REVIEW

This paper is dedicated to the 70th anniversary of the founding of Physiologia Bohemoslovaca (currently Physiological Research)

Structure-Function Relationships and Modifications of Cardiac Sarcoplasmic Reticulum Ca^{2+}-Transport

At the time of 70th Anniversary of Physiological Research, this article is dedicated to honor the leadership of Dr. Josef Zicha and Prof. Dr. Bohuslav Ostadal in promoting the journal.

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Summary

Sarcoplasmic reticulum (SR) is a specialized tubular network, which not only maintains the intracellular concentration of Ca^{2+} at a low level but is also known to release and accumulate Ca^{2+} for the occurrence of cardiac contraction and relaxation, respectively. This subcellular organelle is composed of several phospholipids and different Ca^{2+}-cycling, Ca^{2+}-binding and regulatory proteins, which work in a coordinated manner to determine its function in cardiomyocytes. Some of the major proteins in the cardiac SR membrane include Ca^{2+}-pump ATPase (SERCA2), Ca^{2+}-release protein (ryanodine receptor), calsequestrin (Ca^{2+}-binding protein) and phospholamban (regulatory protein). The phosphorylation of SR Ca^{2+}-cycling proteins by protein kinase A or Ca^{2+}-calmodulin kinase (directly or indirectly) has been demonstrated to augment SR Ca^{2+}-release and Ca^{2+}-uptake activities and promote cardiac contraction and relaxation functions. The activation of phospholipases and proteases as well as changes in different gene expressions under different pathological conditions have been shown to alter the SR composition and produce Ca^{2+}-handling abnormalities in cardiomyocytes for the development of cardiac dysfunction. The post-translational modifications of SR Ca^{2+}-cycling proteins by processes such as oxidation, nitrosylation, glycosylation, lipidation, acetylation, sumoylation, and O-GlcNacylation have also been reported to affect the SR Ca^{2+}-release and uptake activities as well as cardiac contractile activity. The SR function in the heart is also influenced in association with changes in cardiac performance by several hormones including thyroid hormones and adiponectin as well as by exercise-training. On the basis of such observations, it is suggested that both Ca^{2+}-cycling and regulatory proteins in the SR membranes are intimately involved in determining the status of cardiac function and are thus excellent targets for drug development for the treatment of heart disease.

Key words

Cardiac sarcoplasmic reticulum • Ca^{2+}-pump ATPase • Ca^{2+}-release protein • Ca^{2+}-cycling proteins • Cardiac phospholamban • Ca^{2+}-regulatory proteins

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Introduction

Since the observations of Sydney Ringer describing the involvement of Ca^{2+} in cardiac contraction, the role of Ca^{2+} in heart function, metabolism and structure has been a subject of extensive investigations (Ringer 1883, Nayler 1963, Ebashi and Endo 1968, Langer 1968, Katz 1970, Carafoli 1973, Fabiato and Fabiato 1979, Ebashi 1976, Dhalla *et al.* 1982, Dhalla *et al.* 1984, Eisner *et al.* 2000, Bers 2002, Eisner *at al.*

2017, Mackrill and Shiels 2020, Marty and Faure 2016, Synetos *et al.* 2016). It is now clear that not only the extracellular Ca^{2+} is required for maintaining the integrity of myocardial cell membrane but a small amount of Ca^{2+}-influx into cardiomyocytes is also essential for the occurrence of cardiac contraction. Various subcellular organelles such as sarcoplasmic reticulum (SR), sarcolemma, mitochondria and nucleus have been shown to maintain the intracellular concentration of Ca^{2+} at a low level (Lehninger *et al.* 1967, Haugaard *et al.* 1969, Dhalla *et al.* 1970, Dhalla *et al.* 1977, Reddish *et al.* 2017, Santulli *et al.* 2015, Primeau *et al*. 2018, Stammers *et al*. 2015, Zhihao *et al*. 2020). Raising and lowering the concentration of intracellular Ca^{2+} upon depolarization and repolarization of cardiomyocyte have been demonstrated to be associated with cardiac contraction and relaxation processes, respectively. Furthermore, instability of Ca^{2+}-handling mechanisms in cardiomyocyte has been linked to the pathogenesis of cardiac arrhythmias (Ter Keurs and Boyden 2007, Landstrom *et al.* 2017, Greiser 2017, Dobrev and Wehrens 2017) whereas the occurrence of Ca^{2+}-overload has been reported to produce myocardial cell damage and cardiac dysfunction (Zimmerman and Hulsmann 1966, Dhalla 1976, Alto and Dhalla 1979, Santulli *et al.* 2015). In fact, it has become evident that abnormalities in intracellular Ca^{2+} handling are involved in the development of impaired heart function.

By virtue of its ability to release and accumulate Ca^{2+}, SR is to known to be intimately associated with cardiac and skeletal muscle contraction and relaxation processes (Inesi 1972, Martonosi 1972, MacLennan and Holland 1975, Dhalla *et al.* 1982). It is noteworthy that the function of SR for accumulating Ca^{2+} in an energy-dependent manner was discovered in skeletal muscle about sixty years ago (Hasselbach and Makinose 1962, Ebashi and Lipmann 1962, Hasselbach 1964, Ebashi and Ebashi 1962) whereas electrophysiological, biophysical and biochemical studies have provided evidence for Ca^{2+}-release from SR (Lee *et al.* 1966, Fabiato 1983, Dhalla *et al.* 1983, Nabauer *et al.* 1989, Bers 2004, Santulli *et al.* 2017b, Guerrero-Hernandez *et al.* 2020). The involvement of SR Ca^{2+}-transport in muscular contraction is evident from the observations that the activity of SR for Ca^{2+}-handling in skeletal muscle is much greater than that in cardiac or smooth muscles (Adachi 2010, Frank *et al*. 2003, MacLennan and Holland 1975, Yoshida *et al.* 2005, Ganguly *et al.* 1986, Ganguly *et al.* 1983). Furthermore, the SR Ca^{2+}-transport activity in the left ventricle is higher than that in the right ventricle (Afzal and Dhalla 1992, Dhalla *et al.* 1980). It should be mentioned that several observations from different animals have revealed that both heart function and cardiac SR activities are species-dependent (Lüss *et al.* 1999, Dhalla *et al.* 1980, Afzal and Dhalla 1992, Singal *et al.* 1986, Sulakhe and Dhalla 1971, Dhalla *et al.* 1984, Heyliger *et al.* 1985). Depressed cardiac function due to aging and myocardial infarction has also been shown to be associated with decreased SR Ca^{2+}-transport activity (Knyushko *et al.* 2005, Jahng *et al.* 2015, Dhalla *et al.* 2012, Dhalla *et al.* 2009). Thus changes in SR Ca^{2+}-release and Ca^{2+}-uptake activities can be seen to play a critical role in determining the status of cardiac performance in health and disease.

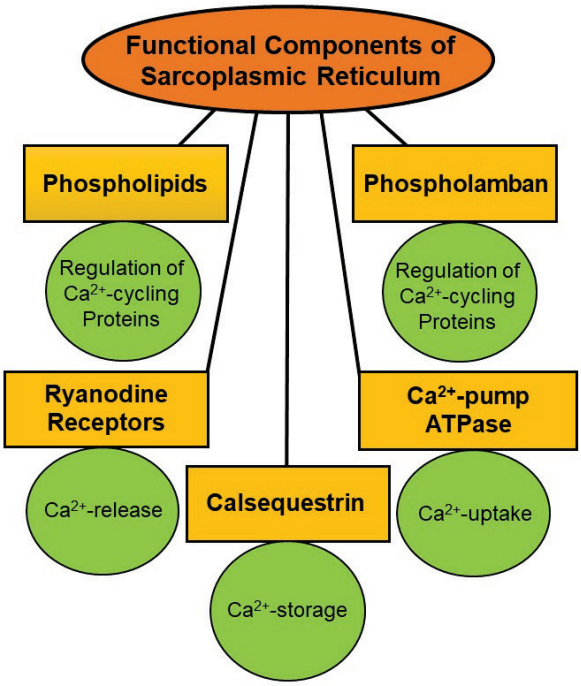

Fig. 1. Some of the major components of the sarcoplasmic reticulum and their functions in cardiomyocytes.

Several proteins and phospholipids have been identified as structural components of the SR membrane (Martonosi *et al.* 1968, Martonosi and Halpin 1971, MacLennan *et al.* 1973, MacLennan *et al.* 1974, MacLennan 1970). Some of the major components in the SR membrane and their functions in the myocardium are shown in Figure 1. It was demonstrated that SR Ca^{2+}-transport activities are regulated by different mechanisms involving several endogenous proteins and phospholipids as well as protein kinases in the cytoplasm

(Martonosi *et al.* 1971, Katz *et al*. 1975, Tada *et al.* 1978, LePeuch *et al.* 1979, Netticadan *et al.* 1999). This review is intended to provide an updated synthesis of the existing literature regarding structure-function of different major protein components of the cardiac SR membrane with particular focus on their relationship with SR Ca^{2+}-pump system. The regulation of cardiac SR Ca^{2+}-transport system by some protein kinases will be described to emphasize the role of protein phosphorylation in modulating cardiac contractile function. Various mechanisms which are known to modify the function of some SR proteins for Ca^{2+}-transport activities will be discussed to show the involvement of Ca^{2+}-handling abnormalities in cardiac dysfunction in heart disease. In addition, the influence of some hormones such as thyroid hormones and adiponectin as well as exercise on cardiac SR activities will be outlined to gain further information regarding structure-function relationships with Ca^{2+}-cycling and regulatory proteins. Since there are several similarities between cardiac muscle and skeletal muscle SR organelles with respect to their functional and biochemical aspects, some of the work for structural components of the skeletal muscle SR has also been included in this review.

Structural and functional aspects of SR

The SR is a tabular network in both skeletal and cardiac muscles. It is a specialized form of the smooth muscle endoplasmic reticulum (ER), which is responsible for the maintenance of intracellular Ca^{2+} homeostasis as well as Ca^{2+} storage (Sommer 1982, Altshuler *et al.* 2012, Prins and Michalak 2011, Rossi *et al*. 2008, Doroudgar and Glembotski 2013, Lam and Galione 2013). From the structural point of view, SR is divided into two well-characterized regions: the terminal cisternae, from where Ca^{2+} ions are released, and the longitudinal tubules, which accumulates Ca^{2+} ions (Beard *et al*. 2004). Cardiac and skeletal muscle cells also contain transverse tubules (T-tubules), which are the extensions of the cell membrane and are closely associated with the terminal cisternae, the primary site of Ca^{2+} storage and release (Hong and Shaw 2017). The longitudinal SR (LSR) are thinner projections, that run between the terminal cisternae and junctional SR (JSR), and are the location for Ca^{2+} ion accumulation. The LSR tubules envelop the myofibrils and the dyadic junctions between terminal cisternae and t-tubules have a specific location at the Z-lines whereas terminal cisternae are a specific form of JSR. Structural variability of dyads has been reported to relate with Ca^{2+}-release in cardiomyocyte (Novotova *et al.* 2020). It is pointed out that a small amount of Ca^{2+} entering upon depolarization of cardiomyocytes has been shown to be sufficient for opening Ca^{2+}-sensitive channels in the SR and causing a marked release of Ca^{2+} into the cytoplasm. This Ca^{2+} then binds with troponin and promotes the interaction of actin and myosin for the occurrence of myofibril contraction. On the other hand, repolarization of cardiomyocyte is associated with lowering the intracellular concentration of Ca^{2+}, mainly due to accumulation in the SR and this then results in myofibril relaxation. These events in cardiac excitation, contraction and relaxation processes involving the SR Ca^{2+}-release and uptake have been described elsewhere (Dhalla *et al.* 1982, Berridge *et al.* 2003, Eisner *et al.* 2017, Bovo *et al.* 2019, Mckillop and Geeves 1991, McKillop and Geeves 1993, Jones *et al.* 1998). It is pointed out that we have described the following 13 SR proteins, which are involved in SR Ca^{2+}-release, Ca^{2+}-uptake, Ca^{2+}-binding and regulation of Ca^{2+}-cycling. Since some of these proteins play multiple roles, their description has not followed any specific order:

Sarcoplasmic reticulum ATPase (SERCA, SR Ca^{2+}-pump ATPase) plays a major role in Ca^{2+} signalling (Jiao *et al.* 2009), and is involved in various aspects of cell function (Clapham *et al.* 2007), such as transcription (Flavell and Greenberg 2008), apoptosis, exocytosis, signal transduction (Dodd *et al.* 2010), and cell motility (Qi *et al.* 2007). SERCA is responsible for the movement of Ca^{2+} against concentration gradient between the SR and the cytosol. There are three different genes coding for 3 SERCA isoforms, which are spliced alternatively into 11 variants (SERCA1a–1b, -2a–2c, and -3a–3f) (Altshuler *et al.* 2012; Brandl *et al.* 1987). It has been demonstrated that SR contains Ca^{2+}-pump ATPases in its membrane that are responsible for pumping Ca^{2+} ions into the tubular network as these are required because Ca^{2+} ions from the cytoplasm cannot passively pass into the SR (Voss *et al.* 1994). These Ca^{2+}-pumps have several forms with SERCA2a mainly found in cardiac and skeletal muscle (Martonosi 1996, Satoh *et al.* 2011, Lamboley *et al.* 2013). It may be noted that SERCA is composed of 13 subunits, M1-M10, A, P and N; the M1-M10 subunits are located in the SR membrane and are responsible for binding Ca^{2+} ions whereas the A, P and N subunits are located on the outer surface of the membrane and are responsible for ATP binding (Primeau

et al. 2018). Smejtek and coworkers (2014) have reported that SR is considered as a complex biomembrane due to the presence of Ca^{2+}-ATPase in the APN domain. Protein components of the LSR and terminal cisternae are quite different, representing the functional specialization of these membrane elements, which are Ca^{2+}-uptake and release, respectively; the major component of the LSR, is SERCA which is responsible for pumping the released Ca^{2+} back into the SR (Van Petegem 2012).

When two Ca^{2+} ions and one molecule of ATP bind to the cytosolic side of the Ca^{2+}-pump ATPase, the pump opens because ATP hydrolyses releases a phosphate group. Consequently, the released phosphate group then binds to the pump, causing a conformational change, allowing the cytosolic side of the pump to open and permitting two Ca^{2+} ions to enter. The cytosolic side of the pump then closes and releasing Ca^{2+} ions into the SR (Toyoshima and Nomura 2002, Le Peuch *et al.* 1983). It has been shown that SERCA 2 gene knockout disrupted SR function and this disruption was associated with heart failure in mice (Bers 2002, Louch *et al.* 2010). Additionally, it has been reported that cardiomyocyte-specific gene knockout resulted in mice that remained alive for 10 weeks following the gene knockout (Louch *et al.* 2010, Andersson *et al.* 2009a). It was also observed that 4 weeks after the gene knockout, SERCA2 protein content was reduced to <5%, without any changes in cardiac function, and it was only after 7 weeks that these mice started developing severe cardiac dysfunction (Andersson *et al.* 2009b). Accordingly, some defect in SERCA2 was suggested to result in the development of cardiac contractile dysfunction.

Ryanodine receptor (RyR) is another major protein in the SR membrane and is responsible for the release of Ca^{2+} from the intracellular stores during excitation-contraction (Wehrens and Marks 2003). This protein is the largest known ion channel, which exists in three isoforms (RyR 1, 2 and 3) (Lanner *et al.* 2010). It consist of four identical subunits, which interact with and are regulated by phosphorylation, redox modifications, and other various small proteins (Meissner 2010). It has been shown that complete absence of RyR2 in cardiomyocytes of knockout mouse model is lethal due to the lack of SR Ca^{2+} release (Kushnir *et al.* 2010). Mutations in RyR2, the predominant form in the heart muscle, are associated with human disorders such as catecholaminergic polymorphic ventricular tachycardia while mutations in RyR1 underlie diseases such as central core disease and malignant hyperthermia (Priori *et al.* 2002, Nakai *et al.* 1990, Valdivia 2007). Thus SR Ca^{2+}-release is not only known to play a critical role in inducing cardiac contraction but alterations in its signaling and function are also considered to be involved in the genesis of cardiac arrhythmias and fibrillation (Landstrom *et al.* 2017, Greiser 2017, Debrev and Wehrens 2017).

The structure-function relationships for SR Ca^{2+}-release channels (both RyR1 and RyR2) under a wide variety of physiological and pathological situations have been described recently (Santulli *et al.* 2017b, Santulli *et al.* 2018, Meissner 2017, Sheard *et al.* 2019). While RyR1 has been reported to be associated with intracellular Ca^{2+}-leak and induction of cardiomyopathy (Chen and Kudryashev 2020), RyR2 is mainly concerned with Ca^{2+}-release for the generation of cardiac contractile force (Lascano *et al.* 2017). The mechanisms for opening the RyR and its functional role in cardiac excitation-contraction coupling have also been discussed elsewhere (Santulli *et al.* 2017a, Van Petegem 2016). The sensitivity of RyR has been shown to govern the stability and synchrony of Ca^{2+}-release during the process of excitation-contraction coupling in the heart (Wescott *et al.* 2016). Several investigators have studied the molecular and cellular control for the regulation of SR Ca^{2+}-release channels. In this regard, it is pointed out that SR Ca^{2+}-release is not only regulated by phosphorylation and dephosphorylation (Yamaguchi 2020, Terentyev and Hamilton 2016) but is also modulated by glycation and oxidation (Ruiz-Meana *et al.* 2019, Zima and Mazurek 2016). SR Ca^{2+}-release is also controlled by SR luminal Ca^{2+} as well as protein-protein interaction (Jones *et al.* 2017, Rani *et al.* 2016, Seidel *et al.* 2015) and its magnitude is dependent upon the RyR cluster size (Galice *et al.* 2018). Different recent studies have revealed the role of RyR in the genesis of arrhythmias and fibrillation (Dridi *et al.* 2020, Campbell *et al.* 2020, Alsina *et al.* 2019). Excessive release of SR Ca^{2+} induced by inositol triphosphate has been demonstrated to produce arrhythmias (Blanch *et al*. 2018) whereas that induced by CAMKinase associated phosphorylation has been shown to produce cardiac dysfunction (Sepulveda *et al.* 2020, Sepulveda *et al.* 2017). Thus targeting RyR and associated pathological SR Ca^{2+}-release has been considered to have a great impact for the treatment of arrhythmias and heart failure (Connell *et al.* 2020).

Phospholamban (PLB) is present in the LSR and it is involved in regulating the activity of the SR Ca^{2+}-pump in the heart. Over the years, numerous

investigators have demonstrated that PLB is an inhibitor protein for the SERCA2 function in the heart; the mechanism of inhibition is accomplished by PLB binding to SERCA, decreasing its affinity to Ca^{2+} and preventing Ca^{2+} uptake into the SR. Accordingly, failure to remove Ca^{2+} from the cytosol, prevents the cardiac relaxation and consequently decrease the muscle contraction (Simmerman and Jones 1998). Nevertheless, hormones such as adrenaline and noradrenaline can prevent PLB from inhibiting SERCA (Dhalla *et al.* 2019). When these hormones bind to the beta 1 adrenoceptor on the cell membrane, they increase the formation of cAMP, activate protein kinase A (PKA), phosphorylate PLB, prevent the inhibition of SERCA and thus promote cardiac muscle relaxation (Le Peuch *et al.* 1983, Moccia *et al.* 2019). Slack and coworkers (1997) showed that PLB is a key determinant of relaxation in slow-twitch skeletal muscle under basal conditions and during isoproterenol stimulation, supporting its important role in the regulation of SERCA activity. In fact, PLB knockout models have revealed that the ratio of PLB to SERCA2a may be a significant determinant of the regulation of the cardiac contraction–relaxation cycle (Frank *et al.* 2003, Periasamy *et al.* 1999).

Inositol-Trisphosphate Receptor (InsP3R) is a Ca^{2+} release channel found widely in the ERSR system in almost all cells. The function of InsP3R is to facilitate Ca^{2+} release from the intracellular Ca^{2+} stores upon binding of Inositol trisphosphate (IP3) and resulting in Ca^{2+} signals that control various physiological processes in the cell (Foskett *et al.* 2007). Furthermore, InsP3R is a Ca^{2+} selective cation channel that is regulated by cytoplasmic Ca^{2+} in addition to InsP3. Its interaction with other ER/SR proteins contribute to the specificity and speed of Ca^{2+} signaling pathways (Yamazaki *et al.* 2011, Zhou *et al.* 2014). It has been reported that genetic hypertension in rats is related to the increase in IP3 concentrations as well as InsP3R-IP3 binding affinity in smooth muscle cells (Narayanan *et al.* 2012). Although the presence of InsP3Rs has also been detected in cardiomyocyte SR membranes, extensive work needs to be carried out to establish their functional significance under both physiological and pathological conditions. Nonetheless, InsP3R has been reported to play some role in the interaction between SR and mitochondria (Dia *et al.* 2020).

Calsequestrin is another protein which is primarily located in the junctional SR and terminal cisternae, in close association with the Ca^{2+} release channel (Lamboley *et al.* 2013). This protein is capable of binding a large amount of Ca^{2+}, reducing free Ca^{2+} in the SR and serving as a Ca^{2+}-store in the SR; calsequestrin is thus, considered as a Ca^{2+} buffering system (Perni *et al.* 2013, Treves *et al.* 2009). Furthermore, Wang and coworkers (2019) reported that calsequestrin binds to the ER luminal domain of inositol-requiring enzyme 1 (IRE1α), inhibiting its dimerization and suppressing the activation of IRE1α at the junctional SR. By using a transgenic mice model, it has been reported that calsequestrin is both a storage and a Ca^{2+}-signaling cascade regulatory protein in the myocardium (Jones *et al.* 1998). It should be mentioned that calsequestrin is considered to be a regulator of RyR2 activity and its malfunction either as a Ca^{2+}-buffer or as a regular may lead to the genesis of arrhythmias. The structure-function of calsequestrin as well as its Ca^{2+}-binding properties are also well described (Wang and Michalak 2020, Loescher *et al.* 2019, Woo *et al.* 2020).

Sarcalumenin (SAR) is a minor glycoprotein in the LSR membrane which is encoded by the SAR gene. and is partially responsible for Ca^{2+} buffering in the lumen of SR. Interestingly, alternative splicing of the same transcript results in two variants of SAR. The large transcript of SAR has a low affinity and high capacity Ca^{2+} binding protein whereas the shorter product lacks the Ca^{2+}-binding domain. Because of the presence of SAR in close vicinity of SERCA protein, it is considered to be involved in the regulation of the SERCA activity (Leberer *et al.* 1990). Some studies with SAR knockout animal models have revealed that SAR plays a crucial role in the maintenance of cardiac function under physiological stresses, by regulating Ca^{2+} transport activity into the SR (Yoshida *et al.* 2005, Jiao *et al.* 2009).

Junctin and Junctate are integral membrane proteins of cardiac and skeletal muscle SR, with moderate affinity, high capacity for Ca^{2+} binding (Treves *et al.* 2000). It should be pointed out that aspartyl beta-hydroxylas, junctin and junctate are three different single gene products, generated by alternative splicing (Feriotto *et al.* 2005). Both junctin and junctate are involved in the regulation of intracellular Ca^{2+} concentrations (Delbono *et al.* 2007, Dinchuk *et al.* 2000, Ha *et al.* 2007). Furthermore, knockout and transgenic mice model studies have shed light on the function of these proteins; it has been suggested that altered expression of junctin or

junctate can modify the cellular Ca^{2+} handling and disturb the balanced activity of other Ca^{2+} regulatory proteins (Treves *et al.* 2004). It should be mentioned that junctin is predominantly a RyR regulator whereas junctate in cardiomyocytes is connected with other membrane proteins such as InsP3R and SERCA (Kwon and Kim 2009, Stamboulian *et al.* 2005). Junctin together with triadin has also been shown to play a role in preventing arrhythmias (Wleklinski *et al*. 2020) However, the exact contribution of these Ca^{2+}-storage site in the SR membrane remains to be established.

Nexilin (NEXN) is an essential component of the junctional membrane complex which is necessary for optimal Ca^{2+} transients and is required for initiation and formation of T-tubules (Hassel *et al.* 2009). Recently, NEXN has been shown to play a role in the maintenance of the tranverse-axial tubular system (Spinozzi *et al.* 2020). Even though, the exact role of NEXN in cardiac function and disease is not well understood, it has been identified as an actin-binding protein (Liu *et al.* 2019). Aherrahrou and coworkers (2016) have evaluated the functional role of NEXN by using a constitutive NEXN knockout mouse model, and have reported that the absence of NEXN may result in premature death of mice due to dilated cardiomyopathy.

Amphiphysin 2 and Mitsugumin29 (Mg 29) are proteins that play a major role in T-tubules formation; amphiphysin 2 induces membrane curvature and tubulations, which is similar to the sarcolemma T-tubules (Lee *et al.* 2002). Knockout of amphiphysin 2 is associated with abnormal T-tubules formation and excitation-contraction coupling defects (Razzaq *et al.* 2001). Since amphiphysin 2 has been shown to be involved in the formation of dyads, it can be seen to play a role in the excitation-contraction coupling (Guo *et al.* 2021, De La Mata *et al*. 2019). On the other hand, Mg29 is a structural protein that is thought to be exclusively expressed in skeletal muscle. Mg29 is a member of the synaptophysin family, which is involved in the fusion of synaptic vesicles with the cell membrane. Mg29 knockout animal model showed structural abnormalities in both the SR and T-tubules, suggesting that it plays a role in assembly and/or docking of such membrane systems (Komazaki *et al.* 2001). Mg29 interacts with transient receptor potential canonical 3. However, Mg29 mRNA is not expressed in mouse heart as it was untraceable by various immunoblotting techniques. Nonetheless, Mg29 mRNA is expressed in human heart at a very low level. Interestingly, it was shown that the gene expression of Mg29 is significantly upregulated in animal models of heart failure (Woo *et al.* 2015, Correll *et al.* 2017). Thus the exact functional role of both amphiphysin 2 and Mg 29 with respect to the structural integrity of SR membrane needs to be determined in future studies.

Junctophilins are a family of integral membrane proteins which provide a structural bridge between the sarcolemma and SR. These proteins are attached to the JSR by a transmembrane domain in the C-terminus and contact the plasma membrane through lipid-interacting motifs in their N-terminus (Takeshima *et al.* 2000). There are several junctophilin isoforms, with isoform 2 being expressed in the heart (Nishi *et al.* 2000, Munro *et al.* 2016). As was demonstrated in knockout animal models, ablation of junctophilin resulted in a less contractile force after electrical stimulation and showed abnormal sensitivity to extracellular Ca^{2+} and altered triad formation as well (Ito *et al.* 2001, Komazaki *et al*. 2002). Since the heterologous expression of junctophilins resulted in the development of junctional-like assemblies between the ER and the plasma membrane (Takeshima *et al.* 2000, Komazaki *et al.* 2002), junctophilins are considered to play an important role in triad organization and stabilization (Nakeda *et al.* 2018). It should be noted that the interaction of junctophilin-2 with L-type Ca^{2+}-channel is important for dyad assembly and intracellular Ca^{2+} dynamics (Gross *et al.* 2021, Poulet *et al.* 2021).

TRIC-A/SRP-27 is a trimeric intracellular cation-selective channel (TRIC-A) or (SRP-27). This SR protein is expressed in excitable tissues, particularly in fast twitch skeletal muscles (Yazawa *et al.* 2007, Bleunven *et al.* 2008). It has been reported that its expression level peaks after 2 months of post-natal development (Zhou *et al.* 2007, Treves *et al.* 2009). Treves and coworkers (2009) have also reported that mice lacking TRIC/SRP-27 are viable and display no overt phenotype. In contrast, other investigators have observed that TRIC-A knockout mice have impaired ER/SR Ca^{2+} release in several cell types and developed hypertension (Yamazaki *et al.* 2011). Evidence has also been presented to suggest that TRIC channels mediate counter potassium movements to facilitate physiological Ca^{2+} release from intracellular Ca^{2+} stores and can be seen to provide a counter-current for SR/ER Ca^{2+} release; thus it may also function as

accessory proteins that directly modulate the RyR/IP3 receptor channel functions (Zhou *et al.* 2014). Recent information on cardiac muscle has revealed the interaction of TRIC-A with RyR2 for handling and storage of Ca^{2+} in the SR tubules (Zhou *et al.* 2020, Zhou *et al*. 2021).

Regulation of SR Ca^{2+}-ATPase protein

Due to its essential role in regulating Ca^{2+} handling and contractility of the heart muscle, the SERCA2a protein has been extensively investigated. The SERCA protein is embedded in the SR membrane and consists of three parts namely, a cytoplasmic face, transmembrane helices (that harbor Ca^{2+} binding sites), and luminal loops (Periasamy *et al.* 2007, Tupling *et al.* 2004, Periasamy *et al.* 2008). The cytoplasmic face of SERCA consists of a phosphorylation domain, a nucleotide domain and an actuator domain. Each domain plays a special role that governs the function of SERCA as a pump. While ATP hydrolysis takes place at the interface between the phosphorylation and the nucleotide domains, the actuator domain provides the hub for Ca^{2+} translocation (Stammers *et al.* 2015, Toyoshima and Inesi 2004). The importance of SERCA function attributes to its essential role in controlling and regulating the handling of Ca^{2+}. ATP hydrolysis facilitates transfer of two Ca^{2+} molecules into the lumen of SR. Therefore, ATP hydrolysis is essential, because it provides the required energy for pumping Ca^{2+} against the concentration gradient, as a much higher concentration gradient is present across the SR membrane (Toyoshima 2009, Smith *et al.* 2013).

Regulation of SERCA function by gene transcription and alternative splicing

The gene which encodes the SERCA Ca^{2+}-ATPase for catalyzing the hydrolysis of ATP associated with the translocation of Ca^{2+} from the cytosol to the SR lumen, is located on human chromosome 12 (Papp *et al.* 1993, Otsu *et al.* 1993). During gene expression, alternative splicing of the SERCA gene results in three different mRNAs species that encode for SERCA2a, SERCA2b, and SERCA2c proteins (Zarain-Herxberg 2006, Gelebert *et al.* 2003). These SERCA proteins are expressed in different body tissues at various rates; SERCA2a is expressed preferentially in cardiac muscle, SERCA2b is expressed in small quantities in muscle cells (Gelebert *et al.* 2003). The SERCA2c isoform is also expressed in cardiac myocytes, but it has a lower affinity for cytosolic Ca^{2+} than SERCA2a and the turnover rate is comparable to that of SERCA2b (Dode *et al.* 2003, Wuytack *et al.* 2002, Dally *et al.* 2006).

The transcription of ATP2a2 gene is regulated by several transcriptional factors that bind to the promotor region. Mitochondrial transcription factors A (TFAM) and B2 (TFB2M) were shown to regulate the transcription of the SERCA2 gene in the myocardium by binding to specific promoter regions (Fujino *et al.* 2012, Watanabe *et al.* 2011). It was demonstrated that the expression of mRNA for SERCA2a in the myocardium is correlated with the expression of both TFAM and TFB2M (Watanabe *et al.* 2011). The overexpression of TFAM and TFB2M was shown to increase the transcriptional activity by 2-folds, in addition to protecting against the stress related decrease in mRNA levels of SERCA2a. The importance of factors such as TFAM and TFB2M was found to be crucial in regulating the transcription of the SERCA gene, as the expression of TFAM was downregulated in the diabetic heart and cardiac failure due to myocardial infarction (Kang *et al.* 2007, Choi *et al.* 2001, Ikeuchi *et al.* 2005, Suarej *et al.* 2003). Furthermore, the Specificity Protein 1 (SP1), another transcriptional factor, was observed to play a role in decreasing the SERCA2a mRNA level due to pressure overload (Brady *et al.* 2003, Takizawa *et al.* 2003).

Role of phospholamban in the regulation of SERCA2a

In cardiac myocytes, SERCA2a activity is inhibited by the SR protein, phospholamban (PLN) (Asahi *et al.* 2003). PLN binds to SERCA2a when the cytosolic Ca^{2+} is low, causing a decrease in SERCA2a affinity for Ca^{2+} (Ha *et al.* 2007, Periasamy and Huke 2001, Periasamy *et al.* 2008*)*. Nevertheless, when Ca^{2+} is high, the inhibitory effect is removed, due to the activation of Ca^{2+}/calmodulin kinase (CaMKII), which phosphorylates PLN (Mattiazzi and Kranias 2011). PLN is similarly regulated by protein kinase A (PKA), which is activated due to β-adrenergic stimulation (Drummond and Severson 1979, MacLennan and Kranias 2003), which eventually phosphorylates PLN and prevents the inhibition of SERCA2a and thus augments cardiac muscle contraction and relaxation (MacLennan and Kranias 2003, Koss *et al.* 1998). The activity of SERCA2a has been reported to increase significantly when PLN is phosphorylated by either CAMKII or PKA; this change enhances the velocity of relaxation and contributes to the relaxant effects of high intramuscular Ca^{2+} and β-adrenergic stimulation as well (MacLennan and Kranias 2003, Koss *et al.* 1998). It is pointed out that

the regulation of cardiac SERCA2a is accomplished by either increasing the gene expression of PLN protein or the phosphorylation of PLN. It has been demonstrated that the expression of PLN in murine ventricular myocytes is much higher than that in atrial myocytes (Koss *et al.* 1998) as well as PLN expression is significantly less in human right atrium when compared to that in the right ventricular (Lüss *et al.* 1999). Although, variations in the level of PLN expression can be seen to contribute to the increased contractile activity in isolated human right ventricule in comparison to right atrium, the exact reason for this difference is far from clear.

Role of sarcolipin in the regulation of SERCA2a

Sarcolipin (SLN) has been shown to attenuate Ca^{2+} sensitivity by binding to SERCA2a and inhibiting its activity in the myocardium by lowering its affinity for Ca^{2+} (Asahi *et al.* 2003, MacLennan and Kranias 2003). It has been suggested that SLN is an uncoupler of SERCA pump activity and increase ATP hydrolysis resulting in heat production (Shaikh *et al.* 2015). When SLN is phosphorylated by serine/threonine kinase 16 (STK16), it facilitates the relaxant effects of β-adrenergic stimulation by promoting the separation of SLN from SERCA2a (Babu *et al.* 2007, Gramolini *et al.* 2006). This observation was supported by studies on PLN knockout mice, overexpressing SLN. It was demonstrated that the inhibitory effect of SLN on SERCA was alleviated when β-adrenergic agonist was administered (Babu *et al.* 2007, Gramolini *et al.* 2006). Furthermore, SERCA2a inhibition by SLN was evident from the reduction of cell shortening in rat myocytes overexpressing SLN after adenoviral gene transfer (Asahi *et al.* 2004). On the other hand, it was reported that SLN mRNA is highly expressed in murine and human atrium but not in human ventricle (Babu *et al.* 2005, Minamisawa *et al.* 2003). Moreover, SLN expression is poorly regulated in patients suffering from cardiovascular disease (Odermatt *et al.* 1997). Interestingly, a substantial increase in the levels of both SLN mRNA and protein was observed in left ventricular samples obtained from patients following surgery for mitral valve regurgitation (Zheng *et al.* 2014). Such evidence may indicate that SLN offers further control over Ca^{2+} handling in human myocytes, mainly in areas like the atrium where PLN is not present and in settings where Ca^{2+} concentrations are elevated (Sahoo *et al.* 2013).

Role of thyroid hormone in the regulation of SERCA2a

Thyroid hormone plays a critical role in the regulation of SERCA2a gene expression in the heart (Nagai *et al.* 1989, Ojamaa *et al.* 2000). It has been shown that administration of thyroid hormone causes significant increase in the mRNA levels in cardiomyocytes of experimental animals (Rohrer and Dillmann 1988, Arai *et al.* 1991, Kinugawa *et al.* 2001) which, results in accelerated uptake of Ca^{2+} into the SR, enhanced relaxation time, and improved force production in the heart. It may be noted that the mRNA levels for SR Ca^{2+}-pump ATPase and RyR2 as well as for myosin heavy chain (β-MHC) were increased in hearts from hypertrophied animals. On the other hand, it has been reported that there occurs a decrease in the mRNA of levels encoding SERCA2a and RyR2 as well as for α-MHC in hearts of hypothyroid animal models (Rohrer and Dillmann 1988, Kinugawa *et al.* 2001, Ji *et al.* 2000, Reed *et al.* 2000). A substantial increase in both mRNA and protein levels for SERCA2a was reported in hearts of hyperthyroid animals (Kinuzawa *et al.* 2001, Kiss *et al.* 1994), and a marked decrease in hearts of hypothyroid animals (Kiss *et al.* 1994). Such an effect of thyroid hormone on SERCA2a in hearts has been shown to be the result of transcriptional regulation, which is facilitated by distinct thyroid hormone-response elements (Hartong *et al.* 1994, Zarain-Herzberg *et al.* 1994). Additionally, the thyroid hormone, triiodothyronine, is involved in the regulation of PLN (Kiss *et al.* 1994). It has been demonstrated in experimental animal models under conditions of hyperthyroidism and hypothyroidism that the levels of PLN mRNA and protein are markedly reduced and increased, respectively (Kimura *et al.* 1994, Chang *et al.* 1997). Moreover, such change in the expression of PLN was reported to boost the effects of thyroid hormone on the functionality of SERCA2a, enhancing the uptake of Ca^{2+} in hyperthyroidism and reducing cardiac performance in chronic hypothyroidism (Kimura *et al.* 1994, Chang *et al.* 1997).

Role of adiponectin in the regulation of SERCA2a

Adiponectin is a hormone peptide of adipocytes (Ahima 2006), the reduction of which plays an essential role in obesity-related cardiovascular disorders (Fortuño *et al.* 2003, Hug and Lodish 2005). Besides its function as an antioxidant and cardioprotective agent, it is also involved in the regulation of SERCA2a function (Pischon *et al.* 2004, Zhang *et al.* 2013, Shibata *et al.* 2012, Villarreal-Molina and Antuna-Puente 2012). It was

suggested that the cardio-protection effect of adiponectin occurs by alleviating the stress of endoplasmic reticulum, thus enabling the recovery of SERCA2a function (Zhang *et al.* 2013). It has been shown in animal models of myocardial ischemia/reperfusion and cardiomyocyte hypoxia/reoxygenation that intravenous administration of adiponectin causes restoration of the function of SERCA2a (Guo *et al.* 2013). Moreover, a substantial increase in the levels of mRNA of SERCA2a in H9C2 cells was demonstrated when cardiomyocytes were cultured in an adiponectin-enriched medium for 60 minutes in comparison to those in adiponectin-depleted medium (Jahng *et al.* 2015, Boddu *et al.* 2014). While the exact mechanism of activation of SERCA2a by adiponectin is not known, it could be due to the enhancement of PLN phosphorylation, thus relieving its inhibition of SERCA2a. In fact, adiponectin administration in rats has been reported to increase PLN phosphorylation in the left ventricle (Guo *et al.* 2013). Therefore, the increase in PLN phosphorylation alleviates inhibition and increases Ca^{2+} sequestering action of the SERCA. Furthermore, it is believed that cardioprotective effect of adiponectin is achieved through the signaling of the regulatory enzyme of energy homeostasis, adenosine monophosphate-activated protein kinase (AMPK). It should be noted that AMPK is responsible for the metabolic regulation of adiponectin (Gonon *et al.* 2008), which has been shown to alter SERCA1a protein levels and SERCA2a mRNA in mice muscle (Morissette *et al.* 2014).

Post-translational modifications of SERCA2a

In addition to PLN and SLN phosphorylations, which regulate SERCA2a function, numerous posttranslational events are known to participate in the modification of SR protein function. Although both SERCA2a and RyR2 are modified by different posttranslational events by similar mechanism, only these affecting the SERCA2a function are given in Figure 2. These events include different processes such as nitrosylation, acetylation, sumoylation, glycosylation, O-GlcNAcylation, and glutathionylation. It is pointed out that nitrosylation or nitration is the addition of a nitro group to proteins, which has been reported to increase due to aging (Knyushko *et al.* 2005). The aging hearts were found to reveal much higher levels of nitrotyrosine in comparison to control hearts (Knyushko *et al.* 2005). Furthermore, nitrotyrosine levels in SR were almost 2 folds higher in the ischemic hearts perfused with high glucose than those perfused with normal levels of glucose (Tang *et al.* 2010). It has been reported that nitration of SERCA2a and RyR proteins occurs through polyol pathway, which plays a central role in oxidative stress due to hyperglycemia as seen in diabetes (Tang *et al.* 2010, Arun and Nalini, 2002). A significant negative correlation was found between SERCA2a as well as RyR tyrosine nitration and maximal SR acitvities. Although nitration of the SERCA2a was confirmed in experimental animal models of chronic disease, its role in modifying the activity of SERCA2a in humans is poorly understood. Nonetheless, it is believed that nitration of certain tyrosine residues may cause distortion in helical interactions and thus restricts the coordinated movement of membrane helices, which is required for optimal SERCA function (Kynyushko *et al.* 2005).

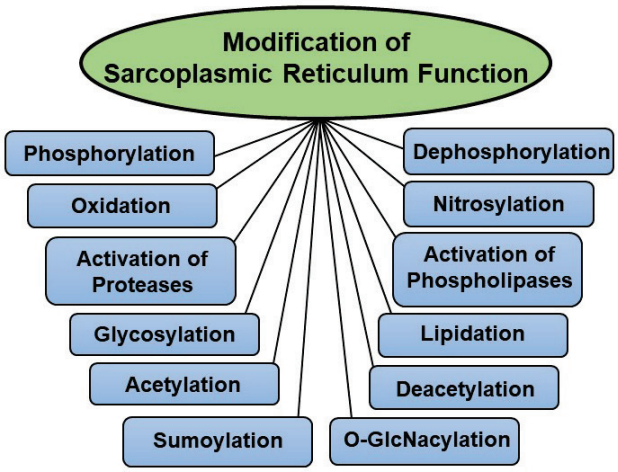

Fig. 2. Modification of cardiac sarcoplasmic reticulum function by some post-translational events.

Sumoylation of SERCA2a is achieved by binding of a small ubiquitin-related modifier type 1 protein, SUMO1 to SERCA2a lysine residue (Kho *et al.* 2015). A significant decrease in SUMO1 in heart failure, has been reported to accompany a decrease in SERCA2a sumoylation (Kho *et al.* 2015). A SUMO1 injection in the pressure overload animal model of heart failure was found to enhance cardiac performance and SERCA2a activity (Kho *et al.* 2011, Kho *et al.* 2015). These studies indicate that sumoylation has cardioprotective properties in the heart. It should be mentioned that downregulation of SUMO1 by a hairpin RNA caused a significant decrease in the level of SERCA2a protein (Kho *et al.* 2011). Moreover, the transfer of SUMO1 gene was

shown to reinstate mRNA expression of SERCA2a, cause enhancement in the left ventricular ejection fraction and maintain the activity of SERCA2a in an animal model of ischemic heart disease (Kho *et al*. 2011). It was suggested that inhibition of acetylation of certain lysine residues of SERCA2a and increase in its sensitivity to ATP underlies the action of sumoylation in maintaining SERCA2a function (Park and Oh, 2013). On the other hand, it is believed that acetylation and deacetylation play a role in the acute modification of SERCA2a activity (Park and Oh 2013, Sack 2012). Although, SERCA2a acetylation and deacetylation are not well defined, some evidence has been presented to show that these processes could play a role in intracellular Ca^{2+} handling in cardiac myocytes (Grillon *et al.* 2012). In diabetes, when glucose levels are high, an increase in SERCA2a glycosylation occur, which has been reported to cause a significant decrease in SERCA2a activity (Clark *et al.* 2003, Belke *et al.* 2004). A substantial decrease in both SERCA2a mRNA and proteins as well as a considerable increase in PLN have been attributed to the increase in glycosylation (Belke *et al.* 2004, Hamm *et al.* 2016, Calligaris *et al.* 2013).

When O-linked N-acetylglucosamine is incorporated into threonine or serine residues, this process is called O-GlcNAcylation, which is known to modify the levels of SERCA2a protein and result in the disruption of Ca^{2+} cycling (Medford *et al.* 2013, Bennett *et al.* 2013). In fact, Clark and coworkers (2003) have reported a significant decrease in SERCA2a protein levels associated with longer Ca^{2+} decay in cardiac myocytes of newborn rat. Additionally, it was shown that O-GlcNAcylation controls SERCA2a gene expression in hearts, which is facilitated by the transcription factor SP1 and is involved in the transcription of many heart function regulatory genes (Dellow *et al.* 2001, Belke 2011, Johnsen *et al.* 2013). A significant reduction in SP1specific O-GlcNAcylation in hearts of swim-trained mice has been reported (Belke 2011). Furthermore, O-GlcNAcylation was also observed to alter the SERCA2a function by phosphorylation of PLN (Hu *et al.* 2005, Watson *et al.* 2010). A significant decrease in total PLN protein level and an increase in phosphorylated PLN has been demonstrated by decreasing the cellular O-GlcNAcylation by adenoviral overexpression of the enzyme O-GlycNAcase (Hu *et al.* 2005). These studies seem to support the view that O-GlcNAcylation affects SERCA2a function in the heart, either by affecting the SERCA2a activity directly or by prompting the PLN phosphorylation.

It is noteworthy that both oxidative stress and nitrosative stress are known to adversely affect the process of glutathionylation where disulphide bonds are formed between cysteine and glutathione in SR proteins (Ghezzi 2005), to increase SERCA activity and boost Ca^{2+} uptake (Lancel *et al.* 2009, Tong *et al.* 2008, Jardim-Messeder *et al.* 2012). Under normal conditions, the SERCA2a sulfhydryl modifications are reversible, but in the case of atherosclerosis, SERCA2a cysteine becomes oxidized irreversibly, to prevent glutathionylation and activation of SERCA function (Tong *et al.* 2008, Jardim-Messeder *et al.* 2012, Adachi 2010). Thus, alterations in the process of glutathionylation of SERCA2a in addition to other post-translational events can be seen to play a major role in inducing Ca^{2+}-handling abnormalities in cardiomyocytes during the development of cardiac dysfunction in heart disease.

Modification of SERCA2a gene expression by miRNAs

MicroRNAs (miRNAs) are small, noncoding RNAs with important functions in development, cell differentiation and apoptosis, gene expression post-translationally, degradation of mRNAs and preventing the translation process (Ambros 2004, Karakikes *et al.* 2013). Since the 3-prime untranslated region (3'-UTR) of the SERCA2a gene harbors the recognition site for miRNA, it has been suggested that miRNAs alter heart function by regulating SERCA2a gene expression. In this regard, a significant increase in miRNA expression was found cause a substantial reduction in SERCA2a protein and was associated with a progressive reduction in fractional shortening (Montgomery *et al.* 2011). On the other hand, a significant increase in the expression of SERCA2a protein was observed when mice were injected with antisense oligonucleotide against miRNA (Zsebo *et al.* 2014, Wahlquist *et al.* 2014). In fact, miRNA knockout mice showed long cytosolic Ca^{2+} decay and lower SR Ca^{2+} load, in comparison to wild-type mice (Huang *et al.* 2013).

Modification of SERCA2a gene expression by exercise

It has been reported that aerobic exercise improves SR Ca^{2+} uptake and contractility of cardiomyocyte in some models of cardiovascular disorders (Natali *et al.* 2002, Wisløff *et al.* 2001, Kemi and Wisløff 2010). In fact, it was shown that aerobic

exercise for 8-weeks in mice caused 30% increase in SR Ca^{2+} uptake; this event was explained by an increase in the protein content of SERCA2a (Kemi *et al.* 2008). Furthermore, 8-weeks of strenuous exercise increased the expression of SERCA2a protein by approximately 40% in the left ventricle, but when exercise was stopped, this increase was reversed within a period of one month (Carneiro-Junior *et al.* 2005). However, it is pointed out that the mechanism of increased SERCA2a activity due to exercise are not well understood. Although, exercise is a burden on the homeostasis of energy metabolism which causes an increase in the number and function of mitochondria, the synthesis of mitochondria requires activation of gene expression which cannot be achieved without the activation of certain transcriptional factors, such as TFAM and TFB2M; both these factors were involved in the regulation of SERCA2a (Watanabe *et al.* 2011). It is also pointed out that the effect of repeated muscular contractions on the activation of TFAM and TFB2M is controversial because some reports on repeated contractions have reported activation of TFAM and TFB2M (Gleyzer *et al.* 2005) whereas others have shown that exercise has no effect on TFAM and TFB2M in skeletal muscles (Norrbom *et al.* 2004). Nonetheless, upregulation of TFAM or TFB2M has been reported to occur due to exercise (Theilen *et al.* 2017, Norrbom *et al,* 2010, Lumini-Oliveira *et al.* 2011). For instance, it has been shown that when diabetic rats showing both reduced SR Ca^{2+} uptake and TFAM expression, were subjected to strenuous exercise for 14-weeks, an attenuation of the decrease in TFAM was observed (Lumini-Oliveira *et al.* 2011). Furthermore, athletes were found to have significantly higher TFB2M mRNA in comparison to less active individuals and the blood flow restricted training for 10 days in comparison to control showed an upsurge in the basal TFB2M levels (Norrbom *et al.* 2010). Therefore, the enhancement in SERCA2a function and Ca^{2+} handling following aerobic exercise can be explained by an increase in induction of TFAM or TFB2M expression.

Different regulatory factors and posttranslational events have also been considered to explain the overexpression of SERCA2a due to exercise. It may be noted that exercise has been reported to regulate the activity of SERCA2a by phosphorylating PLN, as well as by directly modifying the expression of SERCA2a protein (Bupha-Intr *et al.* 2009). Additionally, it was shown that exercise causes a significant increase in SERCA2a protein without affecting total PLN protein and thus inducing a decrease in PLN to SERCA2a ratio (Kemi *et al.* 2007). Furthermore, an enhancement in the inotropic and lusitropic sensitivity to β-adrenergic stimulation was demonstrated as a response to PLN phosphorylation in hypertensive rats subjected to exercise (MacDonnell *et al.* 2005). It was also shown that when aged mice were subjected to exercise, SERCA activity and SR Ca^{2+} uptake were normalized (Bupha-Intr *et al.* 2009) and it was concluded that exercise would be expected to improve SR Ca^{2+} uptake due to the relief of the inhibitory effects of PLN. On the other hand, the enhancement in SERCA2a activity due to exercise was shown to occur by post-translational modifications when mice were subjected to exercise for 6 weeks and a significant reduction in cellular O-GlcNAcylation was noted (Bennett *et al.* 2013, Belke 2011). Upon comparing mice selected for a high running capacity to those with low running capacity, a decrease in O-GlcNAcylated SERCA2a to total SERCA2a ratio was reported (Johnsen *et al.* 2013). Such effect was facilitated by SP1 transcription factor, an O-GlcNAcylation target, which is known to alter the activity of some cardiac genes (Belke, 2011). It emphasized that the role of other posttranslational modifications, such as acetylation, glutathionylation and sumoylation in the overexpression of SERCA2a due to exercise remains to be investigated.

Concluding Remarks

From the foregoing discussion, it is evident that SR plays a critical role not only in determining the status of heart function but also in maintaining the intracellular concentration of Ca^{2+} at a low level. Such functions of SR are carried out by the presence of Ca^{2+}-cycling proteins, ryanodine receptors and Ca^{2+}-pump ATPase (SERCA2a), which are directly involved in Ca^{2+}-release and Ca^{2+}-accumulation for the occurrence of cardiac contraction and relaxation, respectively. Furthermore, the regulation of SR Ca^{2+}-transport activities is carried out by different Ca^{2+}-regulatory proteins such as phospholamban (mainly) and InsP3R as well as different phospholipids. In addition to several structural proteins, some Ca^{2+}-binding and Ca^{2+}-buffering proteins such as calsequestrin and SAR have been demonstrated to determine the SR function. Extensive work has revealed that phosphorylation of phospholamban by protein kinase A or CaM Kinase relieves its inhibitory effect on Ca^{2+}-cycling proteins in the SR membrane, promotes Ca^{2+}-transport activities and augments cardiac function.

On the other hand, activation of different proteases and phospholipases as well as changes in gene expression results in depressing the Ca^{2+}-release and Ca^{2+}-pump activities, induce myocardial cell damage and impair cardiac performance. The functions of SR Ca^{2+}-cycling and Ca^{2+}-regulatory proteins are also markedly altered by several post-translational modifications involving various reactions such as oxidation, nitrosylation, acetylation, lipidation and glycosylation; these alterations are associate with cardiac dysfunction. It should be emphasized that the occurrence of oxidative stress and Ca^{2+}-handling abnormalities are now known to result in the development of SR defects and subsequent myocardial derangements. Thus different components of the SR membrane as well as several processes involved in the modification of their functions are considered to be excellent targets for drug development to improve heart function under a wide variety of pathophysiological conditions.

Abbreviations

Adenosine Monophosphate-Activated Protein Kinase, AMPK; Endoplasmic Reticulum, ER; Inositol Trisphosphate, IP3; Inositol-Trisphosphate Receptor, InsP3R; Junctional Sarcoplasmic Reticulum, JSR; Longitudinal Sarcoplasmic Reticulum, LSR; Myosin Heavy Chain, MHC; Nexilin, NEXN; Phospholamban, PLB or PLN; Ryanodine Receptor, RyR; Sarcalumenin, SAR; Sarcolipin, SLN; Sarcoplasmic Reticulum, SR; Sarcoplasmic Reticulum ATPase, SERCA; Transverse Tubules, T-Tubules; Trimeric Intracellular Cation-Selective Channel, TRIC-A/SRP-27

Conflict of Interest

There is no conflict of interest.

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