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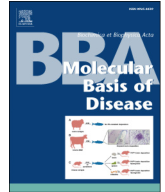
BBADIS-63748; No. of pages: 7; 4C: 2

Biochimica et Biophysica Acta xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis



Review

# Alterations in ryanodine receptors and related proteins in heart failure ☆

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A R T I C L E I N F O

*Article history:*
Received 7 March 2013
Received in revised form 23 April 2013
Accepted 5 June 2013
Available online xxxx

*Keywords:*
Heart failure
Calcium
Ryanodine receptor
Sarcoplasmic reticulum
Contractility

A B S T R A C T

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. This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

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## 1. 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 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 (Fig. 1). 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

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0925-4439/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbadis.2013.06.008

Please cite this article as: S. Ather, et al., Alterations in ryanodine receptors and related proteins in heart failure, Biochimica et Biophysica Acta (2013), http://dx.doi.org/10.1016/j.bbadis.2013.06.008

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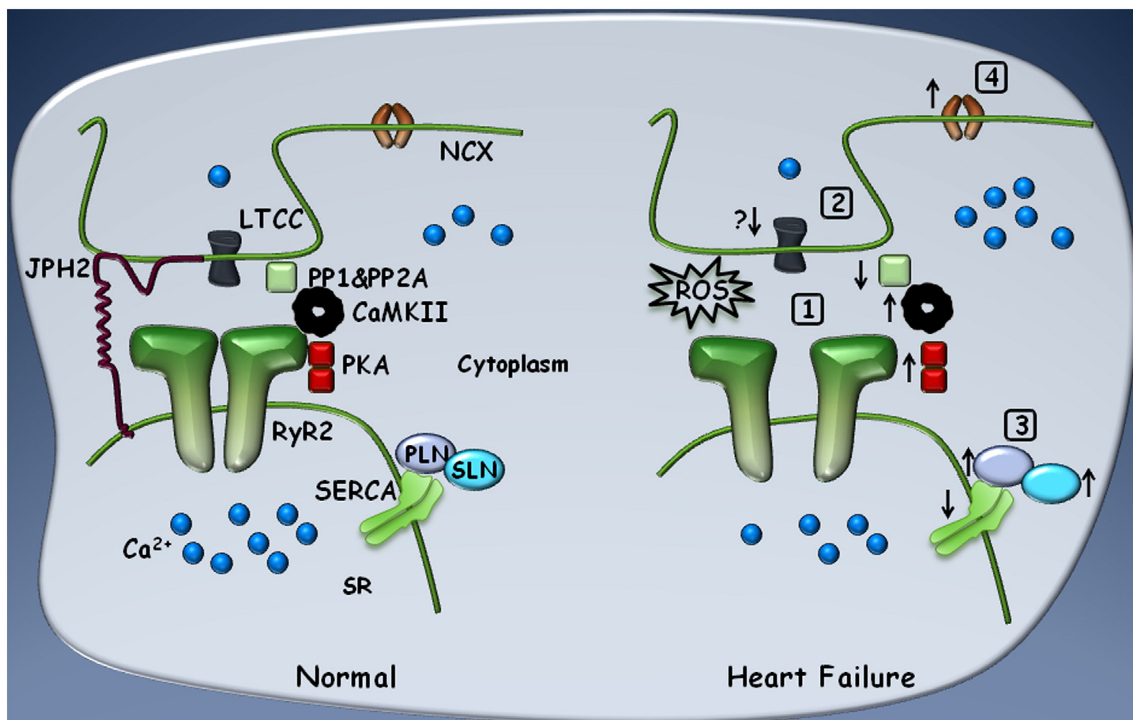


**Fig. 1.** Schematic representation of changes in type 2 ryanodine receptors (RyR2) and related proteins in heart failure (HF). Left, represents $Ca^{2+}$ handling in a cell from normal heart, and right, represents $Ca^{2+}$ handling in a cell from a failing heart. 1) shows increased RyR2 activity represented 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.

of HF, with a focus on the complex pattern of alterations of RyR2 post-translational regulation during HF.

## 2. 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].

## 3. 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 [28]. In the sections below, we have discussed in detail the current state of knowledge.

### *3.1. 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

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