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Calm down when the heart is stressed: Inhibiting calmodulin-dependent protein kinase II for antiarrhythmias

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Abstract

Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) plays a pivotal role in many regulatory processes of cellular functions ranging from membrane potentials and electric–contraction (E-C) coupling to mitochondrial integrity and survival of cardiomyocytes. The review article by Hund and Mohler in this issue of *Trends in Cardiovascular Medicine* highlights the importance of the elevated CaMKII signaling pathways under stressed conditions such as myocardial hypertrophy and ischemia in the detrimental remodeling of ion channels and in the genesis of cardiac arrhythmias. Down-regulation of the elevated CaMKII is now emerging as a powerful therapeutic strategy for the treatment of cardiac arrhythmias and other forms of heart disease such as hypertrophic and ischemic heart failure. The development of new specific and effective CaMKII inhibitors as therapeutic agents for cardiac arrhythmias is challenged by the tremendous complexity of CaMKII expression and distribution of multi isoforms, as well as the multitude of downstream targets in the CaMKII signaling pathways and regulatory processes. A systematic understanding of the structure and regulation of the CaMKII signaling and functional network under the scope of genome and phenome may improve and extend our knowledge about the role of CaMKII in cardiac health and disease and accelerate the discovery of new CaMKII inhibitors that target not only the ATP-binding site but also the regulation sites in the CaMKII signaling and functional network.

The fast pace of progress in the field of Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) signaling in cardiac physiology and pathophysiology has highlighted the importance of this Ca²⁺-regulated protein kinase in the electrical and contractile activity of the heart [1,2]. It is now known that activation of CaMKIIs has pivotal impacts on many regulatory processes of cellular functions ranging from membrane potentials and electric–contraction (E-C) coupling to mitochondrial integrity and survival of cardiomyocytes [2–4]. Accumulated experimental data and clinical observations have consistently shown that CaMKII expression and activity are elevated under stressed conditions of different functional and structural heart diseases in animal models and human patients [1–10]. Both

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cytosolic CaMKII δ C and nuclear CaM-KII δ B were significantly increased in both right and left ventricles of patients with dilated or ischemic cardiomyopathy [11]. Abnormal activation of CaMKII also happens when signaling pathways upstream to CaMKII (e.g., increased activity of catecholaminergic or renin–angiotensin–aldosterone systems) are excessively activated [12–14]. Since CaMKII up-regulation plays a critically important role in the pathologic remodeling of the heart, it is conceivable that down-regulation of CaMKII may serve as a therapeutic strategy for the treatment of heart diseases. In fact, it has been shown that inhibition of CaMKII can prevent pathologic myocardial remodeling and protect against structural heart disease [15]. Clinically, both β blockers and angiotensin-converting enzyme (ACE) inhibitors are proven to ameliorate myocardial hypertrophy and heart failure, and down-regulation of CaMKII has been implicated in a part of the mechanisms of the beneficial effects [11]. CaMKII inhibitors (KN-93 and AIP) significantly improved contractility in human failing myocardium [11].

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Recent studies also suggest that up-regulation of CaMKII in the heart may be responsible for oxidative stress-induced cardiac arrhythmias [6,16–23]. Down-regulation of CaMKII may have antiarrhythmic effects [6,24]. In this issue of *Trends in Cardiovascular Medicine*, Hund and Mohler 25. provided a timely review of recent advances in the study of functional role of CaMKII in cardiac arrhythmias. As summarized in this excellent review, up-regulation of CaMKII may contribute to the genesis of arrhythmias in conditions with increased oxidative stress such as ischemic heart disease through changes in the regulation of several ion channels, including the voltage-gated Na⁺, K⁺, and Ca²⁺ channels; K_{ATP} channels; and Cl[−] channels. Specially, they highlighted the recent advances in the study of CaMKII regulation of the late Na current (I_{Na-L}), its role in cardiac arrhythmias, and the potential as a new therapeutic target of the CaMKII for antiarrhythmias. The rationale for down-regulation of CaMKII and thus I_{Na-L} activity is well supported by the fact that positive feedback loops between increases in I_{Na-L} and the elevated CaMKII activity may be responsible for the ischemia-induced arrhythmias [16,25].

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As a Ca²⁺ signal transducer situated at a converging point for multiple signaling pathways, CaMKII occupies the key position in the network of cellular mechanisms that are known to induce myocardial hypertrophy, heart failure, and cardiac arrhythmias. The beneficial effects of CaMKII down-regulation on mitigating various heart diseases and arrhythmias in animal models and human patients stimulated the interests of the pharmaceutical industry to develop CaMKII inhibitors as safe and effective therapeutic agents in the treatment of cardiac arrhythmias, heart failure, and other forms of cardiac disease involving oxidative stress. However, as indicated in the review by Hund and Mohler [25], to date, approaches to targeting the CaMKII molecule for antiarrhythmic benefit have been unsuccessful with very few drugs available for specific inhibition of CaMKIIs. The tremendous complexity of CaMKII expression and distribution of multi isoforms, as well as the multitude of downstream targets in the CaMKII signaling pathways and regulatory processes, is unquestionably the most important factor limiting the progress in the field [25–27]. CaMKIIs have a total four isoforms (α , β , δ , and γ) of serine/threonine kinases, and CaMKI δ is the predominant isoform in the heart. CaMKI δ has two splice variants: CaMKI δ B and CaMKI δ C [2–4,28,29]. CaMKI δ B contains an 11 amino acid nucleus localization signal that

is absent from CaMKI δ C. Thus, CaMKI δ B is mainly localized in the nucleus and modulates gene transcription and hypertrophic growth, while CaMKII δ C is mainly localized in cytosol and cell membrane and modulates ion channels and Ca²⁺ handling molecules in the E-C coupling machinery of cardiac muscle. Both CaMKII δ B and CaMKII δ C are activated by the binding of Ca²⁺/calmodulin to the regulatory region, which triggers the autophosphorylation at Thr286/287 and causes the conformational change and frees the catalytic region to transfer phosphate from ATP to substrates. The first generation of CaMKII inhibitors is targeting on ATP binding to its catalytic site to prevent activation [27]. The recent availability of crystal structures of CaMKII in the auto-inhibited and activated states, and of the dodecameric holoenzyme, provides insights into the mechanism of action of existing inhibitors. The accumulated structural information of CaMKII regulation will also provide foundations not only for the rational design and optimization of CaMKII-specific inhibitors but also for novel design strategies to develop the future generation of CaMKII inhibitors that extend beyond ATP-binding sites and target at sites of regulation by Ca²⁺/calmodulin or translocation to some of its protein substrates. Novel therapeutic approaches may also target at selective CaMKII isoforms and splice variants. A recent study reported that CaMKII δ β and CaMKII δ C are selectively susceptible to autophosphorylation/oxidation and that augmented generation of autophosphorylated CaMKII δ B (P-CaMKII δ B) (Thr287) is associated with arrhythmia suppression in the female heart, supporting the potential benefit of selective CaMKII splice form targeting and the necessity of gender-selective CaMKII intervention strategies in the treatment of cardiac arrhythmias.

The development of new specific and effective CaMKII inhibitors as therapeutic agents for cardiac arrhythmias and other forms of heart disease also faces the challenge that activated CaMKII can phosphorylate a wide array of proteins and affect a multitude of downstream targets in the signaling network and cellular functions. Therefore, a systematic understanding of the CaMKII signaling and functional network under the scope of genome and phenome is urgently needed to improve and extend our knowledge about the role of CaMKII in cardiac health and disease [30].

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