Published in final edited form as:

Heart Rhythm. 2011 January ; 8(1): 142–144. doi:10.1016/j.hrthm.2010.07.029.

Role for CaMKII in cardiovascular health, disease, and arrhythmia

Peter J. Mohler^{1,2} and Thomas J. Hund¹

¹ Department of Internal Medicine, Division of Cardiovascular Medicine, University of Iowa Carver College of Medicine, Iowa City, IA 52242

² Department of Molecular Physiology & Biophysics, University of Iowa Carver College of Medicine, Iowa City, IA 52242

Keywords

calmodulin kinase II; calcium signaling; electrophysiology arrhythmogenesis; heart failure

The past decade has seen the emergence of CaMKII as a critical regulator of cardiac function. Moreover, mounting evidence indicates that CaMKII is an important mediator of the heart's response to stress. Increasingly, it is apparent that CaMKII is an important nodal point for translating neurohumoral activity to progression of disease and increased susceptibility to arrhythmias. Considering the large number of intracellular substrates for CaMKII, it comes as no surprise that dysfunction in CaMKII signaling has deleterious consequences for heart function. However, despite the findings of hundreds of studies over the past decade, a fundamental question still remains: What are the central roles of CaMKII in cardiovascular function, and how are these roles affected in disease? As the introduction to a new *Heart Rhythm* viewpoint mini-series on CaMKII function in heart, this summary will provide an overview of key focus areas in CaMKII cardiac biology.

CaMKII is a multifunctional serine/threonine kinase with diverse roles in heart. Substrates for the kinase include ion channels, transporters, and accessory proteins in the sarcolemmal and sarcoplasmic reticulum membranes, sarcomere contractile machinery, transcription factors, and signaling molecules (including CaMKII itself) (Figure 1). The large and diverse array of intracellular CaMKII substrates allows for the kinase to regulate a broad range of cellular functions from excitation-contraction coupling to gene transcription to apoptosis. Studies from mouse to human have identified a strong link between CaMKII function and disease. In fact, it has been known for over ten years that CaMKII expression is altered in human heart failure¹. Exciting recent studies using transgenic and knock-out mice have implicated CaMKII in structural remodeling following myocardial infarction as well as the development of hypertrophy and/or heart failure in response to pressure overload (aortic banding)^{2–4}. CaMKII δ (CaMKII γ is also expressed in heart) has also been linked to electrical remodeling following myocardial infarction, as well as atrial and ventricular arrhythmias. The cellular mechanisms through which CaMKII regulates heart structure,

Address correspondence to: Thomas J. Hund, Department of Internal Medicine, University of Iowa Carver College of Medicine, 285 Newton Road, CBRB 2283, Iowa City, IA 52242, Tel:(319) 335-9679, FAX:(319) 353-5552, thomas-hund@uiowa.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

electrical activity and function are less clear. CaMKII has been implicated in regulating both apoptotic and gene transcription pathways, which undoubtedly play important roles in the remodeling process following myocardial insult. Furthermore, CaMKII likely promotes the formation of after depolarizations and arrhythmias through its targeting of sarcolemmal ion channels (e.g. L-type Ca^{2+} channels, Na^+ channels) and/or Ca^{2+} cycling proteins (e.g. sarcoplasmic reticulum (SR) ryanodine receptor Ca^{2+} release channels, phospholamban). A major question for future research is identification of the cellular pathways through which CaMKII affects heart structure and function in ischemic and non-ischemic cardiomyopathy. Moreover, is there a targeted fashion by which the deleterious effects of CaMKII on heart function can be blocked?

Considering the strong association between CaMKII and disease, it is logical to ask: What benefit, if any, does the cell derive from expressing CaMKII? It is unlikely that CaMKII has evolved as simply a pro-disease/arrhythmia molecule in the heart. Mounting evidence support an important role for CaMKII in mediating the heart's "fight-or-flight" response to beta-adrenergic stimulation. For example, transgenic mice expressing a CaMKII inhibitory peptide display a blunted increase in heart rate in response to isoproterenol treatment⁵. Yet, CaMKII δ knockout mice show normal heart function at baseline and improved function in response to aortic banding^{2, 4}. Thus, transient CaMKII activation in response to stress may activate systems to increase heart rate and contractility. However, chronic activation, as in disease, leads to further damage in a perpetuating negative cycle. Is CaMKII, then, a vestigial molecule in the human heart, a remnant from an earlier time-point in evolution where acute stress and not coronary artery disease presented a greater threat? If so, can we safely pharmacologically ablate CaMKII activity in vulnerable patients while minimizing potentially negative side effects?

This is undoubtedly an exciting time for CaMKII biology. Recent studies from several groups (many of whom are represented in this view-point mini-series) have identified critical intracellular targets for CaMKII that link the kinase to new roles in health and disease. The known family of CaMKII substrates includes voltage-gated Ca^{2+} channels, Na^+ channels, K^+ channels, transcription factors and accessory proteins and continues to grow each year (Figure 1). Novel pathways for CaMKII activation have been identified. New causal roles for CaMKII in disease and arrhythmias have been discovered. As we look forward, one must wonder whether it will be possible to isolate a single regulatory event responsible for an observed cell or organ phenotype? Moreover, how is CaMKII localized to each of its many targets? Are specific CaMKII microdomains differentially regulated in disease and can specific CaMKII microdomains be differentially targeted to treat disease? Will we uncover human arrhythmia mutations that block/augment CaMKII regulation of a substrate? This *Heart Rhythm* mini-series aims to provide unique insight into some of these complex issues surrounding CaMKII signaling in heart and will address the following major themes.

Cardiac membrane excitability is dictated by the activities of key membrane ion channels. Thus, the first theme in this mini-series will address the molecular mechanisms and functional consequences of CaMKII regulation of several of these critical membrane ion channels (Drs. Pitt, Maier, Nerbonne). One clear example of the key role of CaMKII in regulation of membrane excitability is regulation of the primary voltage-gated sodium channel, Nav1.5. Dr. Lars Maier (Georg-August-University; Gottingen, Germany) will review literature on how CaMKII phosphorylation alters voltage-gated Na^+ channel activity. In addition to regulation of cardiac voltage-gated sodium channels, CaMKII has also been linked with voltage-gated calcium channel activity. In fact, several CaMKII phosphorylation sites have been identified on the alpha and beta subunits of voltage-gated Ca^{2+} channels^{6, 7}. Moreover, CaMKII phosphorylation increases L-type Ca^{2+} channel mode 2 gating

characterized by long mean open times thereby increasing the likelihood of potentially life-threatening after depolarizations. In his view-point, Dr. Geoffrey Pitt (Duke University, Durham, NC) will provide insight into the multi-faceted roles of CaMKII for calcium channel function at excitable myocyte membranes. While other ion channels (e.g. L-type Ca^{2+} channels) have been the focus of more intense study, it is clear that both acute and chronic CaMKII activity can alter the activity and/or expression of K^{+} channels important for action potential repolarization. Namely, CaMKII has been shown to regulate $\text{Kv}4.2/4.3$ responsible for transient outward K^{+} current (I_{to}) as well as $\text{Kir}2.1$ that carries the inward rectifier K^{+} current (I_{K1})^{8, 9}. The importance for these pathways in disease remains an area of active study, and is the topic of Dr. Jeanne Nerbonne's (Washington University, St. Louis, MO) view-point article in this mini-series.

A second focus topic of this mini-series will be in the area CaMKII regulation of Ca^{2+} cycling from the sarcoplasmic reticulum (Drs. Wehrens and Kranias). Regular cycling of intracellular calcium between SR and cytosolic compartments is critical for normal heart function. CaMKII is known to regulate several proteins involved in Ca^{2+} release from SR Ca^{2+} stores and reuptake during relaxation. Specifically, CaMKII phosphorylates ryanodine receptor SR Ca^{2+} release channels to alter channel open probability, which has been implicated in creating "leaky" RyR channels in heart failure, as well as atrial fibrillation. In a complementary role, phospholamban interacts with the SR Ca^{2+} ATPase to control Ca^{2+} reuptake into the SR. CaMKII phosphorylation of phospholamban at a specific threonine residue (T17) interrupts this interaction and increases Ca^{2+} uptake into the SR. In their view-point articles, Dr. Xander Wehrens (Baylor College of Medicine) and Dr. Evangelia Kranias (University of Cincinnati) will review past findings linking CaMKII with SR calcium regulation in normal cardiac physiology and in human and animal cardiovascular disease.

Notably, CaMKII not only regulates coupling between membrane excitability and cell contraction (excitation-contraction coupling) but also coupling between cardiomyocyte activity and gene transcription (excitation-transcription coupling). Furthermore, the cardiac hypertrophic response has been linked to activation of alternative gene expression profiles. CaMKII regulates gene transcription via MEF2- and NFAT-dependent transcription, providing a plausible mechanistic link between myocardial insult, altered gene expression, and chronic remodeling. Dr. Donald Bers' (UC Davis) view-point will identify the mechanisms for CaMKII regulation of excitation-transcription coupling as well as the consequences for heart function and disease.

Finally, studies from multiple groups have identified an association between CaMKII and heart disease, suggesting that CaMKII signaling may provide a unique opportunity for the development of novel therapies. Thus, the final theme of the mini-series will be CaMKII function in the diseased heart (Drs. Mark Anderson, Joan Heller Brown, Silvia Priori and Carlo Napolitano). CaMKII is activated by Ca^{2+} /CaM under normal conditions. However, in the setting of heart disease there are multiple neurohumoral and oxidizing agents that may produce an overactive kinase. Dr. Anderson (University of Iowa) will discuss our current knowledge regarding the relevant pathways and likely mechanisms for dysfunctional CaMKII activity in disease. Increased CaMKII activity has been linked to SR Ca^{2+} leak through RyR SR Ca^{2+} release channels and arrhythmias. Drs. Priori and Napolitano (New York University/University of Pavia) will discuss a potential role for CaMKII in a specific arrhythmia, catecholaminergic polymorphic ventricular tachycardia, characterized by abnormal RyR Ca^{2+} release channel activity, spontaneous SR Ca^{2+} release and lethal ventricular arrhythmias following beta-adrenergic stimulation. Finally, it is well documented that CaMKII expression is increased in human, mouse, and large animal models of heart failure. Dr. Heller Brown (UC San Diego) will discuss the evidence linking CaMKII to the development of hypertrophy and heart failure.

We hope that this *Heart Rhythm* mini-series on CaMKII biology in heart will convey the extent to which recent advances have impacted the prevailing view of heart function in normal and diseased settings. As should be clear, while we have learned a great deal about the many roles of CaMKII in heart, important questions remain. Perhaps the most important question going forward is will these (and future) advances in the laboratory translate into improved therapies for the clinic.

Acknowledgments

Funding

This work was supported by the National Institutes of Health (HL096805 to TJH; HL084583 and HL083422 to PJM), the Pew Scholars Trust (PJM), and a Fondation Leducq Award to the Alliance for Calmodulin Kinase Signaling in Heart Disease.

References

1. Hoch B, Meyer R, Hetzer R, Krause EG, Karczewski P. Identification and expression of delta-isoforms of the multifunctional Ca^{2+} /calmodulin-dependent protein kinase in failing and nonfailing human myocardium. *Circulation research* 1999;84:713–721. [PubMed: 10189359]
2. Backs J, Backs T, Neef S, et al. The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. *Proceedings of the National Academy of Sciences of the United States of America* 2009;106:2342–2347. [PubMed: 19179290]
3. Zhang R, Khoo MS, Wu Y, et al. Calmodulin kinase II inhibition protects against structural heart disease. *Nat Med* 2005;11:409–417. [PubMed: 15793582]
4. Ling H, Zhang T, Pereira L, et al. Requirement for Ca^{2+} /calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. *The Journal of clinical investigation* 2009;119:1230–1240. [PubMed: 19381018]
5. Wu Y, Gao Z, Chen B, et al. Calmodulin kinase II is required for fight or flight sinoatrial node physiology. *Proceedings of the National Academy of Sciences of the United States of America* 2009;106:5972–5977. [PubMed: 19276108]
6. Grueter CE, Abiria SA, Dzhura I, et al. L-type Ca^{2+} channel facilitation mediated by phosphorylation of the beta subunit by CaMKII. *Mol Cell* 2006;23:641–650. [PubMed: 16949361]
7. Erxleben C, Liao Y, Gentile S, et al. Cyclosporin and Timothy syndrome increase mode 2 gating of $\text{CaV}1.2$ calcium channels through aberrant phosphorylation of S6 helices. *Proceedings of the National Academy of Sciences of the United States of America* 2006;103:3932–3937. [PubMed: 16537462]
8. Li J, Marionneau C, Zhang R, et al. Calmodulin kinase II inhibition shortens action potential duration by upregulation of K^{+} currents. *Circulation research* 2006;99:1092–1099. [PubMed: 17038644]
9. Wagner S, Hacker E, Grandi E, et al. Ca/calmodulin kinase II differentially modulates potassium currents. *Circ Arrhythm Electrophysiol* 2009;2:285–294. [PubMed: 19808479]

Figure 1. CaMKII targets diverse intracellular substrates to regulate heart function

CaMKII targets critical sarcolemmal ion channels important for cell excitability including voltage-gated Na⁺ channels (Na_v1.5), L-type Ca²⁺ channels (Ca_v1.2, α, δ and β-subunits), as well as repolarizing currents Kv4.3 (transient outward K⁺ current, I_{to}) and Kir2.1 (inwardly rectifying K⁺ current, I_{K1}). CaMKII also regulates SR Ca²⁺ release and reuptake via direct phosphorylation of RyR2 SR Ca²⁺ release channels and phospholamban (PLB). In the nucleus, CaMKII phosphorylates HDAC5, a repressor of MEF2, to regulate transcription of hypertrophic gene program.