CaMKII functions as a local calcium sensor in the heart. At baseline, the autoinhibitory domain prevents substrate binding to the enzyme. In cardiac myocytes, intracellular Ca\(^{2+}\) rises because of transmembrane influx through L-type Ca\(^{2+}\) channels (\(I_{\text{Ca}}\)) or the Na/Ca exchanger and release from internal stores such as the sarcoplasmic reticulum (SR). When intracellular Ca\(^{2+}\) rises, it binds to the EF-hand motifs at the N- and C-terminals calmodulin, an \(\approx 150\) amino acid ubiquitous intracellular protein. The Ca/CaM complex then binds to the regulatory domain of CaMKII and removes the inhibition of the autoinhibitory domain. Of note, activated CaMKII can be autophosphorylated at Thr287, which allows the enzyme to remain in the active state in the absence of an elevated intracellular Ca\(^{2+}\). Ultimately, dephosphorylation by intracellular protein phosphatases returns the enzyme to the inactive state.

A number of cellular targets for CaMKII have been identified using in vitro expression systems, CaMKII inhibitors in vivo, and transgenic mice. Nuclear CaMKII\(\delta\) activates a hypertrophic program via transcription factors such as CREB directly by phosphorylation and MEF2 indirectly by phosphorylating class II histone deacetylases to release its inhibition. Cytoplasmic CaMKII\(\delta\) associates with the L-type Ca\(^{2+}\) channel to allow Ca\(^{2+}\)-dependent facilitation (an increase in \(I_{\text{Ca}}\) at increased stimulation frequencies) and phosphorylates the ryanodine receptor to increase SR leak. Thus, CaMKII activation can affect intracellular Ca\(^{2+}\) and alter its own activity.

Transgenic mice overexpressing of either CaMKII\(\delta_2\) or CaMKII\(\delta_3\) in the heart develop a dilated cardiomyopathy, with the phenotype being more severe for the cytoplasmic isoform. Transgenic overexpression of the CaMKII inhibitory peptide AC3-I, on the other hand, improves cardiac function and Ca\(^{2+}\) handling following myocardial infarction, protects against isoproterenol-induced hypertrophy and LV dysfunction, decreases phospholamban (PLN) phosphorylation at Thr17 and SR Ca\(^{2+}\) load, increases basal \(I_{\text{Ca}}\), and eliminates Ca\(^{2+}\)-dependent facilitation. Thus, CaMKII lies downstream from and parallels activation by the \(\beta\)-adrenergic nervous system, suggesting that CaMKII blockade may have beneficial effects similar to \(\beta\)-adrenergic blockers. In addition, CaMKII overexpression alters Ca\(^{2+}\) handling and ion channels in a way that would promote afterdepolarizations and arrhythmias. In a calcineurin overexpression mouse heart failure model, CaMKII suppression by KN93 reduces spontaneous arrhythmias, whereas CaMKII suppression by overexpression of AC3-I improves LV function and suppresses arrhythmias in Langendorff-perfused hearts.

In the current issue of Circulation Research, Li et al study in detail the electrical remodeling in transgenic mice overexpressing the CaMKII inhibitory peptide AC3-I. Transgenic mice have shorter action potential durations (APDs) and QT intervals despite increased \(I_{\text{Ca}}\) because of upregulation of the inward rectifier current \(I_{\text{Kr}}\) and the transient outward current \(I_{\text{to}}\), with no significant changes in channel RNA or protein expression. These electrophysiological changes result from chronic AC3-I overexpression and are not reversed by modification of PKA activity or mimicked by transient treatment of wild-type myocytes with AC3-I. Of note, the remodeling is eliminated when the AC3-I mice are crossed with PLN knockout mice, demonstrating that CaMKII-mediated alterations in PLN and, presumably, SR Ca\(^{2+}\) uptake/release are required for the electrical remodeling.

These findings extend our understanding of electrical remodeling in the heart. Most animal models and human studies of heart failure show APD prolongation because of decreases in outward K\(^+\) currents (usually \(I_{\text{Kr}}\) and \(I_{\text{to}}\)) or changes in \(I_{\text{Ca}}\) and its inactivation. APD prolongation could prolong \(I_{\text{Ca}}\) and preserve contractile force, although it increases the risk of triggered arrhythmias and could contribute to Ca\(^{2+}\) overload. The study by Li et al demonstrates that CaMKII inhibition at physiologically relevant levels can upregulate repolarizing K\(^+\) currents. This raises the possibility that manipulations that inhibit CaMKII could both improve ventricular function and reverse maladaptive electrical remodeling.
remodeling in conditions such as heart failure. In other words, CaMKII inhibition may be antiarrhythmic in a way analogous to β-adrenergic blockade.

The mechanism by which CaMKII inhibition leads to increased K+ current expression is unknown. The absence of any change in RNA or protein levels suggests either an increase in surface expression or a posttranslational modification that increases current. CaMKII inhibition and changes in SR Ca2+ dynamics could modify a previously unrecognized ion channel, ion channel β subunit, binding protein or chaperone. Alternately, changes in CaMKII and SR Ca2+ handling could lead to posttranslational modifications in the ion channels themselves directly via mechanisms such as phosphorylation or indirectly via changes in adrenergic activity. Whereas Li et al showed that acute manipulations of PKA do not affect repolarizing current levels, they did not rule out the possibility that more chronic changes may have an impact. It is also possible that an unrecognized effect of the transgene could lead to the phenotype by a circuitous route, and it will be important to document similar findings in another model system.

A number of other questions also remain unanswered. It is not clear which CaMKII isoform is responsible for the major physiological effects. Similarly, the source of Ca2+ responsible for enzyme activation, the role of local changes in intracellular [Ca2+], and the importance of rapid versus slow changes in intracellular [Ca2+] are unknown. The applicability of finding in the mouse to those in larger animals and humans is uncertain. Direct relevance to prevention of arrhythmias and sudden death in a clinically relevant model needs to be shown.

In summary, Li et al have identified an unexpected feedback regulation involving CaMKII, PLN, and sarcolemmal K+ channels in the mouse. The mechanisms underlying this regulation will be important to discern. Time will tell, however, whether the findings can be applied to the arrhythmogenic human heart.

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References


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