Timothy syndrome is a rare genetic disorder characterized by QT prolongation (designated LQT8), arrhythmias and sudden death, structural heart disease, cognitive defects with autism, syndactyly (webbed fingers and toes), hypoglycemia, and immune deficiencies.1,2 A single mutation (G406R) in exon 8a of the cardiac L-type calcium channel (CACNA1C, Ca,1.2, α1c) was shown to cause Timothy syndrome in multiple unrelated subjects, whereas mutations (G406R, G402S) in the alternatively spliced exon 8 (which is expressed at ∼3-fold–higher levels than exon 8a) cause a similar syndrome lacking syndactyly.3,4 These 3 mutations decrease voltage-dependent inactivation of Ca1,2, which is predicted to slow the inactivation of ICa,L during each action potential, prolong action potential and QT interval duration, increase the amplitude and duration of Ca2+ transients, and predispose to afterdepolarizations and arrhythmias.3–5

The CaMKII inhibitory peptide AC3-I have shorter action potential durations and QT intervals as a result of upregulation of the inward rectifier current IK1 and the transient outward current Ito,f, with no significant changes in channel RNA or protein expression.11 CaMKII expression may also play a role in heart failure. Transgenic mice overexpressing CaMKII in the heart develop dilated cardiomyopathy.12 CaMKII suppression by KN93 or by overexpression of the CaMKII inhibitory peptide AC3-I eliminates Ca2+-dependent facilitation, improves cardiac function, and suppresses arrhythmias in a calcineurin overexpression mouse heart failure model or after myocardial infarction.13,14

In this issue of the Circulation, Thiel et al used isolated rat cardiomyocytes infected with dihydropyridine-resistant wild type and G406R Ca1,2 channels to study the mechanisms underlying proarrhythmia in Timothy syndrome.15 As expected, myocytes infected with mutant G406R channels had action potential prolongation, afterdepolarizations, and decreased voltage-dependent inactivation. In addition, the Timothy syndrome mutation increased CaMKII autophosphorylation, enhanced ICa,L facilitation, and slowed ICa,L inactivation. Of note, inhibition of CaMKII with the AC3-I inhibitory peptide normalized action potential duration, prevented afterdepolarizations, and normalized ICa,L facilitation and inactivation. Moreover, myocytes infected with mutant channels had larger but briefer Ca2+ transients, no change in SR Ca2+ content, and an increase in Ca2+ spark frequency. The authors concluded that although changes in voltage-dependent inactivation may initiate the cardiac abnormalities in Timothy syndrome, downstream changes mediated by CaMKII on Ca2+-dependent facilitation and SR Ca2+ release channels (ryanodine receptors) are required for the arrhythmia phenotype.

The findings by Thiel et al are potentially important for several reasons. First, the mechanistic link between changes in ICa,L and arrhythmia susceptibility in Timothy syndrome appears more complex than previously thought. Second, this is the first evidence that CaMKII directly participates in arrhythmia susceptibility in a human inherited channelopathy. Third, although Timothy syndrome is rare, abnormalities in Ca2+ handling may cause arrhythmias and sudden death in common cardiac conditions including heart failure.12–14 CaMKII-mediated changes in ICa,L facilitation and ryanodine receptor leak can be studied in these other pathological states.
and the potential efficacy of CaMKII inhibition can be assessed. Finally, the findings raise the intriguing possibility that CaMKII-related proteins may contribute to the extracardiac phenotypes including autism.

A number of additional studies are required to confirm the conclusions. As pointed out by the authors, the findings need to be replicated in myocytes from a larger animal with cardiac action potentials more similar to those of humans. Although canine wedge studies have been performed using the Ca$^{2+}$ channel opening drug BayK8644 to model increases in I_{Ca,L},¹⁶ additional studies using intact hearts and whole animal models expressing mutant channels are necessary. In addition, long-term expression of the mutation may lead to different findings than short-term viral exposure, as seen with the effects on K$^+$ channel expression caused by transgenic overexpression of the AC3-I peptide.¹¹ Studies using G406R Ca$_{1.2}$ knockin mice could address many of these questions.

During the last 15 years, ion channelopathies have been shown to cause a number of inherited arrhythmia syndromes, including long-QT syndrome (K$^+$, Na$^+$, and Ca$^{2+}$ channels), short-QT syndrome (K$^+$ channels), Brugada syndrome (Na$^+$ channels), short-QT and Brugada syndrome (Ca$^{2+}$ channels), and catecholaminergic polymorphic ventricular tachycardia (SR Ca$^{2+}$ release channels).¹⁷ Given the importance of I_{Ca,L} to cardiac electrical and mechanical function, it is surprising how few pathogenic mutations have been identified. Two potential causes could underlie this finding: Mutations could be rare because they are highly lethal, or they could be only rarely identified because they are well tolerated. The evidence suggests that both may be true. Marked increases in I_{Ca,L} occur as a result of physiological β-adrenergic stimulation; similarly, L-type Ca$^{2+}$ channel blockers are well tolerated but do not prevent arrhythmias or sudden cardiac death despite decreasing intracellular Ca$^{2+}$ load. The mutations that lead to Timothy syndrome are all located in the 8th exon and all affect voltage-dependent inactivation. Similarly, only a few mutations characterized by marked loss of Ca$^{2+}$ channel function have been identified in individuals with an overlap syndrome consisting of short-QT intervals and Brugada-like ECG abnormalities.¹⁸ Thus, it is possible that whereas modest changes in the amplitude of I_{Ca,L} are well tolerated, changes in its time course disrupt important signaling mechanisms including CaMKII and are poorly tolerated. If true, heterozygous mutations that alter channel number or current amplitude would have a limited phenotype, whereas rare mutations that alter channel properties in specific ways would lead to highly lethal arrhythmia syndromes.

In summary, the study by Thiel et al has expanded our understanding of the pathophysiological mechanisms underlying Timothy syndrome. In addition, it may ultimately provide new insights into the role of CaMKII in arrhythmia susceptibility, into Ca$^{2+}$ handling in other organs including the brain, and into the regulatory pathways that are controlled by cardiac Ca$^{2+}$ channels. In addition, at least some hope exists that these findings could ultimately lead to novel therapeutic options to treat or prevent life-threatening arrhythmias.

Disclosures

None.

References


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