Regulatory mechanism of calcium/calmodulin-dependent protein kinase II in the occurrence and development of ventricular arrhythmia (Review)

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Abstract. Ventricular arrhythmia (VA) is a highly fatal arrhythmia that involves multiple ion channels. Of all sudden cardiac death events, ~85% result from VAs, including ventricular tachycardia and ventricular fibrillation. Calcium/calmodulin-dependent pro-tein kinase II (CaMKII) is an important ion channel regulator that participates in the excitation-contraction coupling of the heart, and as such is important for regulating its electrophysiological function. CaMKII can be activated in a Ca^{2+}/calmodulin (CaM)-dependent or Ca^{2+}/CaM-independent manner, serving a key role in the occurrence and development of VA. The present review aimed to determine whether activated CaMKII induces early afterdepolarizations and delayed afterdepolarizations that result in VA by regulating sodium, potassium and calcium ions. Assessing VA mechanisms based on the CaMKII pathway is of great significance to the clinical treatment of VA and the de-velopment of effective drugs for use in clinical practice.

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Contents

1. Introduction

Arrhythmias, particularly ventricular arrhythmias (VAs), have a relatively high morbidity and mortality among the population, with ~250,000 deaths reported annually in the USA alone (1). Similarly to ventricular fibrillation (VF), VA has been reported to occur in >10% of all patients with acute myocardial infarction (AMI) prior to hospitalization, and survival in these patients remains poor (2). A total of 17 million deaths occur per year, worldwide, as a result of cardiovascular disease, 50% of which are attributable to sudden cardiac death (SCD) (2). The major cause of SCD is VA, particularly ventricular tachycardia (VT) and VF, which account for ~85% of all SCD events (3,4).

VA is an arrhythmia that originates in the ventricles that does not require any myocardial tissue above the His bundle to maintain (5). VA is particularly common in clinical practice and includes premature ventricular contraction, VT and VF (6,7). Reentry and triggered activity are the two main mechanisms of tachyarrhythmia. Reentry occurs when a beat encounters ventricular myocardium modified by fibrosis, scarring or conduction abnormalities (6). Triggered activity is caused by early afterdepolarizations (EADs), which are induced by reducing the repolarization reserve, either due to increas-ing inward currents, reducing outward currents or both, occurring in the second and third stages of the action potential (AP) (6,8). Delayed afterdepolarizations (DADs) are mediated by Ca^{2+} dysregulation after the fourth stage of the AP. Abnormal depolarizations reach the membrane potential threshold and further

give rise to a spontaneous AP between two regular APs (6,8,9). According to mechanistic studies (10,11), the occurrence and development of VA events during the acute phase of AMI can be attributed to diastolic Ca^{2+} leak and disturbed Ca^{2+} homeostasis. This can be induced by enhanced sympathetic tone and is accompanied by the formation of reentry circuits, further increasing vulnerability to VT (12).

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a versatile serine/threonine kinase that is found widely in muscle, nerve and immune tissues (13). CaMKII serves multiple regulatory effects, including excitation-contraction coupling, excitation-transcription coupling, Ca^{2+} handling and mitochondrial function in cardiomyocytes (14,15). Chronic activation of CaMKII causes significant cardiomyocyte remodelling and alterations in Ca^{2+} handling, ion channels, cell-to-cell coupling and metabolism, leading to increased susceptibility to VA (15-21). The present review aimed to assess the participation of CaMKII in the occurrence of EADs and DADs by targeting L-type Ca^{2+} channels (LTCCs), phospholamban (PLB), ryanodine receptors (RyRs), voltage-gated Na^+ (Na_v) channels and multiple voltage-gated K^+ channels, which further result in VA (18,19).

2. Molecular structure, function, subtypes and distribution of CaMKII

Molecular structure and function of CaMKII. CaMKII is a serine/threonine kinase that is composed of two stacked hexamers assembled from 12 monomers (22,23). Each monomer is composed of an N-terminal catalytic region, an intermediate regulatory do-main and a C-terminal associated region (15,23). The catalytic region contains an ATP and target substrate binding site, which is responsible for the regulation of kinase activity (23). Under basic conditions, the function of the catalytic region is inhibited by interacting with the intermediate regulatory region (23). The intermediate regulatory region interacts with Ca^{2+}/calmodulin (CaM) at a K_D of 10-50 nM, which not only activates CaMKII by preventing the inhibitory effect of the catalytic region, but also increases the activity of CaMKII by phosphorylating threonine 287 (Thr287) (18,23). The C-terminal associated domain is responsible for the oligomerization of individual CaMKII molecules to form a mature dodecameric-holoenzyme (Fig. 1) (18).

CaMKII subtypes and distribution. CaMKII has four subtypes (α, β, γ and δ), and each subtype has a different basic affinity for Ca^{2+}/CaM (in order of highest to lowest, γ, β, δ and α) (15,18). The CaMKIIδ and CaMKIIγ subtypes are mainly present in myocardial tissue (18). CaMKIIδ has four splice variants (δA, δB, δC, and δ9), among which CaMKIIδB and CaMKIIδC are observed primarily expressed in the heart (18,23). CaMKIIδB contains an 11-amino acid nuclear localization sequence, which is preferentially localized in the nucleus, thereby exerting an important influence on the transcriptional activity of genes involved in cardiac hypertrophy (18,23). CaMKIIδC is the main cytoplasmic form, which is involved in membrane excitability and regulation of intracellular Ca^{2+} homeostasis (15,23). The ratio of δB to δC in the multimer can regulate the localization of holoenzymes, and stable hetero-oligomers are formed by these CaMKII subtypes (18,23,24).

3. CaMKII activation mechanism

Ca^{2+}/CaM dependent CaMKII activation pathway. In the presence of ATP, the pseudo-substrate section of the intermediate regulatory region of CaMKII can inhibit the func-tion of the N-terminal catalytic region, resulting in the inactivation of CaMKII (23). When Ca^{2+} content increases, Ca^{2+} combines with CaM (a ubiquitous intracellular Ca^{2+} binding protein) to form Ca^{2+}/CaM (24). The intermediate regulatory region binds to Ca^{2+}/CaM, which causes conformational changes in the pseudosubstrate region and releases the catalytic domain, exposing the substrate and ATP binding sites, further resulting in CaMKII activation (Fig. 1) (23,24).

Ca^{2+}/CaM independent CaMKII activation pathway. In the presence of ATP, continuously increasing Ca^{2+}/CaM sustainably combines with the intermediate regulatory region of CaMKII, which results in the autophosphorylation of Thr287. Thr287 autophosphorylation significantly increases the affinity of Ca^{2+}/CaM to the intermediate regulatory region, slowing the release of Ca^{2+}/CaM and retaining residual activity even after the dissociation of Ca^{2+}/CaM, further resulting in CaMKII activation (3,16,24). A previous study by Erickson *et al* (25) showed that the methionine 281/282 (Met281/282) site is oxidized in the presence of reactive oxygen species (ROS). Oxidation of Met281/282 can not only lead to the autonomous activation of CaMKII by preventing the recombination of the catalytic domain and the intermediate regulatory region, but also promote CaMKII activation at low intracellular Ca^{2+} concentrations by increasing the capability of CaMKII to be activated by Ca^{2+}/CaM (3,18). In addition, O-linked glycosylation at serine 280 (Ser280) and nitric oxide (NO)-dependent nitrosation at cysteine 290 (Cys290) can activate CaMKII. Ser280 O-linked-glycosylation of CaMKII has been demonstrated to promote Thr287 autophosphorylation (Fig. 1) (18,26).

4. CaMKII regulates cardiac Na_v channels to induce VA

Na_v channels and sodium ion current. Under normal conditions, Na_v channels rapidly activate and inactivate, resulting in a transient Na^+ current ($I_{Na,T}$), which allows for AP depolarization (phase 0 of the AP). However, even under physiological conditions, a minor population of Na_v channels may fail to inactivate, giving rise to a late Na^+ current ($I_{Na,L}$) that persists throughout the AP. Importantly, amplification of $I_{Na,L}$ in disease set-tings has been demonstrated to increase arrhythmia susceptibility (27).

CaMKII regulates Na_v channels. CaMKII has a VA-inducing effect by regulating Na_v channels. Previous studies have demonstrated that acute CaMKII overexpression may shift Na_v channel resting potential to more negative membrane potentials, enhancing in-termediate inactivation and slowing recovery from inactivation, thereby reducing the fraction of available Na^+ channels. However, this also slows $I_{Na,T}$ inactivation, enhances $I_{Na,L}$ and increases intracellular Na^+ concentrations. These effects increase susceptibility to arrhythmia (27,28) Additionally, serine 571 of $Na_v1.5$ is in the Na_v pore-forming subunit and is a key site of CaMKII phosphorylation. Na_v channels can be

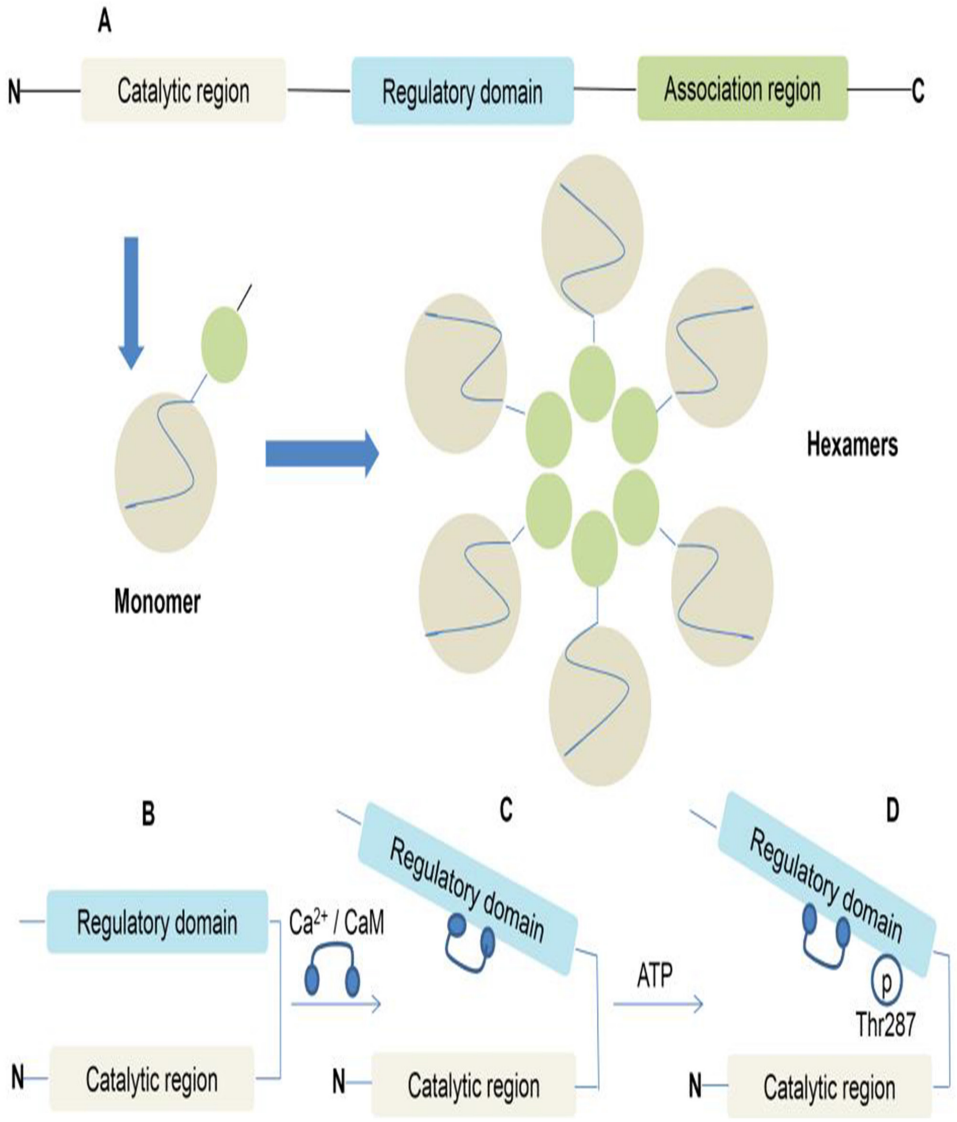

Figure 1. CaMKII structural domains and regulation. (A) CaMKII monomers are com-posed of an N-terminal catalytic region, an intermediate regulatory domain and a C-terminal associated region. Two stacked hexamers assembled from 12 monomers form CaMKII. (B) Under basal conditions, the catalytic domain of CaMKII is inhibited through direct interaction with the regulatory domain. (C) CaMKII is activated by the binding of Ca^{2+}/CaM. (D) Ca^{2+}/CaM binding also exposes sites in the regulatory domain, resulting in alternative activation modes. For example, the autophosphorylation of Thr287 by a neighbouring active subunit (autophosphorylation) induces a high activity mode subunit. Similar autonomy is observed with oxidation at the exposed Met281/282 site, O-linked glycosylation at Ser280 or NO-dependent nitrosation at Cys290. CaMKII, calcium/calmodulin-dependent protein kinase II; Ca^{2+}/CaM, calcium/calmodulin; Thr287, threonine 287; p, phosphorylation; N, N-terminus; C, C-terminus.

continuously opened or reopened to produce long-lasting $I_{Na,L}$ via phosphorylation at this subunit (16,29). Increased $I_{Na,L}$ can significantly prolong the AP duration (APD) and increase the Na^+ load in cardiomyocytes, which can enhance the Na^+-Ca^{2+} exchanger (NCX) activity in the reverse mode (3 Na^+ extruded from the cell in exchange for 1 Ca^{2+}), further increasing the Ca^{2+} load in cardiomyocytes (Fig. 2) (30-33). A prolonged APD in combination with an increased Ca^{2+} load can induce EADs and DADs, eventually lead-ing to VA. In addition, $I_{Na,L}$ can enhance the Ca^{2+} regulation capacity through the feed-back regulation of CaMKII, thereby participating in the occurrence of VA (16).

5. CaMKII regulates K^+ channels to induce VA

K^+ channels and K^+ current. The K^+ current formed by the K^+ channels of the heart is a key determinant of heart excitability. There are three types of K^+ currents in the heart: Transient outward K^+ current (I_{to}), inward rectifier K^+ current (I_{K1}) and delayed rectifier K^+ current (I_K). I_{to} is mainly generated by the activation of voltage-gated K^+ channels with subunits that mainly consist of KV4.2, KV4.3 and KV1.4. I_{to} produced by KV4.3 is primarily involved in the formation of the first phase of the AP (the early stage of rapid repolarization) (34). I_{K1} is primarily produced by activation of the inward rectifier K^+ channel, which is important for maintaining the resting cell membrane potential and the third phase of the AP (end of rapid repolarization). The inward rectifier K^+ channel pore-forming subunit is composed of Kir2.1 and Kir6.2. I_{K1} is generally considered to be antiarrhythmic as it stabilizes the resting membrane potential (35). I_K is mainly produced by the activation of delayed rectifier K^+ channel groups with pore-forming subu-nits consisting of K_v1.5, human ether-a-go-go-related

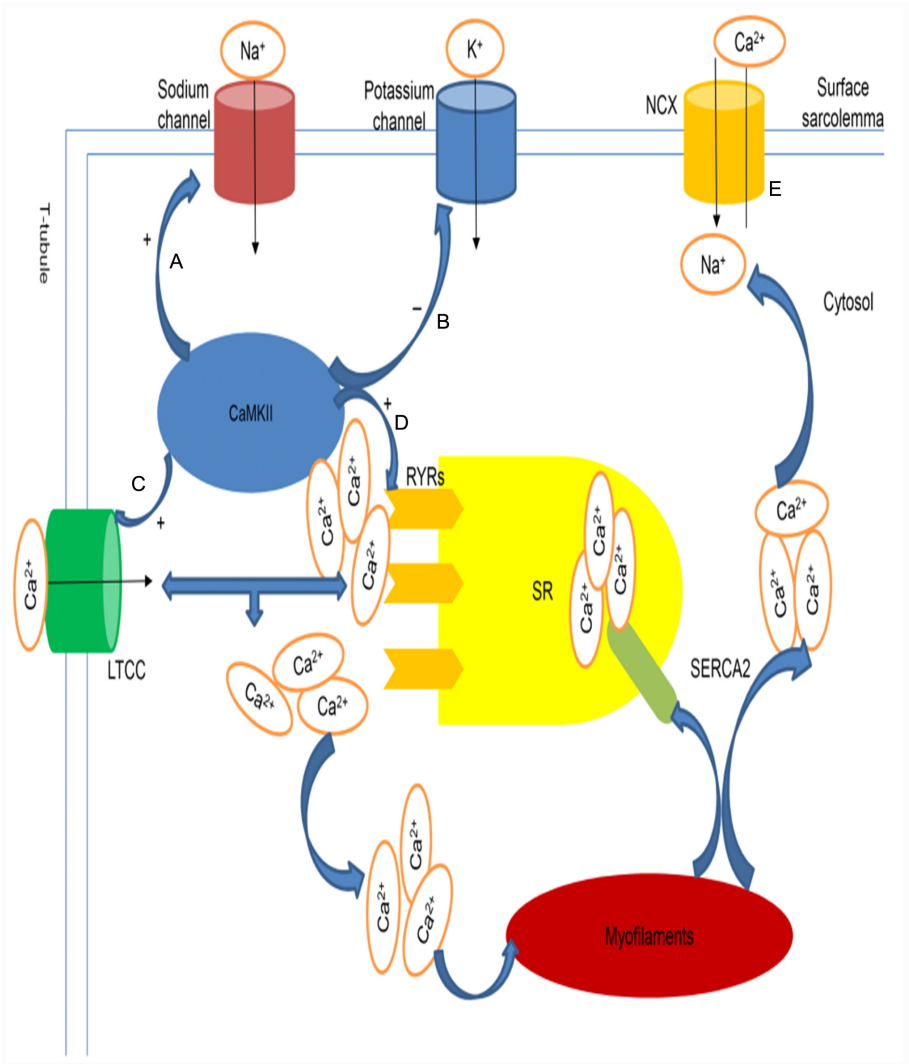

Figure 2. Proposed model of CaMKII-induced ventricular arrhythmia. (A and E) CaMKII increases late Na^+ currents by phosphorylation at the Serine 571 site, further prolonging the APD and decreasing NCX function, which results in increased Ca^{2+} load (B). CaMKII reduces the outward K^+ current, inward rectifier K^+ current and delayed rectifier K^+ current intensity, further prolonging the APD (C-E). CaMKII increases Ca^{2+} overload in the cytosol by phosphorylating LTCCs and RyRs. LTCCs coupled with Ca^{2+} induces further Ca^{2+} release from RyRs. Ca^{2+} is returned to the SR by SERCA2 and extruded via the NCX after participating in myofilament contraction. CaMKII, calcium/calmodulin dependent protein kinase II; APD, action potential duration; NCX, Na^+-Ca^{2+} exchanger; LTCCs, L-type Ca^{2+} channels; RyRs, ryanodine receptors; SR, sarcoplasmic reticulum; SERCA2, sarco(endo)plasmic reticulum calcium ATPase 2.

gene and K_v7.1, participating in the formation of the second and third phases of the AP (36).

CaMKII regulates K^+ channels. CaMKII induces VA by participating in the regulation of I_{to}, I_{K1} and I_K. Chronic CaMKII activation reduces I_{to} intensity by reducing the mRNA and protein expression levels of the KV4.2 and KV4.3 subunits. In addition, de-creased expression of the KV4.3 subunit can cause feedback that activates CaMKII. The KV4.3 subunit can also bind to the Ca^{2+}/CaM binding site of CaMKII (34). Activation of a large amount of CaMKII can increase its ability to regulate K^+ channels. Chronic CaMKII activation also reduces the intensity of I_{K1} by reducing the mRNA and protein expression levels of the Kir2.1 and Kir6.2 subunits (36,37). A slow change in I_{K1} intensity causes the resting membrane potential to be unstable, such that the depolarization current can be transformed into larger DADs, leading to the occurrence of VA (37,38). Chronic activation of CaMKII can phosphorylate the serine 484 site of the KV7.1 subunit, leading to a decrease in I_K intensity (39). It has been suggested that reduction in I_{to}, I_{K1} and I_K intensity can lead to prolongation of the APD, which promotes the occurrence of VA (Fig. 2) (36).

6. CaMKII regulates Ca^{2+} channels to induce VA

Ca^{2+} cycle. The excitation-contraction coupling of cardiomyocytes is a highly coordinated process that links electrical signals with mechanical contractions. LTCCs can produce an L-type Ca^{2+} current ($I_{Ca,L}$) that participates in the formation of the second phase of the AP. LTCCs coupled with Ca^{2+} induces Ca^{2+} release from RyR channels. Increased Ca^{2+} binds to troponin and triggers myofilament contraction. When ventricular myocytes enter the diastolic phase, Ca^{2+} in the cytoplasm is returned to the sarcoplasmic reticulum (SR) through sarco(endo)plasmic reticulum calcium ATPase 2 (SERCA2) (40,41).

CaMKII regulates Ca^{2+} homeostasis. CaMKII serves an important role in the regulation of Ca^{2+} homeostasis and has

a VA-causing effect. CaMKII activation can increase LTCC phosphorylation, which generates a greater $I_{Ca,L}$ (32). The serine 2814 site of RyR_2 is phosphorylated upon CaMKII activation, which occurs when the release of Ca^{2+} stored in the diastolic SR abnormally increases (31,42-44). Abnormally released Ca^{2+} propagates along adjacent RyR_S on the SR and activates them to trigger further Ca^{2+} release (8,12). Increased intracellular Ca^{2+} concentrations can participate in the regulation of Na_v channel function through CaMKII activation, thereby adjusting the flow of Na^+ (45). Excess Ca^{2+} in the cytoplasm is extruded via the NCX, which produces an inward current (I_{ti}; Fig. 2). When I_{ti} is sufficient to depolarize the myocardial cell membrane, Na_v channels can be activated, which triggers additional APs and further results in DADs (8,29,31,40,43). When $I_{Ca,L}$ or I_{ti} is greater than the outward current (mainly K^+ current) during the later period of the AP, the APD can be prolonged, which leads to the occurrence of EADs (8). The occurrence of DADs and EADs will eventu-ally lead to VA. However, the threonine 17 (Thr17) site of PLB, which is mainly expressed in the SR to regulate SERCA2 activity, is a specific target of CaMKII phosphorylation. PLB phosphorylation at Thr17 helps to limit cytosolic Ca^{2+} overload by increasing SERCA2 activity and accelerating SR Ca^{2+} reuptake, which is beneficial for improving Ca^{2+} cycle dysfunction and reducing the risk of VA (46-48).

7. Summary and outlook

In summary, VA is a highly fatal arrhythmia, involving the regulation of multiple ion channels. CaMKII serves an important regulatory role in the mechanism of VA. Overexpression of CaMKII can promote the occurrence of DADs and EADs by increasing the extent of $I_{Na,L}$, decreasing the intensity of I_{to}, I_{K1} and I_K, and increasing Ca^{2+} in the cytoplasm, thereby inducing VA. Additionally, CaMKII activation is closely related to connexin 43 dysregulation; however, CaMKII activation also indirectly decreases the expression and subcellular localization of connexin 43 in intercalated discs. Both effects potentially increase arrhythmogenic susceptibility (49-53).

CaMKII inhibition also has a potential proarrhythmic effect. Early ischemia may increase CaMKII activation due to a progressive increase in Ca^{2+} concentration and excessive formation of ROS (54,55). CaMKII activity is detrimental in this process; however, it is beneficial during the first minutes of ischemia, as it has a regulative effect on conduction and can avoid ischemia-mediated conduction block (55). Previous studies have demonstrated that CaMKII upregulation is of great significance to maintaining conduction during ischemia. Therefore, intervening through CaMKII activity can cause the heterogeneous depression of conduction during ischemia, exacerbating the arrhythmia substrate and resulting in a proarrhythmic condition (20,55).

It is necessary to develop novel drugs based on mechanistic research. Currently, effective clinical treatments for VA include non-pharmacological treatments, such as defibrillation, radiofrequency catheter ablation and pharmacological interventions that include blockers of Na^+ channels (class I), β-receptors (class II), K^+ channels (class III) and Ca^{2+} channels (class IV), as well as miscellaneous agents such as digoxin and adenosine. However, each treatment has specific limitations. For example, the pharmacological treatment of VA results in substantial toxicities and the potential for proarrhythmic side effects (35). Therefore, it is necessary to develop novel antiarrhythmic drugs based on a comprehensive understanding of the proarrhythmic mechanisms of CaMKII. At present, pharmacological inhibitors of CaMKII (such as KN93 and GS-680), peptide inhibitors (such as CN19o) and CaMKII-targeted interference drugs (such as RNAi) have been developed, though these inhibitors are associated with bioavailability limitations and poorly understood *in vivo* effects (23). Therefore, the molecular mechanism underlying the role of CaMKII in VA requires further examination. For example, whether there are other sites of CaMKII phosphorylation in Na^+, K^+, Ca^{2+} and other ion channels still requires further study. Related VA-specific drugs, such as targeted inhibi-tors of CaMKII phosphorylation sites on ion channels, also require further development.

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Availability of data and materials

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Authors' contributions

KM searched literature and further analysed the data, and wrote, revised and finalized the manuscript. GM analyzed the data from literature, drafted the article and produced the final manuscript. ZG conceived the current review and revised the manuscript. WL and GL conceived and designed the study, revised the manuscript and produced the final version. All authors agree to be responsible for all aspects of the article. All authors have read and approved the final manuscript. LW and LG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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