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Alterations in Ryanodine Receptors and Related Proteins in Heart Failure

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Abstract

Sarcoplasmic reticulum (SR) Ca^{2+} release plays an essential role in mediating cardiac myocyte contraction. Depolarization of the plasma membrane results in influx of Ca^{2+} through L-type Ca^{2+} channels (LTCCs) that in turn triggers efflux of Ca^{2+} from the SR through ryanodine receptor type-2 channels (RyR2). This process known as Ca^{2+}-induced Ca^{2+}release (CICR) occurs within the dyadic region, where the adjacent transverse (T)-tubules and SR membranes allow RyR2 clusters to release SR Ca^{2+} following Ca^{2+} influx through adjacent LTCCs. SR Ca^{2+} released during systole binds to troponin-C and initiates actin-myosin cross-bridging, leading to muscle contraction. During diastole, the cytosolic Ca^{2+} concentration is restored by the resequestration of Ca^{2+} into the SR by SR/ER Ca^{2+}-ATPase (SERCA2a) and by the extrusion of Ca^{2+} via the Na^+/Ca^{2+}-exchanger (NCX1). This whole process, entitled excitation-contraction (EC) coupling, is highly coordinated and determines the force of contraction, providing a link between the electrical and mechanical activities of cardiac muscle. In response to heart failure (HF), the heart undergoes maladaptive changes that result in depressed intracellular Ca^{2+} cycling and decreased SR Ca^{2+} concentrations. As a result, the amplitude of CICR is reduced resulting in less force production during EC coupling. In this review, we discuss the specific proteins that alter the regulation of Ca^{2+} during HF. In particular, we will focus on defects in RyR2-mediated SR Ca^{2+} release.

Introduction

Excitation-contraction (EC) coupling represents a signaling cascade that allows the cardiac action potential to trigger myocyte contraction.[1] Depolarization of the cardiomyocyte membrane leads to activation of voltage-gated L-type Ca^{2+} channels (LTCC) located in plasma membrane invaginations known as transverse (T)-tubules. Ca^{2+} influx through LTCC triggers a much greater release of Ca^{2+} from the sarcoplasmic reticulum (SR) via the ryanodine receptor type-2 (RyR2), a process known as Ca^{2+}-induced Ca^{2+} release (CICR). [2] This abrupt elevation in the cytosolic Ca^{2+} concentration allows Ca^{2+} to bind to troponin C, triggering the release of troponin I (TnI) from the myofilament, initiating contraction of cardiomyocytes. During muscle relaxation, cytosolic Ca^{2+} is actively pumped back into the

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SR via sarco/endoplasmic reticulum Ca^{2+-}ATPase 2a (SERCA2a) and extruded from cardiomyocytes via the Na^{+}/Ca^{2+} exchanger (NCX).[3, 4]

Heart failure (HF) is a major cause of morbidity and mortality in Western countries.[5] It is a physiological state in which cardiac output does not meet the demands of the body. Classically, systolic HF is caused by a reduction in ejection fraction and has higher mortality,, compared with HF with preserved ejection fraction.[6] In this review, we will focus on role of alterations in Ca^{2+} handling proteins in the pathogenesis of HF with reduced ejection fraction. In response to HF, the heart undergoes maladaptive changes that ultimately result in depressed intracellular Ca^{2+} cycling and decreased SR Ca^{2+} concentrations. Thus, subsequent action potentials lead to depressed CICR, releasing less Ca^{2+} and producing less force during EC coupling. Depressed CICR can result from a reduction in (1) trigger Ca^{2+} current through LTCC, (2) reuptake of Ca^{2+} into the SR, and/or (3) SR Ca^{2+} release through RyR2. Over time, these alterations contribute to reduced SR Ca^{2+} loading, and as such, interfere with the frequency-dependent enhancement of myocyte contractility. In this review, we discussed specific alterations in Ca^{2+} handling proteins associated with the pathogenesis of HF, with a focus on the complex pattern of alterations of RyR2 post-translational regulation during HF.

Regulation of ryanodine receptors during excitation-contraction coupling

RyR2 represents the primary channel mediating the intracellular Ca^{2+} release that triggers cardiomyocyte contraction during EC coupling.[7] This homotetrameric transmembrane protein with a molecular weight of 565-kDa per monomer is located on the SR membrane.[8] The amplitude of Ca^{2+} release via RyR2 is strongly modulated by second messengers (Ca^{2+}, Mg^{2+}, cAMP) and various intracellular proteins. One major regulatory subunit interacting with RyR2 is the 12.6-kDa cytosolic FK506-binding protein (FKBP12.6), also known as calstabin2.[9, 10] FKBP12.6, a peptidyl-prolyl *cis-trans* isomerase, tightly associates with RyR2, stabilizing its closed conformational state and facilitating channel closure.[11, 12] Other accessory proteins that bind to RyR2 and inhibit channel open probability include calmodulin and sorcin.[13, 14] Moreover, our studies have recently revealed that a structural protein junctophilin-2 (JPH2) also binds to RyR2 and inhibits its activity levels.[15]

Altered RyR2 regulation in HF

In addition to regulation by accessory and structural proteins, posttranslational modifications of RyR2, such as oxidation,[16, 17] S-nitrosylation,[18–20] and phosphorylation[21–23] have also been shown to regulate channel activity. The open probability of RyR2 is strongly regulated by protein kinases that phosphorylate distinct residues on the channel, and phosphatases that dephosphorylate RyR2 channel subunits. Several such enzymes are associated with the RyR2 channel macromolecular complex, including protein kinases A (PKA), Ca^{2+}/CaM-dependent protein kinase II (CaMKII), and phosphatases PP1 and PP2A allowing for rapid and selective regulation of the channel activity.[21, 22, 24, 25] Several studies have been conducted to determine the relative importance of each of these regulatory proteins, especially PKA and CaMKII, in modulating RyR2 activity in the failing heart.[26–31] Results of these studies are discordant regarding the relative importance of CaMKII versus PKA in modulating RyR2 activity. Our recent work suggests that this apparent discordance may be due to different pathophysiological mechanisms in ischemic versus non-ischemic HF.[ref 28] In the sections below, we have discussed in detail the current state of knowledge.

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Regulation of RyR2 by PKA Phosphorylation in HF

One of the first reported changes in RyR2 regulation associated with HF pathogenesis was altered PKA phosphorylation.[21] This discovery by the Marks lab has led to many related studies on phosphorylation-dependent regulation of RyR2 in healthy and diseased hearts. Many, but not all, studies have demonstrated increased phosphorylation of the main PKA phosphorylation site on RyR2, serine 2808 (S2808) in HF.[21, 26, 28, 32–36] Chronically increased S2808 phosphorylation on RyR2 may promote diastolic SR Ca^{2+} leak that, in turn, depletes SR Ca^{2+} stores and reduces EC coupling.[37, 38]

Recently, some new insights were obtained in genetically altered mice in which the S2808 site was either constitutively activated (S2808D) or genetically inactivated (S2808A). Shan *et al.* demonstrated that S2808D knock-in mice developed spontaneous HF and exhibited increased mortality after experimental myocardial infarction (MI), as a result of severe SR Ca^{2+} leak.[29] Conversely, it was shown that S2808A knock-in mice were relatively protected from the development of HF following experimental MI.[35] In contrast, another study showed that, although MI increased phosphorylation of RyR2 at the S2808 site, genetic inhibition of S2808 phosphorylation in S2808A mice did not protect mice from developing ischemic HF.[26] The reasons for these discrepant findings remain unknown at this time, although differences in the time-points chosen for the assessment of cardiac function after MI and differences in the size of the infarction may have contributed.

In contrast to the above findings, a recent study by Benkusky *et al.*[36] demonstrated that S2808A knock-in mice were not protected from non-ischemic HF due to pressure overload. Consistent with this finding, Respress *et al.*[28] showed that there was only a non-significant increase in S2808 phosphorylation on RyR2 in WT mice subjected to non-ischemic HF. In this particular model of non-ischemic HF caused by transverse aortic constriction, no significant changes were observed in the phosphorylation status of S2808 on RyR2, as well as the PKA phosphorylation site S16 on phospholamban (PLN). Consistent with these findings in animals, patients with non-ischemic dilated cardiomyopathy (DCM) also did not show increases in the phosphorylation status of S2808 on RyR2.[28] Thus, it seems that the potential involvement of S2808 phosphorylation on RyR2 in HF development may depend on the disease etiology, with current evidence suggesting that enhanced PKA-dependent phosphorylation of S2808 on RyR2 may only play a role in the development of *ischemic* HF.

Regulation of RyR2 by CaMKII in HF

In addition to PKA, RyR2 channels are also phosphorylated by CaMKII, which primarily phosphorylates a nearby site (serine 2814) on RyR2.[22, 27] Hoch *et al.* were among the first group of scientists to demonstrate increased expression of the CaMKII-δ_C isoform in cardiac muscle of patients with HF.[39] Following this report, Zhang *et al.* showed that cardiac-specific overexpression of CaMKII-δ_C in mice causes abnormal Ca^{2+} handling and development of HF.[40] Conversely, Zhang *et al.* showed that overexpression of AC3-I, a peptide inhibitor of CaMKII, delayed the onset of HF in mice following MI.[41] Various studies have demonstrated that increased RyR2 phosphorylation by CaMKII upregulation contributes to enhanced SR Ca^{2+} leak in HF.[37, 38, 42] The role of CaMKII phosphorylation of RyR2 in HF is further supported by the findings that pressure overload increases CaMKII phosphorylation of RyR2, enhances diastolic SR Ca^{2+} release events, and promotes HF in mice, and the fact that this phenotype can be reversed by genetic inhibition of CaMKII activity in CaMKII-δ deficient mice.[43, 44] These studies suggest a dominant role of abnormal CaMKII regulation of RyR2 in HF.

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Our recent studies provided additional insights into the importance of the S2814 phosphorylation site on RyR2 as a downstream target of CaMKII in HF. Respress *et al.*[28] demonstrated that patients with non-ischemic DCM, but not ischemic cardiomyopathy, exhibited increased levels of CaMKII phosphorylation of RyR2. Genetic inhibition of CaMKII phosphorylation of S2814 on RyR2 (S2814A) in mice protected against pressure overload induced non-ischemic HF but not against MI-induced ischemic HF.[28] Taken together, these studies identified RyR2 as a downstream target of CaMKII in HF and suggest that CaMKII phosphorylation of RyR2 is important in the pathogenesis of *non-ischemic* HF.[28]

Regulation of RyR2 by PP1 and PP2A in HF

The fact that RyR2 phosphorylation can be chronically increased in HF despite downregulation of β-adrenergic receptors raised the idea that RyR2 hyperphosphorylation might be the result of altered local signaling, rather than defective global cAMP and Ca/CaM-dependent signaling. Seminal by Marx *et al.* revealed that RyR2 is in fact a macromolecular channel complex that contains protein kinases (PKA, CaMKII) and protein phosphatases (PP1, PP2A) targeted to the pore-forming channel subunits.[21] Although PP1 and PP2A have similar catalytic mechanisms, substrate recognition mechanisms on RyR2 for PP1 and PP2A may be distinct. For example, Huke *et al.* showed that whereas PP1 can dephosphorylate both S2808 (the major PKA site) and S2814 (the major CaMKII site), PP2A can only dephosphorylate the S2814 site on RyR2.[45]

There is also emerging evidence that reduced PP activity may contribute to altered RyR2 phosphorylation levels in HF. For example, *Ai et al.* demonstrated reduced amounts of PP1 and PP2A within the RyR2 complex.[37] In addition, pharmacological inhibition of PP2A activity in cardiomyocytes results in hyperphosphorylation of RyR2 at site S2814, promoting diastolic Ca^{2+} release events.[46, 47] Together, these studies suggest that reduced PP1 and PP2A activity in the RyR2 macromolecular complex can underlie the abnormal Ca^{2+} handling seen in the failing heart.[46, 47] However, similar to the controversy regarding the role of PKA and CaMKII in the specific etiologies of HF, recent studies by Belevych *et al.* showed that levels of PP1A catalytic subunits did not change in a tachycardia-induced HF dog model, whereas both regulatory and catalytic subunits of PP2A were downregulated in this model.[46] This is in contrast to other studies which showed reduced protein levels and PKA phosphorylation of inhibitor-1 (I-1, an inhibitor of phosphatase-1) in human failing hearts, implicating the role of altered PP1 activity.[48] Overexpression of a truncated, constitutively active I-1 form reversed contractile dysfunction in previously failing myocytes.[49, 50] Moreover, genetic overexpression of I-1 in mice enhanced contractility, leading to an increase in RyR2 phosphorylation at S2814, but not S2808, and increased diastolic SR Ca^{2+} release events and arrhythmogenicity.[51]

In addition to PPs, cyclic nucleotide phosphodiesterases (PDEs) have also been identified in the RyR2 complex, where they regulate intracellular levels of cAMP and cGMP.[21] Within the cardiac PDE family, multiple isoforms are expressed varying in mechanistic action as well as subcellular location.[52] Of the six major classes, PDEs 2/3/4 regulate the activity of PKA through the hydrolyzing of cAMP.[53] Specifically, PDE4B mediates cAMP at the level of the plasma membrane,[54] while PDE3A and PDE4D are thought to directly regulate cAMP levels on the SR.[55] Therefore, these isoforms aid in the control of β-adrenergic stimulation, PKA-mediated phosphorylation of RyR2, and cardiomyocyte contraction.[33] In contrast, PDE4 inhibition increases the frequency of SR Ca^{2+} release,[33] and the incidence of atrial fibrillation upon β-adrenergic stimulation, suggesting that PDE is another critical regulator of RyR2 phosphorylation through cAMP/ PKA activation. Based on current literature, lack of PDE-mediated regulation of PKA through dysregulation of β-adrenergic receptor/cAMP compartmentalization also contributes to RyR2

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hyperphosphorylation, cardiac remodeling, and HF. Specifically, it has been shown that reduced levels of PDE4D3 in patients with HF may contribute to RyR2 hyperphopshorylation and channel defects.[33] In summary, the exact roles of PP1, PP2A, and PDE4 in RyR2 phosphorylation and HF pathogenesis remains to be elucidated, although emerging data suggest that the balance between kinase, phosphatase, and phosphodiesterase activity is altered in HF.

RyR2 and oxidation in HF

Redox signaling serves as another important posttranslational modulator of RyR2 open probability.[16, 17, 56] Each monomer of RyR2 contains roughly 90 cysteine residues, 20 of which are in a reduced state under normal conditions. Many of these cysteines are potential targets for various redox modifications, including S-nitrosylation, S-glutathionylation, and disulfide crosslinking.[18] Endothelial nitric oxide synthase (eNOS), which is localized to caveolae where it compartmentalizes with beta-adrenergic receptors and LTCC, allows NO to inhibit β-adrenergic-induced inotropy.[57–60] In contrast, neuronal NOS (nNOS) has an opposite, facilitative effect on contractility, wherein, it stimulates SR Ca^{2+} release via RyR2.[18, 19] This opposite effect is further evidenced by the observation that nNOS deficiency reduces inotropic response, whereas eNOS deficiency enhances contractility due to corresponding changes in SR Ca^{2+} release.[20] In addition to redox modulation by nitrosylation, cardiac SR is reported to contain NADH oxidase as well as NOX2 oxidase (that utilizes NADPH instead of NADH) both of which regulate the RyR2 complex under physiological conditions.[61–63]

In HF, a shift in the cellular redox potential creates a more oxidized state with increases in reactive oxygen species (ROS) and NO.[64–66] This shift in balance has a significant impact on SR Ca^{2+} handling proteins affecting EC coupling, in particular RyR2.[64–66] In the initial phases of HF, increases in NO levels may be an adaptive response to myocardial dysfunction, elevated cytokines, and increases in ROS.[64] This is evidenced by the observation that S-nitrosylation (>3 sites per monomer) leads to *reversible* RyR2 activation.[18] However, as HF becomes more advanced, oxidation of proteins supersedes nitrosylation. Whereas, nitrosylation is a reversible process, oxidation leads to *irreversible* activation (beyond a certain threshold).[18] Moreover, oxidation of reactive thiols induces cross-linking between RyR2 subunits resulting in channel activation that can be reversed by S-nitrosylation.[56] In addition, nNOS deficiency leads to an increase in ROS that may lead to oxidation of reactive thiols on RyR2.[67] Thus, whereas S-nitrosylation seems to control the basal redox state of the channel and is an adaptive process in initial stages of HF, oxidation is a pathological process found in advanced HF.[16] Finally, in addition to the direct effects of ROS on RyR2, oxidation can also activate RyR2 by means of CaMKII oxidation and activation.[68] Recent evidence suggests that CaMKII activity can be enhanced by methionine oxidation of M281/M282.[68] These findings highlight the complex and interdependent nature of various posttranslational modifications of RyR2 that can alter channel activity during HF. For more information regarding the role of oxidative stress in HF, please see the review article by Tsutsui *et al.*[69]

RyR2 and structural proteins in HF

Structural remodeling also plays an important role in the pathogenesis of HF.[70] One of the important aspects of structural remodeling at the cellular level is the remodeling of T-tubules, which can indirectly impact Ca^{2+} handling.[71] HF leads to a reduction in the overall density as well as irregularities in T-tubule patterning.[70, 72, 73] Specifically, the changes include an increase in longitudinal component and a reduction in the transverse component.[74] As indicated above, proper CICR is critical for contraction in cardiomyocytes. T-tubules ensure that LTCC and RyR2 are in close proximity to each other

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for optimal CICR. Disruptions in the dyadic distance leads to desynchronized CICR and a reduction in the force of contractility.[15, 70, 71, 74] An important role of T-tubule disruption in HF pathogenesis is also indicated by the fact that mechanical unloading reverses T-tubule remodeling and normalizes CICR in left ventricle in a rat model of ischemic HF as well as in right ventricle in a rat model of pulmonary artery hypertension.[70, 75] In addition to its effect on CICR, T-tubule disruption in HF also alters propagation of action potential further hampering EC coupling.[76] Recently, our lab and Wei *et al.*[15, 73] found that junctophilin-2 (JPH2), a structural protein, may be a critical mediator of T-tubule remodeling in HF. Our data revealed that an acute reduction in JPH2 levels lead to variability in dyadic distance, loss of EC coupling gain, resulting in aberrant SR Ca^{2+} leak through RyR2 and eventual HF development.[15] Complementary to our results, Wei et al showed that in early stages of heart failure in a rat model of HF, the T tubule disruption was accompanied by reduction in JPH2 levels.[73] Overall, there is strong evidence that alterations in T-tubule structure alter SR Ca^{2+} regulation and play an important role in the pathogenesis of HF. These structural changes are intertwined with electrical remodeling, and together, have become critical therapeutic targets for the treatment of HF. Current research is aimed at determining whether downregulation of JPH2 is in response to or an actual cause of HF.

L-type Ca^{2+} channels in HF

EC coupling in failing hearts can also be depressed due to altered regulation of the LTCC (CaV1.2) on the plasma membrane. The LTCC is composed of a pore-forming α_{1C} subunit and the auxiliary subunits β, $\alpha_{2\delta}$, and γ, which are involved in channel trafficking to the sarcolemma and modulation of the voltage-dependence of channel gating.[77, 78] While some investigators have reported an increase in $I_{Ca,L}$ in left ventricular hypertrophy and HF, others have demonstrated an unaltered or downregulated LTCC in HF.[78] This contradiction is evidenced by the fact that although the single-channel activity of LTCC is enhanced in failing heart, whole-cell current is unaltered.[79] A recent study showed that failing hearts have impaired Cav1.2 trafficking.[80, 81] These investigators demonstrated that `Bridging integrator 1' (BIN1), a membrane scaffolding protein that causes Cav1.2 to traffic to T tubules, is reduced in human failing cardiomyocytes. Hong *et al.* reported that although the total Cav1.2 was not changed in the failing heart, lack of BIN1 leads to reduced abundance of Cav1.2 channels in T-tubules that in turn reduces $I_{Ca,L}$.[81] In a more recent study, Goonasekera *et al.* showed that reduced LTCC led to a compensatory elevation in neuroendocrine stimulation and RyR2-mediated SR Ca^{2+} leak, which actually increased the gain of ECC.[82] This enhanced ECC gain resulted in pathologic cardiac hypertrophy and failure through calcineurin/nuclear factor of activated T cells (calcineurin/NFAT) signaling. Although these findings require further investigation, they suggest complex reciprocal signaling between the LTCC and intracellular pro-hypertrophic signaling pathways.

SERCA2a in HF

The cardiac isoform of SERCA (SERCA2a) controls the rate of cytosolic Ca^{2+} removal and the refilling of SR Ca^{2+} load in cardiomyocytes. Decreased expression and activity of SERCA2a leads to impaired SR Ca^{2+} uptake and reduced SR Ca^{2+} load in cardiomyocytes, which, in turn, compromises SR Ca^{2+} release and impairs cardiomyocyte contractility.[83] Reduced SERCA2a function is a hallmark of failing hearts and has been found in many experimental models of HF and end-stage HF patients.[83] Normalization of SERCA2a function has been shown to increase contractility and improve hemodynamics along with survival in rodent and large animal models of HF.[84–88] These animal studies have led to SERCA2a gene therapy that is currently being evaluated in a clinical trial.[83]

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The activity of SERCA2a is directly regulated by accessory subunits, including phospholamban (PLN) and sarcolipin (SLN). PLN, a small protein comprised of 52 amino acid residues, has proven to be the major inhibitory regulator of SERCA2a. Similar to the regulation of RyR2, PKA and CaMKII also play an important role in the regulation of PLN, as they can phosphorylate PLN at sites Ser16 and Thr17, respectively.[89, 90] In its dephosphorylated state, PLN exists predominantly as monomers that bind to and inhibit SERCA2a activity. On the other hand, phosphorylated PLN forms pentameric complexes, which have a lower affinity for SERCA2a, allowing for enhanced activity. The role of PLN in the pathogenesis of HF has been confirmed in animal models where inhibition of PLN restored SR Ca^{2+} load, delaying the progression of cardiac dysfunction and pathological remodeling.[90, 91] However, loss of PLN did not rescue other genetic mouse models of HF, questioning a causal association between the two.[92]

In addition to PLN, SLN, a 31-amino acid protein, also regulates SERCA2a activity.[93] SLN can bind to SERCA2a through PLN and cause a “superinhibition” of SERCA2a.[94, 95] Transgenic mice with cardiac-specific overexpression of SLN exhibit an impairment of cardiac contractility and ventricular hypertrophy, associated with a reduced amplitude and increased decay time of Ca^{2+} transients in isolated papillary muscle.[96] Moreover, mice lacking both PLN and SLN display increased SERCA2a pump activity, resulting in elevations in the amount of SR Ca^{2+} load and systolic Ca^{2+} transient.[97] However, over time, constitutive activation of SERCA2a in this mutant model becomes detrimental to cardiac function.[97] These findings suggest the importance of the dynamic regulation of SERCA2a by PLN and/or SLN in the maintenance of cardiac contractility under normal conditions and during pathological states.

Furthermore, the small ubiquitin-like modifier type 1 (SUMO1) has also been shown to regulate the activity of SERCA2a through a novel posttranslational modification, termed SUMOylation, which is thought to increase the intrinsic activity of SERCA2a ATPase.[98, 99] Kho *et al.* found that the level of SERCA2a and SUMO1 were reduced in animal models of HF and in failing cardiomyocytes isolated from HF patients.[99] In the same study, using a transverse aortic constriction-induced HF mouse model, the authors demonstrated that SERCA2a levels could be restored by increasing SUMO1 expression using gene transfer, thereby improving cardiac performance and decreasing mortality.

NCX1 in HF

Another membrane protein essential in Ca^{2+} homeostasis in cardiomyocytes is the Na^{+}/Ca^{2+}-exchanger type 1 (NCX1). During diastole, NCX1 removes 1 Ca^{2+} ion from the cytosol in exchange for influx of 3 Na^{+} ions. As such, this represents another major mechanism, along with SERCA2a, of restoring cytosolic Ca^{2+} to pre-systolic levels. HF is characterized by elevated cytosolic Ca^{2+} levels due to reduction in CICR and reduced SERCA2a activity as detailed above, which in turn leads to a compensatory increase in NCX1 expression and activity.[100–103] However, the upregulation of NCX1 may become maladaptive over long periods of time due to several reasons. First, in contrast to SERCA2a, NCX1 does not replete SR Ca^{2+} stores and, thus, does not help in restoring the diminished CICR. Second, upregulation and/or increased activity of NCX1 can be potentially pro-arrhythmogenic.[102–105] Overall, the role of NCX is unclear in the pathogenesis of contractile dysfunction in HF but its detrimental role in causing lethal arrhythmias in the setting of HF has been established by several studies.

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Conclusion

Several studies have confirmed that diastolic Ca^{2+} leak from the SR is increased in myocytes isolated from animals as well as patients with HF. In addition, there is abundant evidence that remodeling of the RyR2 macromolecular channel complex and changes in posttranslational modifications contribute to channel dysfunctions that underlie this SR Ca^{2+} leak. This enhanced SR Ca^{2+} leak observed in HF can impair cardiac performance, although defects in SERCA2a and NCX1 regulation may further exacerbate the excitation-contraction coupling defects in HF. The cellular consequences of persistent SR Ca^{2+} leak probably include reduced SR Ca^{2+} loading, which suppresses the next systolic SR Ca^{2+} release and contractile event. Additional studies are required to determine how different post-translational modifications conspire to generate SR Ca^{2+} leak in failing hearts, and how one can intervene therapeutically to restore SR Ca^{2+} handling and cardiac function. A better understanding of the molecular mechanisms underlying defects in RyR2 may spur the development of novel therapeutic approaches to specifically inhibit SR Ca^{2+} leak pathways in HF.

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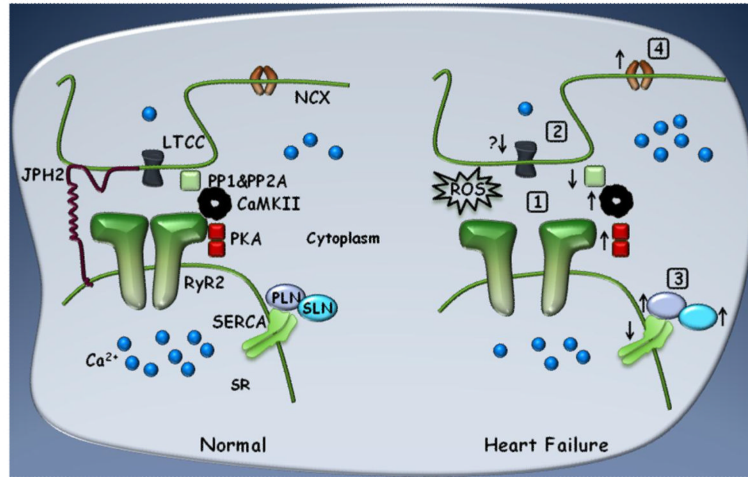

Figure 1.

Schematic representation of changes in Type 2 Ryanodine receptors (RyR2) and related proteins in heart failure (HF). Left, represents Ca^{2+} handling in a cell from normal heart, and right, represents Ca^{2+} handling in a cell from a failing heart. 1) shows increased RyR2 activity represented by a wide open RyR2 due to post-translational modification by increased protein kinase A (PKA) and Ca^{2+}/CaM-dependent protein kinase II (CaMKII) activity, reduced protein phosphatases (PP) 1 and PP 2A activity, reduced junctophilin 2 (JPH2) leading to abnormalities in T-tubule structure and increased oxidation by reactive oxygen species (ROS), 2) represents complex changes in L-type Ca^{2+} channel (LTCC) as discussed in the text, 3) represents reduced SR/ER Ca^{2+}-ATPase (SERCA2a) activity and corresponding increased phospholamban (PLN) and Sarcolipin (SLN) activity, and 4) represents increased Na^{+}/Ca^{2+} exchanger (NCX) activity, in heart failure. ↑ represents increase and ↓ represents decrease.