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Ca^{2+}/Calmodulin-dependent Protein Kinase II in Heart Failure

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Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CaMKII) is now recognized to play a central role in myocardial biology and disease. CaMKII appears to grade myocardial performance and regulate heart rate (HR) by catalyzing the phosphorylation of major proteins involved in cardiac excitation-contraction coupling. Under pathological stress, CaMKII activates hypertrophic and inflammatory transcriptional pathways and promotes apoptosis. Animal studies suggest that CaMKII inhibition may be an effective approach for treating common forms of structural heart disease.

Introduction

Heart failure (HF) is a global burden, with the lifetime risk in the developed world above 20% and a consuming focus for patients, clinicians, scientists, and policymakers. Aggressive control of hypertension and treatment of MI, the two primary causes of HF in the developed world, have reduced the incidence of myocardial hypertrophy and the mortality of myocardial infarction (MI). Yet, the net effect of such successes in the context of aging of the population and increased burden from risk factors such as diabetes, dyslipidemia, and obesity, is an increased incidence of HF [1]. Hypertension and MI, lead to systolic left ventricular dysfunction that converts to the clinical syndrome of HF when the cardiac output is inadequate to meet metabolic requirements. Failing myocardium is marked by electrical instability due to action potential prolongation that that favors arrhythmias and sudden death. Evidence now supports that pharmacological targeting of intracellular signaling [2], in particular CaMKII, a sensor of dysregulated Ca^{2+} homeostasis and redox, will inhibit conversion of early stages of cellular pathophysiology to symptomatic HF and sudden death.

CaMKII: An intelligent design

It hardly seems possible to design a better mediator of normal beat-to-beat cardiac function and adaptation to physiological needs than CaMKII, a unique ‘molecular device’. The ideal ‘device’ might detect HR and modify i) the strength of contraction so that blood would be pumped faster at higher HR in order to maintain sufficient ejection volumes; ii) stimulate rate of relaxation in diastole to accommodate elevated HR; iii) respond to stress and enable the “fight-or-flight” response commanded by adrenergic nerves by modifying cardiac

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rhythm; iv) over longer time periods would adjust cardiac gene expression with positive remodeling to increase the size and strengthen heart muscle.

Signal transduction in myocardium engages an array of broad specificity or multifunctional protein kinases such as protein kinase A (PKA), protein kinase C (PKC), and CaMKII, and it appears that CaMKII possesses many of the properties of the ideal signaling device for an excitable tissue. These properties are encoded in its structural design.

CaMKII: From the ground up

Four highly conserved isoforms of CaMKII (α, β, γ and δ) are widely expressed, with the δ isoforms predominating in heart. The functional domains of CaMKII enable it to i) catalyze a transfer of phosphate from ATP onto specific sites on select substrate proteins; ii) greatly increase its activity in response to cellular stimulation, via exposure to Ca^{2+} (complexed to CaM); ii) modify its level and persistence of activity based on the frequency and duration of Ca^{2+} spikes (e.g. to HR); iv) direct its localization in either a static or dynamic fashion. Figure 1A is a schematic of the catalytic domain of CaMKII with a 'gate' of the active site that keeps the kinase completely inactive until an increase in cellular free Ca^{2+} enables Ca^{2+}/CaM to wrap around its target sequence in the gate and pull it open. Not shown beyond this domain are sites for alternative splicing that produces isoforms with different Ca^{2+} sensitivity and intracellular targeting. Finally, there is an association domain that allows the kinase to assemble into a holoenzyme of twelve subunits.

A unique feature of CaMKII is that it is not only activated and deactivated with the rise and fall of Ca^{2+} with each heart beat, but can effect cardiac signaling based on HR and action potential duration (APD). It is sensitive to the frequency and duration of the Ca^{2+} spikes [4] based on cooperative inter-subunit autophosphorylation, a molecular switch that prolongs its activated state. Activated CaMKII autophosphorylates at Thr^{287} of CaMKIIδ (same as Thr^{286} on some isoforms) at a 'hinge' of the autoinhibitory gate (Fig. 1A). Addition of the phosphate residue disables the inhibitory gate so the kinase can't deactivate until dephosphorylated. It becomes autonomous of Ca^{2+}/CaM.

This regulation is 'usurped' by a similar molecular switch, oxidation by reactive oxygen species (ROS) of two methionine residues ($Met^{281}Met^{282}$ in CaMKIIδ) just preceding the critical Thr^{287}, which similarly disrupts the inhibitory domain to generate a persistently activate or autonomous activity [5]. Following activation by Ca^{2+}/CaM, the activity of the oxidized kinase persists without Ca^{2+}/CaM or an autophosphorylated Thr^{287}, until reversed by the action of methionine sulfoxide reductase.

Proteins kinases, such as CaMKII, PKA, and PKC, are multifunctional, i.e. they orchestrate diverse cellular responses to hormones via their second messengers by virtue of many key functional proteins that they phosphorylate. For cardiac CaMKII these include phospholamban, the type 2 ryanodine receptor (RyR2), and L-type Ca^{2+} channel (LTCC). CaMKII signaling is further enhanced by static and dynamic targeting to specific intracellular sites or by tethering to anchoring proteins. For example, one cardiac isoform, δ_B (or δ_3) [6], contains a spliced sequence that targets it to the nucleus where it can regulate expression mRNA for structural and other proteins that promote hypertrophy [7,8].

Dynamic targeting occurs by exposure of an anchor binding site upon displacement of the inhibitory domain by Ca^{2+}/CaM (Fig. 1B) and autophosphorylation (and perhaps oxidation). For example, targeting to T-tubules [9] likely occurs by autophosphorylation-dependent translocation to the LTCC (δ_C; [10]), which it phosphorylates and regulates [11]. Less is understood mechanistically about its targeting to SR via RyR2 (δ_C; [12]), and the IP3 receptor on the nuclear membrane (δ_B; [13]).

CaMKII can be a force for good

The properties of CaMKII may be ideal for dynamic regulation of fundamental cardiac functions in response to low or high metabolic needs. Positive attributes of CaMKII are exemplified by its orchestrated effects on LTCC in facilitation and of Na^+ channels in the "fight-or-flight" response [14]. CaMKII is responsible for "facilitation" of peak Ca^{2+} influx and slowed inactivation of the Ca^{2+} current seen in physiological responses such as the 'treppe' phenomenon and function in parallel with its activation of RyR2 to couple heart rate with contractile force [15,16]. Ca^{2+} entry via the LTCC triggers an amplified release of Ca^{2+} into the cytoplasm from the sarcoplasmic reticulum that activates the kinase and induces its attachment to the LTCC which it then phosphorylates [17]. This facilitates Ca^{2+} current during subsequent heart beats by shifting channel gating to frequent long openings [15]. This, coupled with HR dependent phosphorylation of RyR2 by CaMKII [16], increases the force of contraction so that sufficient blood can be pumped despite the shorter duration of the cardiac cycle at high HR. CaMKII completes this adaptation by speeding diastolic relaxation. It increases rate of re-uptake and sequestration of Ca^{2+} into SR by frequency-dependent activation of the Ca^{2+} ATPase [19].

The automaticity of the sinoatrial node (SAN) sets the basic HR that is increased via β-AR stimulation, and recent evidence implicates CaMKII in mediating approximately half of this increase [14]. The prevailing explanation that invoked signaling via cAMP and the cyclic nucleotide-gated ion channel (HCN4) to depolarize the cell by an inward pacemaker current (I_f) has been challenged by the finding that up-regulation of HR in response to exercise or β-adrenergic agents persists in HCN4 knock-out animals [20,21]. The I_f-independent pathway is mediated by CaMKII via coordination of SAN Ca^{2+} homeostasis. The CaMKII pathway does not appear to regulate basal HR, but mediates the chronotropic β-AR response by enhancing SR Ca^{2+} filling, diastolic SR Ca^{2+} release, and the diastolic depolarization rate.

Too much of a good thing?

It is perhaps not surprising that the role of CaMKII in fundamental processes in excitation-contraction coupling and β-AR mediated response to stress and exercise also positions it to participate in disease. Hyperactivity of the enzyme due to changes in Ca^{2+} homeostasis and redox can elicit pathophysiological responses such as early after depolarizations (EADs), ventricular dilation with abnormal contractile function and proarrhythic electrical remodeling [17]. Experimentally, this was first noted by a variety of animal models in which constitutively activated CaMKII was introduced or its endogenous level manipulated [22]. Physiological states leading to hyperactivation of the kinase trigger proarrhythmic and proapoptotic signaling. Indeed, CaMKII level and activity are increased in failing human myocardium and in animal models of HF [23,22].

CaMKII is implicated in adverse left ventricular remodeling, the process leading to dilation and distortion of normal chamber size and architecture that disadvantage contractile function following MI and other forms of structural heart disease marked by neurohumoral activation. A mechanistic understanding of the link between β-AR stimulation as part of the neurohumoral activation and CaMKII come from a reevaluation of the dogma associating β-AR and cAMP signaling. It turns out that in parallel with β-AR signaling via cAMP and its downstream effects, there is a Ca^{2+}-linked pathway initiated preferentially by the β_1-AR, whose sustained activation leads to increased free Ca^{2+} and SR Ca^{2+} overload that produce a CaMKII mediated apoptosis [24]. CaMKII appears to associate preferentially with the β_1-AR [25] in a novel complex with β-arrestin and Epac (exchange protein directly activated by cAMP) that couples increased cAMP to CaMKII activation. A genetic animal model in which mice express a peptide inhibitor of CaMKII designed based on its autoinhibitory domain exhibits protection from structural heart disease induced by excessive β-AR and MI

[26]. Inhibition of CaMKII largely prevents cardiac hypertrophy, dilation and dysfunction while preserving the β-AR contractile responses. The findings are consistent with animal models showing that overexpression of CaMKII produce features of remodeling in heart failure, such as myocardial dilation and dysfunction of Ca^{2+} homeostasis. The findings suggest that a therapeutic approach based on inhibition of CaMKII could share the beneficial effect of β-AR antagonists, but preserve the inotropic response to catecholamines.

Additional CaMKII-mediated processes are engaged by neurohumoral activation in heart disease. The pathologically stressed heart is subjected to increased ROS, e.g. via angiotensin II. ROS prolongs the state of CaMKII activation via oxidation of $Met^{281}Met^{282}$ and like excessive β-AR stimulation of CaMKII leads to apoptosis [5]. ROS produces a facilitation of LTCC that is independent of Ca^{2+} influx but requires Ca^{2+} increase via SR and activation of CaMKII [27]. Interestingly, the effect was blocked by a small molecule inhibitor, KN-93, typically used to dissect CaMKII involvement but unlike Ca^{2+}-dependent facilitation, was insensitive to substrate-mimetic peptide inhibitors of the kinase. ROS also produces increased APD and EADs that involved a reduction in I_{Na} and an increase in I_{Ca}, two processes induced by activated CaMKII. ROS induced EADs were suppressed by pharmacological inhibition of CaMKII [28]. Finally, chronic involvement of β-AR signaling is accompanied by up-regulation of the Ca^{2+}-Na^{+} exchanger (*Ncx1*). This effect requires CaMKII, as it is absent in the CaMKIIδ_C null mouse [29].

Excessive activation of CaMKII can underlie arrhythmia and HF, a condition characterized by increased high activity Ca^{2+} channel gating (mode 2), SR Ca^{2+} leak and dysregulated Ca^{2+} homeostasis, EADs, and accelerated cardiomyocyte death [18]. Such hyperactivity can occur with prolonged action potential duration due to genetic causes (long QT syndrome), structural heart disease, and exposure to drugs that inhibit K^{+} channels. This produces a feed-forward effect whereby increased Ca^{2+} influx further increases the kinase that in turn increases facilitation of the LTCC [15]. The kinase modifies several K^{+} channels either directly (acute) or via changes in gene expression (chronic), further broadening the AP and is therefore proarrhythmic [30]. In contrast, CaMKII inhibition increases cell membrane expression of some K^{+} channels leading to action potential shortening [31]. Higher Ca^{2+} influx due to facilitation and APD promotes SR Ca^{2+} overload and EADs and oscillations in membrane potential that can induce arrhythmia [22].

Failing human cardiomyocytes express higher levels of both CaMKII and a regulatory subunit isoform (β_{2a}) of the LTCC that is targeted by CaMKII [32]. β_{2a} markedly increase the opening probability of the pore forming α subunit ($Ca_V1.2$). Expression of β_{2a} produces many of the hallmarks of activated LTCC in heart failure cardiomyocytes—increased $Ca_V1.2$ opening, SR Ca^{2+} leak and action potential prolongation, leading to activation of CaMKII and apoptosis involving CaMKII [18]. The predominant mode of regulation of LTCC by CaMKII involves binding to a site on the β_{2a} subunit that positions it for phosphorylation of Thr^{498} [11]. Regulation of opening probability of the channel is ablated by mutation of this Thr^{498} to a non-phosphorylatable Ala^{498} residue. The proarrhythmic and proapoptopic pathway involving CaMKII, phosphorylated β_{2a} subunit, and increased I_{Ca} is demonstrated by the finding that the β_{2a} subunit is necessary for EAD induction and that premature cell death due to overexpression of the β_{2a} subunit is obviated by mutation of the CaMKII binding site on the β_{2a} subunit or of the Thr^{498} phosphorylation site [18].

The key role for the δ-isoform in modulating heart function and development of HF in response to pressure overload was demonstrated by genetic knock-out of CaMKIIδ, with minimal change in the other isoforms [33,34,3]. A germline knock-out is viable because the kinase is not critical for basal cardiac structure and function. The knock-outs confirm that HDAC4 (which is responsible for transmitting some CaMKII effects on hypertrophic gene

expression), phospholamban (at Thr^{17}) and the RyR2 (at Ser^{2815}) are phosphorylated by CaMKII. The role of CaMKII in pressure overload was modeled by transverse aortic constriction (or aortic banding) that increases the work of ejecting blood from the heart and resembles a clinically artificial scenario, acute-onset severe aortic valve stenosis. Aortic banding for 6 weeks [34] produced a clear left ventricular dilation and conversion to heart failure in wild-type mice but the knock-outs were spared. Surprisingly, both wild-type and knock-out displayed myocardial hypertrophy and induction of hypertrophic proteins at an early stage of aortic banding (2 weeks) [34]. Although CaMKII also produces hypertrophy, the effect in the knock-outs may be due to a normal or compensatory effect of a distinct protein kinase termed PKD or the CaMKII γ isoform. Neither in these animals, nor in human subjects, does hypertrophy on its own always convert to HF, and in rodents, at least, such a transition appears to require CaMKIIδ. The relationship of left ventricular hypertrophy to systolic heart failure remains incompletely defined.

HF is associated with Ca^{2+} overload and elevated diastolic Ca^{2+} due to a higher frequency of SR Ca^{2+} sparks (elementary sarcoplasmic reticulum Ca^{2+} release events due to opening of a few ryanodine receptors). This appears to be due to phosphorylation of the RyR2, potentially by CaMKII [35]. HF is also associated with a blunted force-frequency relationship, which may be due to a reduced HR dependent phosphorylation of RyR2 due to a CaMKII in failing myocardium that is highly autonomous of Ca^{2+} [16].

CaMKII is expressed at higher levels in atrial fibrillation patients and mice overexpressing $CaMKII\delta_C$ are prone to arrhythmias in heart failure that appears to be due to the SR Ca^{2+} leak [36]. Atrial myocytes from AF patients had a higher level of autophosphorylated CaMKII that led to phosphorylation of Ser^{2814} on RyR2 [37]. Furthermore, there is a larger size and frequency of Ca^{2+} sparks compared to patients in normal sinus rhythm under conditions of normal Ca^{2+} load. In addition to implicating CaMKII by association, the study found that elevated diastolic Ca^{2+} in AF patients could be normalized to the level seen in sinus rhythm normal patients by pharmacological inhibition of CaMKII.

The level and activity of CaMKII is increased several fold in human HF and several animal models of HF. HF is associated with increased risk of ventricular tachyarrhythmia, fibrillation, and sudden death that may be due to altered Na^+ channel gating. Here too, CaMKII may participate in the pathology, as it associates with and phosphorylates Na^+ channels to alter gating and reduce channel availability at high HR [38].

Approaches to therapeutic intervention with CaMKII

There is an unmet need for new therapeutic approaches that target the conversion of the underlying cellular pathophysiology and structural changes of the failing myocardium to the later symptomatic HF and sudden death. Efforts to date have primarily targeted cell surface receptors and ion channels that control blood pressure and chronotropic and inotropic regulation of the heart. Recent data point to intracellular signaling under the control of an alphabet soup of protein kinases that modify diverse cellular functions [2]. In particular, targeting CaMKII, a unique sensor of both Ca^{2+} and the redox state, may enable more selective control of dysfunctional signaling. Pharmacologically, inhibition could be achieved by direct reduction of kinase activity with a small molecule (or potentially a peptide) that blocks binding of ATP, protein substrates, or Ca^{2+}/CaM or indirectly by inhibiting essential targeting to anchors and substrates. It may also be possible to develop inhibitors that shift its sensitivity to the frequency of Ca^{2+} spikes, i.e. to reduce its activation at a given HR while still allowing its graded activation.

Summary and Conclusions

CaMKII is involved in multiple aspects of heart failure and arrhythmias. Based on a cellular and animal studies, CaMKII is now a validated target for treating clinically common forms of heart disease, including heart failure and arrhythmias. Although unproven clinically, animal models of CaMKII inhibition suggest that targeted reduction of CaMKII activity can result in preserved physiological function but resistance to maladaptive responses to disease stress that lead to heart failure and arrhythmias. A concept for developing new CaMKII-based therapies is outlined.

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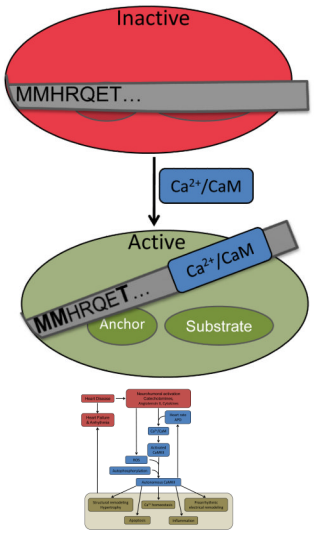

Figure 1.

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activation is potentiated by autophosphorylation and oxidation to effect key processes in the evolution of heart failure. (A) Ca^{2+}/CaM binds and displaces the kinase inhibitory domain to activate the kinase, exposing its substrate binding site (Substrate) to promotes catalysis as well as a site (Anchor) by which it tethers to some proteins. Kinase activity is made autonomous of Ca^{2+} signaling and thus potentiated by either oxidation of two methionine residues (**M**et^{281}**M**et^{282}) or a critical threonine (**T**hr^{287}) that may serve as a 'wedge' to keep the inhibitory 'gate' open. (B) Hypertension and myocardial infarction (MI) initiate neurohumoral signaling that excessively activate CaMKII and phosphorylation of key substrates that elicit structural and electrical remodeling and apoptosis that promote transition to symptomatic heart failure, arrhythmia and sudden death. (Modified from [3])