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Calcium Cycling Proteins and Their Association With Heart Failure

L Hadri[1] and **RJ Hajjar**[1]

[1]Cardiovascular Research Center, Mount Sinai School of Medicine, New York, New York, USA

Abstract

Heart failure (HF) has reached epidemic proportions in the United States and is one of the most important challenges to public health. Severe congestive HF is associated with substantial morbidity and mortality. HF afflicts approximately 5 million patients and contributes to 3 million hospitalizations and 300,000 deaths yearly.[1] Late-stage HF has a poor prognosis, and therapeutic options are limited. Defective excitation–contraction (EC) coupling in HF may result from altered density or function of proteins relevant for Ca^{2+} homeostasis.

EC COUPLING

EC coupling is the process of electrical excitation of myocytes leading to contraction of the heart. EC coupling consists of processes involved in Ca^{2+} activation of contractile proteins and the subsequent removal of calcium, thereby facilitating relaxation. During the cardiac action potential, Ca^{2+} enters through L-type Ca^{2+} channels that trigger Ca^{2+} release from the sarcoplasmic reticulum (SR) through ryanodine receptors (RyRs). The resulting rise in intracellular calcium concentration causes sarcomeric shortening and muscle contraction.[2] Ca^{2+} reuptake into the SR through SR Ca^{2+}-ATPase (SERCA2a) and, via sarcolemmal Na^{+}/Ca^{2+} exchanger, lowers intracellular Ca^{2+} concentration, thereby causing dissociation of Ca^{2+} from troponin C and resulting in cardiac relaxation (Figure 1).[2] Alterations in EC coupling play a critical role in the pathophysiology and electrical remodeling in human HF. This review focuses on the contributions of abnormal calcium cycling protein handling to the deterioration of ventricular myocyte contractility in the failing heart.

Alteration of protein calcium cycling in HF

The pathophysiologic effects of altered calcium homeostasis result from either an upregulation or a downregulation of calcium cycling proteins; these effects are categorized as ventricular remodeling or electrical remodeling, a series of arrhythmogenic effects that involves prolongation of both the duration of the action potential and the Ca^{2+} signal.[2] The most notable EC coupling abnormalities are (i) a decrease in the Ca^{2+} re-entry mechanism

Correspondence: RJ Hajjar (roger.hajjar@mssm.edu).

CONFLICT OF INTEREST

R.J.H. is the scientific cofounder of Celladon, with plans to commercialize AAVI–SERCA2a for the treatment of heart failure. L.H. declared no conflict of interest.

into SR, predominantly regulated by the activity of SERCA2a, and (ii) dysregulated SR Ca^{2+} release from RyRs (Figure 1).

β-Adrenergic receptors

Cardiac sympathetic function plays an important role in the regulation of heart function and has been studied extensively in recent decades. The human heart expresses two subtypes of adrenergic receptors (ARs): β1 and β2.[3] Both subtypes can couple to stimulatory G proteins to activate adenylyl cyclase, increase cyclic adenosine monophosphate (cAMP) production, and activate protein kinase A (PKA). PKA phosphorylates at least three key Ca^{2+} regulators: (i) L-type Ca^{2+} channels, (ii) RyR, which enhances Ca^{2+} influx and increases the velocity and the amplitude of SR Ca^{2+} release and therefore the contractility, thereby mediating the inotropic and chronotropic effects of βARs,[4] and (iii) phospholamban (PLB; in serine 16), which relieves SERCA2a inhibition and contributes to SR Ca^{2+} reuptake, thereby mediating the lusitropic effect of βARs.[5] The β1AR subtype is implicated in dysfunction of the adrenergic system in HF.[6] Studies in mice have shown that overexpression of β1ARs causes early hypertrophy and interstitial fibrosis, followed by marked cardiac dysfunction with aging.[7,8] By contrast, transgenic mice overexpressing β2ARs at higher absolute levels did not develop cardiomyopathy with age.[9] Moreover, adenovirus-mediated overexpression of β2ARs resulted in improved ventricular function and functional recovery of unloaded HF in a rabbit model.[10] β2 agonists have also been shown to have a beneficial effect on left ventricular (LV) remodeling after myocardial infarction in a rat model.[4] Furthermore, stimulation of cardiac myocytes with β2-agonists appeared to provide protection against apoptosis.[11] The reported differences between the effects of β1- and β2-receptor overexpression are remarkable. Given that both subtypes activate cAMP signaling, the observed differences must be due to nonclassical, receptor-specific pathways such as β2-receptor coupling to protein G (Gαi) and mitogen-activated protein kinases. In addition, compartmentation of cAMP signaling may be responsible for differences between β1- and β2-receptor-generated cAMP.[6] Moreover, the remaining βARs are desensitized in the failing heart because of increased levels of G-protein-coupled receptor kinase activity. Inhibition of upregulated G-protein-coupled receptor kinase activity has been proposed as a therapeutic strategy for HF.[6]

RyR

RyR2 is a macromolecule complex; its phosphorylation level is most likely caused by changes in the local complex of kinases (PKA, Ca^{2+}-calmodulin-dependent protein kinase (CaMKII)), phosphatases (PP1 and PP2A), and phosphodiesterase 4D3.[6] Alteration in RyR2 and associated molecules can cause functional and/or structural changes in the heart, leading to HF and sudden cardiac death. Marks and colleagues reported that chronic hyperphosphorylation of RyR2 on serine 2809 by PKA is characterized by dissociation of calstabin 2 from RyR, followed by instability of RyR2.[12] This results in a diastolic SR Ca^{2+} leak that depletes the SR of Ca^{2+} and contributes to impaired contractility. Indeed, mice engineered with RyR2 lacking the PKA phosphorylation site are protected from HF progression after myocardial infarction.[13] Recently, a mouse model mimicking chronic PKA hyperphosphorylation of RyR2 demonstrated the mechanism through which β-blockers improve cardiac function in HF.[14] It has been suggested that in failing hearts chronic PKA

hyperphosphorylation can be sustained by reducing levels of phosphatase and phosphodiesterase 4D3 within the RyR2 complex.[6] Phosphodiesterase 4D deficiency in the RyR complex promotes HF and arrhythmias.[15] Finally, several groups have shown that CaMKII is also critical for RyR phosphorylation on serine 2814/2815, which leads to the SR Ca^{2+} leak.[6] CaMKII expression and activity are upregulated in human HF and in animal models.[6] The absence of CaMKIIδ significantly attenuated the development of pressure overload-induced HF and improved survival, cardiomyocyte apoptosis, and fibrosis. These findings suggest that CaMKIIδ-mediated changes in Ca^{2+} handling, including phosphorylation of RyR2 at the CaMKII site and increased Ca^{2+} leak in the diastolic SR, underlie the decompensation process from cardiac hypertrophy to HF.[16] There is ongoing debate over the relative importance of PKA as compared with CaMKII in the regulation of RyR2 in the heart.

SERCA2a

In healthy human hearts, 75% of Ca^{2+} is removed by SERCA2a and ~25% by the Na^{+}/Ca^{2+} exchanger. The small size and slow decay of Ca^{2+} transient in the failing heart has been shown to be related to reduced Ca^{2+} transport by SERCA2a.[17] Abnormal Ca^{2+} handling in failing hearts is caused, in part, by decreases in SERCA2a mRNA, protein, and/or activity in animal models and also in HF in humans regardless of the etiology of the HF.[17] Restoration of SERCA2a expression and increasing the activity level of SERCA2a in experimental models of HF have received a great deal of attention in the past few years, by our group and others. Improved contraction and accelerated relaxation of the heart have been shown in mice overexpressing cardiac SERCA2a.[18] In neonatal rat cardiomyocytes with normal or depressed SERCA2a expression, adenovirus-mediated transfer of SERCA2a resulted in enhanced SR Ca^{2+} uptake and accelerated decay of Ca^{2+} transients.[19,20] Furthermore, catheter-based transfection with adenovirus encoding SERCA2a restored LV cardiac function in rats that were in transition to HF.[21,22] In addition, SERCA2a gene transfer restored energetic functions and decreased ventricular arrhythmia in a rat model of ischemia and improved LV mechanical and energetic functions in diabetes-induced HF in rats.[22,23] Long-term overexpression of SERCA2a achieved by slow, selective intracoronary infusion of adeno-associated virus serotype 1 (AAV1) and AAV6 carrying SERCA2a resulted in successful transduction (increased SERCA2a protein and mRNA levels), improved ventricular remodeling, preserved systolic function, and increased coronary blood flow in an overload model of HF[24,25] and also in an ischemic model of HF[26] in swine. A major advantage of SERCA2a overexpression is its ability to exert beneficial effects on heart function with both long- and short-term expression. Two clinical trials using AAV encoding SERCA2 are under way: CUPID (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) and a phase II, randomized, double-blinded, placebo-controlled study, started in 2007, that is using AAV1–SERCA2a (Mydicar; Celladon, La Jolla, CA) in patients with congestive HF. The results of the phase I study showed an acceptable safety profile with an improvement of LV function and remodeling.[27,28] In the phase II trial, 39 patients with advanced HF were randomized to receive an intracoronary low dose (6×10^{11} DNase-resistant particles), middle dose (3×10^{12} DNase-resistant particles), or higher dose (1×10^{13} DNase-resistant particles) of AAV1–SERCA2a or a placebo. At 6 months, the patients who received AAV1–SERCA2a demonstrated

improvement or stabilization in NYHA class, MLWHFQ, 6MWT, VO_2 max, NT-proBNP levels, and LV end-systolic volumes. Significant increases in time to adjudicated cardiovascular events and a decreased frequency of cardiovascular events per patient were observed to be associated with AAV1–SERCA2a. No increases in adverse events, disease-related events, laboratory abnormalities, or arrhythmias were observed in patients treated with AAV1–SERCA2a relative to those who received placebo.[17] Other clinical trials to study the effects of overexpression of SERCA2a include one in the United Kingdom in patients with ischemia who have been put on an LV assist device using AAV6–SERCA2a or saline and a phase II single-center, double-blind, randomized placebo-controlled, parallel study that will be carried out at the Institute of Cardiology Pitié-Salpêtrière, Paris, France, with the primary objective of investigating the impact of AAV6.CMV–SERCA2a on cardiac remodeling parameters in patients with severe HF.[29]

PLB

PLB is an SR protein containing 52 amino acids that associates with SERCA2a and inhibits the Ca^{2+} transport rate of SERCA2a in its unphosphorylated state, whereas PLB phosphorylation by either PKA or CaMKII reverses this inhibition.[6] An increase in PLB/SERCA2a stoichiometry, the basal level of PLB phosphorylation, or the ability of βARs to mediate PLB phosphorylation could contribute to a decrease in SR Ca^{2+} concentration and therefore Ca^{2+} homeostasis in HF. In failing hearts, the phosphorylation levels of PLB at serine 16 and threonine 17 are decreased.[6] Using transgenic and gene transfer approaches, increasing the levels of PLB relative to SERCA2a in isolated cardiomyocytes has shown a significant alteration in intracellular Ca^{2+} mobilization and prolongation of the relaxation phase of the Ca^{2+} transient, decrease in Ca^{2+} release, and increase in resting Ca^{2+} concentration.[6,17] On the other hand, inhibition of the effects of PLB is a promising approach to target the Ca^{2+} handling pathway in HF. Indeed, decreasing PLB expression by gene transfer of a dominant negative PLB mutant in a large animal HF model or by PLB knockout mice, PLB antisense RNAs, and intracellular inhibitory PLB antibodies has been shown to prevent the development of HF and to restore cardiac function[5]; these effects can be attributed to increased SERCA2a activity and a higher SR Ca^{2+} load. Successful treatment of HF was recently demonstrated in a rat model of aortic banding by RNA interference targeting PLB. RNA interference against PLB for long-term treatment in an HF animal model using rAAV9 showed that PLB protein concentration was decreased significantly, resulting in restoration of cardiac function and reduction in pathological hypertrophy, dilation, and fibrosis.[30] These findings support the notion that targeting PLB can enhance cardiac contractility. PLB ablation also provided evidence that targeting PLB may rescue HF by increasing SR Ca^{2+} uptake and enhancing contractile performance.[31] Recently, it has been reported that CaMKII-TG–PLB-KO crossbred mice demonstrated enhanced SR Ca^{2+} uptake through PLB ablation; improvements were also reported in myocyte Ca^{2+} transients in transgenic mice with CaMKII-mediated HF. However, the KO–TG mice showed exaggerated HF, with a more rapid onset of lethality and a further decrease in contractile function. The enhanced SR Ca^{2+} content exacerbates the already high level of diastolic Ca^{2+} spark activity, potentially increasing arrhythmias and further worsening overall heart function.[32] The data are consistent with the hypothesis that, in the face of

phosphorylation-activated RyR2 channels, depletion of Ca^{2+} stores through PLB ablation or during sympathetic activation can exacerbate the SR Ca^{2+} leak, thereby increasing mitochondrial Ca^{2+}-mediated cell death or activating other Ca^{2+}-dependent processes that contribute to cardiac dysfunction.[32] Moreover, PLB mutations that do not directly influence the PLB–SERCA interaction may indirectly contribute to the development of HF.[6] Also, human mutations encoding a premature stop codon (with no detectable PLB protein) were reported to cause hypertrophy in heterozygous individuals and severe dilated cardiomyopathy in homozygous individuals.[6] Another PLB mutation (deletion of arginine in position 14) was identified in a family suffering from severe HF and was subsequently shown to encode a super-inhibitory PLB.[33] These findings demonstrate that, in contrast to mice (in which PLB deficiency enhances myocardial function without adverse effects), PLB is essential for cardiac health in humans, and its absence results in lethal HF.

Protein phosphatase Inhibitor 1 (I-1)

I-1, a ubiquitously expressed 28-kDa protein, is a potent and highly specific inhibitor of phosphatase 1 (PP1) activity when it is phosphorylated by cAMP-dependent PKA. In the heart, I-1 has been associated with Ca^{2+} homeostasis and contractile function. In particular, upon stimulation of the β-adrenergic axis, PKA phosphorylates threonine 35 in I-1, resulting in PP1 inhibition and amplification of the contractile response.[34] I-1 has been shown to be markedly downregulated in the failing human heart; this finding is consistent with increased PP1 activity and decreased PLB phosphorylation.[35,36] Overexpression of the PP1 catalytic subunit in mice demonstrated significantly decreased phosphorylation of PLB and depressed cardiac function.[36] Ablation of I-1 was associated with depressed basal cardiac function, and, in work-performing hearts, it was associated with a modest decrease in basal contractile parameters.[36] Cardiac-specific overexpression of a truncated, mutated, and constitutively active form of I-1 (I-1c; T35D) restored contractile properties in failing rat hearts[37] and in failing human cardiac myocytes under isoproterenol treatment.[36] Furthermore, infection of adult and neonatal rat cardiac myocytes with an adenovirus encoding the full-length I-1 was associated with a marked increase in PLB phosphorylation and cardiac contractility.[38] Recently, it has been shown that inducible expression of constitutively active I-1 enhances basal cardiac function and protects against ischemia/reperfusion injury in a mouse model.[39] These data suggest that increased I-1 activity enhances Ca^{2+} cycling and improves mechanical recovery as well as cell survival after an ischemic insult. However, a recent study reported that, although I-1c overexpression improved cardiac contractility in young mice at rest, it was deleterious and arrhythmogenic after adrenergic stress and with aging.[40]

In summary, dysregulation of Ca^{2+} cycling proteins plays an important role in the pathophysiology of HF. Therefore, the evolution of our understanding of HF and correction of calcium cycling proteins represents a major step toward new therapies. Reversal of HF by gene transfer was made possible through the interface between basic science and clinical investigations. Pursuing this collaborative process promises future progress in our ability to manage HF.

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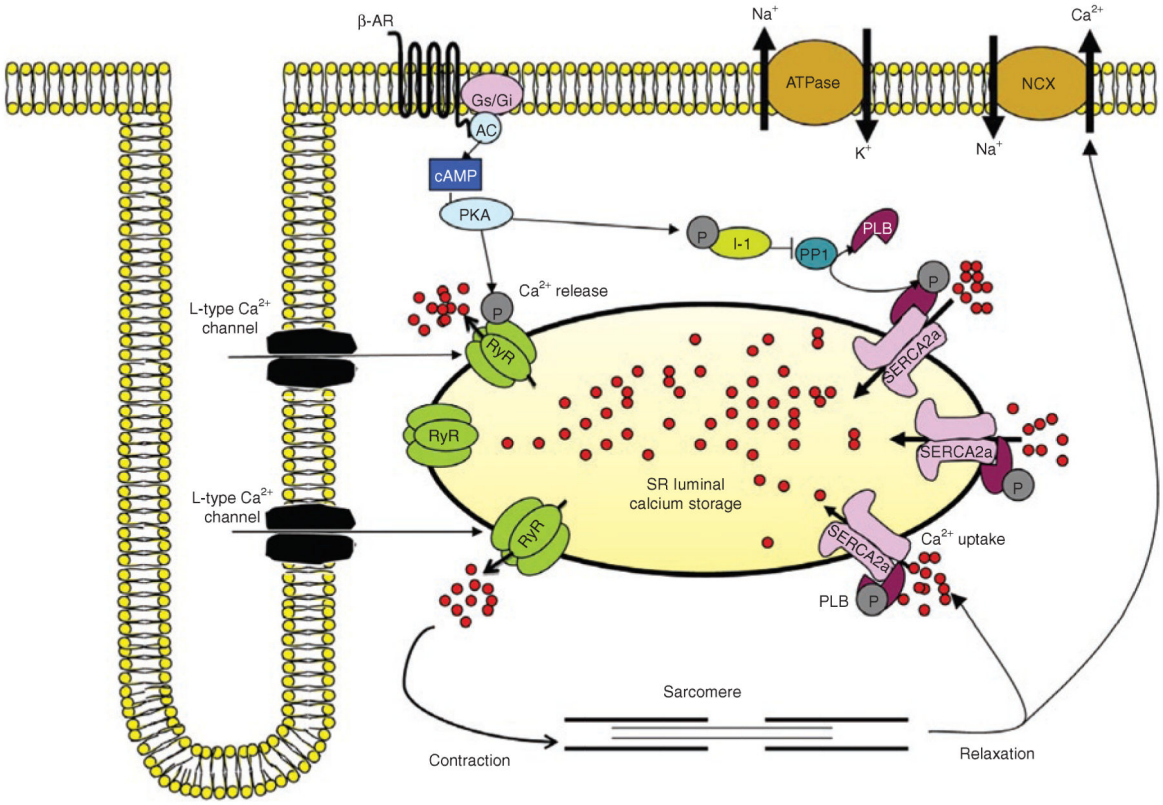

Figure 1.

Excitation-contraction signaling in cardiomyocytes. Ca^{2+} influx through L-type Ca^{2+} channels. AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; Gi, inhibitory G protein; Gs; stimulatory G protein; I-1, protein phosphatase inhibitor-1; NCX, sodium–calcium exchanger; PKA, protein kinase A; PLB, phospholamban; PP1, protein phosphatase 1; RyR, ryanodine receptor; SERCA2a, sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; β-AR, β-adrenergic receptor.