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Non-ion channel therapeutics for heart failure and atrial fibrillation: are CaMKII inhibitors ready for clinical use?

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Abstract

The Ca^{2+}-calmodulin dependent protein kinase II (CaMKII) is an established central mediator of electrophysiological and contractile responses to cardiac stress, and its hyper-activation in cardiac diseases has been linked to heart failure (HF) and atrial and ventricular arrhythmias. Here we summarize the evidence supporting the role of CaMKII as a critical nodal point for therapeutic intervention against HF and atrial and ventricular tachyarrhythmias. Targeting of CaMKII in heart with inhibitors possessing appropriate selectivity might represent a novel therapeutic approach for HF and arrhythmias.

Keywords

CaMKII; heart failure; atrial fibrillation; arrhythmia; small molecules

The multifunctional Ca^{2+}-calmodulin dependent protein kinase II (CaMKII) is prominent for its central roles in the nervous system and heart [1], where it controls a diverse range of Ca^{2+}-dependent processes, from learning and memory at the neuronal synapse to cellular growth and death in the myocardium. In cardiomyocytes, CaMKII directly regulates numerous ion channels and Ca^{2+}-handling proteins [2], and controls the expression of an ever-increasing number of transcripts [3, 4] and their downstream products (Figure 1). Functionally, these actions are thought to orchestrate many of the electrophysiological and contractile adaptations to common cardiac stressors, such as fast atrial and ventricular activation rates, chronic adrenergic stimulation, and oxidative challenge [5], Indeed, besides

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canonical activation via Ca^{2+}/calmodulin binding [6], CaMKII activity is regulated by a number of post-translation modifications including oxidation [5], S-nitrosylation [7], *O*-GlcNAcylation [8] and via a not fully resolved cAMP-Epac-NOS pathway [9].

CaMKII Role in Heart Failure and Atrial Fibrillation

In the context of disease, CaMKII has been shown to contribute to a remarkably wide variety of cardiac pathologies [10], of which heart failure (HF) is the most conspicuous. Hyperactivity and chronic activation of CaMKII is an established contributor to pathological cardiac remodeling, and is widely thought to directly promote arrhythmia and contractile dysfunction during HF [11, 12] (see also reviews: [10, 13]). CaMKII upregulation in HF directly promotes increases in late Na^+ current (I_{NaL}) [14] and diastolic sarcoplasmic reticulum (SR) Ca^{2+} leak [12] via the ryanodine receptor (RyR), which are the primary molecular defects in two genetically-linked arrhythmogenic syndromes, long QT type-3 and catecholaminergic polymorphic ventricular tachycardia. Indeed, several non-failing arrhythmia-susceptible phenotypes, which result from specific genetic channelopathies, functionally mimic constitutive channel phosphorylation by CaMKII [14-16],

While CaMKII may play a lesser arrhythmogenic role in paroxysmal forms of atrial fibrillation (AF) [17], this kinase is overexpressed and hyperactive in patients with persistent (chronic) AF (cAF) [18, 19] and many experimental AF models [20-25]. CaMKII upregulation in AF paradigms and AF patients and in electrical storm [26] promotes cardiac arrhythmogenesis likely through phosphorylation of the same targets that are relevant for HF ([17, 18, 27, 28]), although regulation of atrial-dominant ion channels and transport regulators has also been reported (e.g., I_{Kur} [29], $I_{K,Ca}$ [30] and sarcolipin [31]

Arrhythmogenic CaMKII-Na^+-Ca^{2+} Positive Feedback

An arrhythmogenic synergistic interaction between upregulated CaMKII and perturbed Na^+ and Ca^{2+} fluxes has been hypothesized in both failing ventricular and atrial cardiomyocytes, and computational models of cardiomyocyte electrophysiology, Ca^{2+}- and Na^+-handling, and signaling have begun to quantitatively confirm this notion [32, 33], Elevated I_{NaL} prolongs action potential duration (APD) and enhances the propensity for early afterdepolarizations, a well-known arrhythmia trigger. But longer APD and briefer diastole also cause Na^+ and Ca^{2+} loading, which increases spontaneous SR Ca^{2+} releases and the likelihood of delayed afterdepolarizations. This Ca^{2+} loading also promotes CaMKII activation that reinforces I_{NaL} and RyR hyperactivation to further prolong APD, raise Na^+ and SR Ca^{2+} load and leak. This generates a pathological positive feedback loop that promotes both mechanical cardiac dysfunction (systolic and diastolic) and arrhythmogenesis. High $[Na^+]$, also lowers mitochondrial $[Ca^{2+}]$ [34], thus limiting Ca^{2+}-dependent dehydrogenases that help match energy supply with demand (and can increase reactive oxygen species to further activate CaMKII, RyR sensitivity and I_{NaL}). Breaking the CaMKII-Na^+-Ca^{2+} positive feedback loop is therefore an attractive mean to normalize Ca^{2+}, Na^+ and membrane potential dynamics in HF (and AF), but should not be achieved at the expense of systolic function. CaMKII inhibition may be well suited to facilitate this outcome.

Need for Small Molecule Inhibitors Targeting Cardiac CaMKII

Because CaMKII contributes to both the acute and chronic manifestations of major cardiac diseases, but may be only minimally required for physiological homeostasis, it has come to be one of the most promising therapeutic drug targets in cardiac biology. However, currently available CaMKII inhibitors, including inhibitory peptides and the small molecule KN-93, have limited efficacy and imperfect selectivity and are not suitable for clinical use. Furthermore, while abundant *in vitro* data is available linking CaMKII to arrhythmias in hypertrophic or failing hearts, only a few studies have directly tested the antiarrhythmic effect of CaMKII inhibition in HF *in vivo* [35]. Thus, development of more specific and deliverable small molecule CaMKII antagonists remains a key priority for the field [36].

In the paper by Neef *et al.* [37] in this issue of the *Journal of Molecular and Cellular Cardiology*, a novel ATP-competitive CaMKII inhibitor AS105 was characterized and shown to potently (*in vitro* IC_{50} in the nanomolar range) inhibit both nonphosphorylated and phosphorylated CaMKII, despite competing with millimolar [ATP] in cardiomyocytes. When tested for its functional effects, AS105 reduced SR Ca^{2+} leak in atrial cardiomyocytes from human donors and ventricular cardiomyocytes from healthy and CaMKIIδ_c overexpressing mice with HF. In human atrial cells, AS105 significantly reduced the likelihood of arrhythmogenic spontaneous SR Ca^{2+}-release events. In failing mouse ventricular cardiomyocytes, AS105 improved SR Ca^{2+} loading and release, and overall contractility.

While AS105 seems to provide a valuable tool for advancing CaMKII research, by overcoming many of the limitations inherent to the use of KN-93, including off-target effects, low potency (μM) and block of nonphosphorylated CaMKII only [36], this and other ATP-competitive or allosteric CaMKII inhibitors might not yet be ready for clinical application. Besides issues with cell penetration, particularly of substrate competitors with peptide structure like AIP and AC3-I, it is of critical importance for utilization in the clinic (and especially for chronic use) that CaMKII inhibitors exert no clinically relevant actions on α- and β-isoforms of CaMKII in brain, thereby preventing detrimental effects on memory and neuronal plasticity. Optimization of pharmacokinetic properties of small molecule CaMKII inhibitors will be required to minimize central nervous system penetration via the blood-brain barrier. Also, systemic CaMKII inhibition may have negative effects on fertility [38]. Therefore, the success of CaMKII-dependent therapeutic strategies will require the development of cardiac-specific CaMKII inhibitors. Of note, CaMKIIγ can substitute for CaMKIIδ in heart [39], rendering it likely that successful CaMKII inhibition in heart will require the inhibition of both CaMKIIδ and CaMKIIγ. Also, the existence of multiple CaMKII isoforms, each with various splice-variants, may provide opportunities to selectively target cardiac-specific pathological processes. Finally, a future approach to minimize CaMKII inhibition outside the heart might be gene therapy with viral vectors for localized expression of peptides or proteins to the heart. Advances in vector technology and delivery techniques now allow for efficient, safe and long-term gene transfer to the heart, although recent results from large clinical trials have provided mixed results [40]. Gene transfer of the SERCA2a cDNA by delivering a recombinant AAV1 (AAV1.SERCA2a) in patients with advanced HF pioneered the cardiac field. However, after the initial promise of

the Calcium Up-regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) clinical trial [41], CUPID2 study was neutral and failed to demonstrate the efficacy of AAV1.SERCA2a gene transfer in improving clinical outcomes of patients [42]. Suboptimal dosage might partially explain the neutral results, and thus future studies employing AAV1.SERCA2a gene transfer at appropriate dosages are needed to definitely disprove the viability of SERCA2a gene transfer for HF treatment.

Conclusions

After decades invested in the development of ion-channel blockers, CaMKII inhibition has emerged as a promising treatment strategy for control of HF and susceptibility to atrial and ventricular arrhythmias. Further refinement and development of small molecule ATP-competitive CaMKII inhibitors can pave the way to utilization of these drugs in the clinic. Although specificity is a major concern when using ATP-competitive CaMKII inhibitors, which might exert potential off-target effects on over 500 other kinases, successful employment of ATP-competitive inhibitors in oncology clearly demonstrates that appropriate selectivity is achievable. Local delivery of ATP-competitive CaMKII inhibitors with appropriate selectivity might represent a novel therapeutic approach against HF and arrhythmias.

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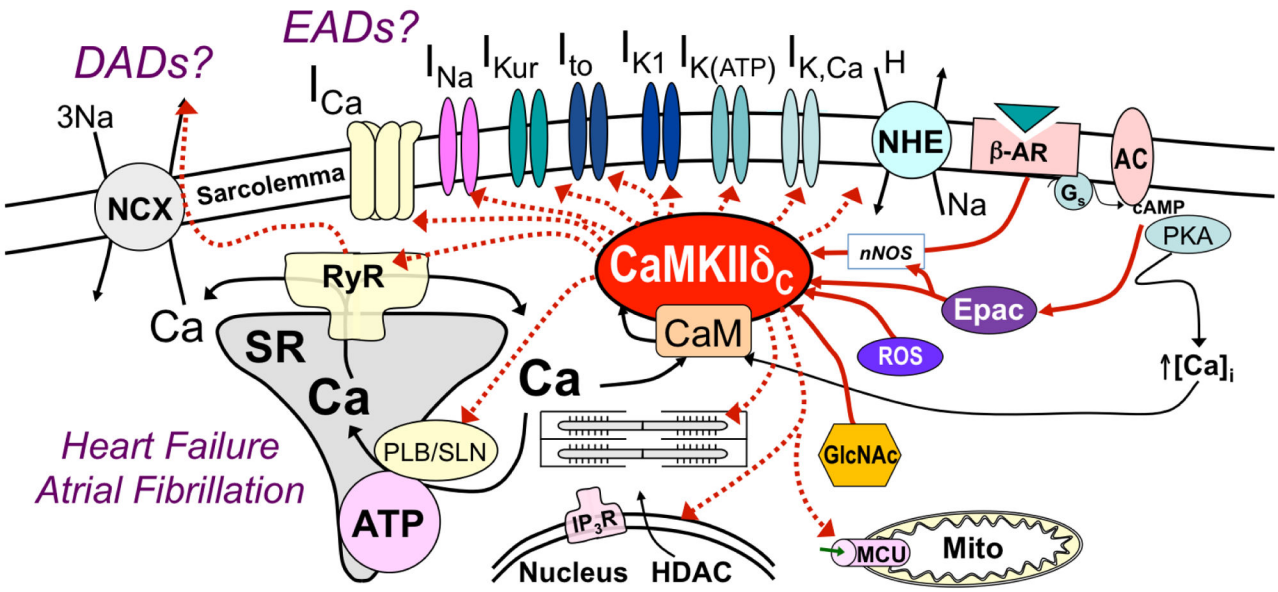

Figure 1:

Mechanisms by which CaMKII regulates cardiomyocyte electrophysiology, Ca^{2+} handling, transcription and mitochondrial function. CaMKII is activated by Ca^2/calmodulin binding, β-adrenergic activation (via Epac/NOS1), ROS, and GlcNAc. Epac: exchange protein activated by cAMP; NOS1: nitric oxide synthase 1; ROS: reactive oxygen species; GlcNAc: O-Linked β-N-Acetylglucosamine.