cell dysfunction, increased inflammation, and cell death. However, different CaMK II-δ variants show different or even opposite functions, and CaMK II may be a key target for regulating the severity of inflammatory degeneration.[96,97] Trum et al briefly summarized the pathophysiological role of CaMK II in heart failure and the cardiac changes of glucose and ketone metabolism in heart failure.[98] Jiang et al reviewed the relationship between CaMK II and various substances in the pathological process of cardiomyocyte apoptosis and necrosis, myocardial hypertrophy and arrhythmia, as well as its role in the development of diseases in complex networks. Drugs targeting CaMK II for the treatment of heart disease are also introduced.[99] Yang et al briefly summarized CaMK II with various post-translational modifications and its characteristics in myocardial I/R injury. They focused on the molecular mechanisms of CaMK II involved in the regulation of myocardial I/R-induced cell death, including cardiomyocyte necrosis and focal sagging.[100] Reyes et al reviewed the cellular and molecular biology of CaMK II, discussed its role in cardiovascular physiological and pathological signal transduction, and considered new discoveries and methods for developing CaMK II therapies.[101] These studies have played a positive role in the research and application of CaMK II. This paper systematically analyzes the structural characteristics and distribution of CaMK II, the mechanism of action, and the relationship between CaMK and cardiovascular disease, so as to provide a new reference for the study of CaMK II.

The extensive distribution of CaMK II and the diversity of isozymes determine the diversity and complexity of its function. We know that CaMK II can regulate multiple ion channels. CaMK II can phosphorylate NaV1.5 channels, increase INa L, downregulate Kir2.1, increase ROS production, activate NCX, cause sodium and calcium overload, lead to ion level disorder, electrical signal change, and induce arrhythmias.[15–17,27] The mechanism of CaMK II involved in I/R injury may be related to mitochondrial energy metabolism, oxidative stress, apoptosis, inflammatory response, and autophagy dysfunction. CaMK II-δ9 is the most abundant splicing variant of CaMK II-δ in the heart. The differential regulation of CaMK II-δC and CaMK II-δB on myocardium may be achieved by acting on inflammation.[42–44,48] The different or even opposite effects of different CaMK II-δ subtypes provide more directions for the study of CaMK II diversity. The mechanisms of arrhythmias are complex. CaMK II can interfere with arrhythmias by regulating multiple ion channels or participating in complex mechanisms such as oxidative stress and inflammatory response.[22,56,59] Due to the extensive mechanisms of action of CaMK II, such as participation in apoptosis, oxidative stress, inflammatory response, mitochondrial energy metabolism, it can act on cardiomyocytes, smooth muscle cells, thereby affecting cardiac/vascular structure and function, inducing cardiac hypertrophy, hypertension, cardiotoxicity, dilated cardiomyopathy and other diseases.[66,72,76,78] The development of CaMK II inhibitors is of great significance for improving cardiac function and mitochondrial energy metabolism disorders, regulating blood pressure, and reversing ventricular remodeling.

In addition, a small number of studies[88,102,103] have preliminarily explored the reactions mediated by natural compounds through CaMK II signaling molecules, such as Panax Notoginseng saponins, astragaloside IV, and *Lycium barbarum* polysaccharides, to reverse ventricular remodeling, restore cardiac systolic and diastolic functions, and reduce myocardial injury via autophagy and regulation of ion homeostasis. Aerobic exercise and acupuncture treatment also play a protective role by modulating CaMK II, inhibiting cardiomyocyte apoptosis, and improving cardiac function.[104,105]

Currently, most of the in vivo and in vitro studies have focused on the mechanisms, with limited studies focusing on the clinical and pharmacological aspects. CaMK II is still considered a traditional inhibitor, and there is still a long way ahead before it can be used in the clinical setting. New inhibitors need to be developed, and the mechanisms of different subtypes should be explored. We expect that specific targeted research will be conducted in the future, with the use of new inhibitors or compounds independently or in combination.

Conclusion

Based on this, this paper analyzes the structural characteristics and distribution of CaMK II, the mechanism of action of CaMK II, and the relationship between CaMK II and CVDs, including ion channels, I/R injury, arrhythmias, myocardial hypertrophy, cardiotoxicity, hypertension, and dilated cardiomyopathy. According to the current research results, CaMK II is an important regulatory molecule in the occurrence and development of CVDs. Although the clinical application of CaMK II inhibitors faces significant challenges, the effects and regulatory mechanisms of different CaMK II subtypes in different CVD models exhibit significant variations. Highly specific CaMK II subtype inhibitors are likely to become new therapeutic drugs, providing new treatment methods and targets for clinical diseases.

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Author Contributions

All authors contributed significantly to the work reported, including theme design, literature search and screening, and figures production, drafting, reviewing, and revising of articles, or all of these areas. All authors have participated in the submission of the article to the journal and agreed to be accountable for all aspects of the work.

Yu-Qing Tan and Wang Zhang have contributed equally to this work and share first authorship. Jun Li and Heng-Wen Chen have contributed equally to this work and are corresponding authors.

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Disclosure

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