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New Insights in Cardiac Calcium Handling and Excitation-Contraction Coupling

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Abstract

Excitation-contraction (EC) coupling denotes the conversion of electric stimulus in mechanic output in contractile cells. Several studies have demonstrated that calcium (Ca^{2+}) plays a pivotal role in this process. Here we present a comprehensive and updated description of the main systems involved in cardiac Ca^{2+} handling that ensure a functional EC coupling and their pathological alterations, mainly related to heart failure.

Keywords

Calcium; RyR; Mitochondria; SerCa; Contraction; Heart Failure

1 Introduction

Each heartbeat is the result of calcium (Ca^{2+}) release and reuptake. During this cycle, the presence of this cation is essential to convert electric stimulation (action potential) in mechanic output (contraction), in a process commonly termed excitation-contraction (EC) coupling (Santulli et al. 2017a; Fabiato and Fabiato 1975). The action potential is the electrical signal that depolarizes the plasma membrane of cardiac myocytes, allowing the entrance of a relatively low amount of extracellular Ca^{2+}, which in turn induces high Ca^{2+} release from the sarcoplasmic reticulum (SR) (Lenzi and Caniggia 1953). Cytosolic Ca^{2+}

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binds to myofilaments, activating contractile machinery (Ebashi et al. 1967; Reddy and Honig 1972). This "Ca^{2+}-induced Ca^{2+} release" (CICR), represents a positive feedback mechanism that allows the functional coupling between plasma membrane and SR (Katz 1967; Fabiato and Fabiato 1979; Fabiato 1983; Isenberg and Han 1994).

2 Microanatomy of EC Coupling

In cardiac cells, the structural units that mediate CICR are termed "diads" (Page et al. 1971; Soeller and Cannell 1997), consisting in specialized cellular micro-domains each composed by terminal cisternae of SR, also known as junctional SR, localized in close proximity to a tubular invagination of the plasma membrane, the transverse tubule (T-tubules) (Soeller and Cannell 1997; Shacklock et al. 1995; Clark et al. 2001). On the side of plasma membrane, along T-tubules, there are voltage-gated Ca^{2+} channels (T-Type and L-type, also known as dihydropyridine receptors, DHPRs), whereas on the side of SR cisternae there are intracellular Ca^{2+} release channels (ryanodine receptors, RyRs) (Pinali et al. 2017; Crocini et al. 2016; Li et al. 2015; Fameli et al. 2014).

Ca^{2+} channels on T-tubules are activated by depolarization and through them Ca^{2+} from the extracellular compartment goes in the cytosol, and activates RyR channels located on the SR of the same diad (Keizer and Levine 1996; Nakai et al. 1997). It has been estimated that for each Ca^{2+} channel opened on T-tubules, about 4–6 RyR channels are activated on SR, which in turn can activate neighboring RyR channels, resulting in massive release of Ca^{2+} from SR (Wang et al. 2001; Paolini et al. 2004).

3 Troponin, Tropomyosin, and Ca^{2+}: How Force Is Produced

The troponin complex consists of three subunits: tropomyosin-binding (T), inhibitory (I), and Ca^{2+} sensor (C). Troponin-T anchors the other two subunits on tropomyosin. Troponin I, under resting intracellular levels of Ca^{2+}, competes with tropomyosin for a common binding site on actin myofilaments, forcing tropomyosin into a position where it sterically blocks the binding of myosin heads (Lehman et al. 2013; Rao et al. 2014). The binding of cytosolic Ca^{2+} to Troponin-C induces conformational changes leading to the so-called activated state, in which myosin-binding sites on actin are exposed (Wang et al. 1999; Lehman et al. 2009). Then, the formation of cross-bridges between actin and myosin produces the sliding of myofilaments one over the other, eventually resulting in muscle contraction (Brunello et al. 2014; Kawai et al. 2006; Piazzesi and Lombardi 1996).

The inodilator levosimendan is a Ca^{2+} sensitizer that acts via binding the Ca^{2+}-saturated Troponin-C (Gustafsson et al. 2017). In particular, hydrogen-bond donor and acceptor groups on the pyridazinone ring and on the mesoxalonitrile–hydrazone moieties of levosimendan bind to a hydrophobic pocket of the Ca^{2+}-saturated amminoterminal domain of Troponin-C (Robertson et al. 2008). The main consequence of levosimendan binding is that the Ca^{2+}-saturated Troponin-C is stabilized in the presence of the drug, thereby promoting contractile force without an increase in the amplitude of intracellular Ca^{2+} transient. Levosimendan also acts via activation of ATP-sensitive K^+ channels (Grossini et

al. 2009). In clinical trials levosimendan exhibited non-consistent results, especially in terms of mortality (Mebazaa et al. 2007; Polzl et al. 2017; Landoni et al. 2017).

Ca^{2+} handling within cardiac myocytes is in a delicate and dynamic equilibrium, which relies on several physiological modulators and subcellular systems, structurally and functionally related. Importantly, the amount of Ca^{2+} extruded by the cell during relaxation must be the same as the amount entering during the contraction (Karlstad et al. 2012). After the contraction phase, several mechanisms contribute to relaxation. Notably, Ca^{2+} is a fundamental determinant also during relaxation, since the correct functioning of channels responsible for cytosolic Ca^{2+} removal strictly depends on Ca^{2+} concentration (Allen et al. 1988; Plummer et al. 2011; Subramani et al. 2005).

4 Ca^{2+} Handling in the Pathogenesis of Heart Failure: New Insights

An accurate cardiac Ca^{2+} handling warrants the appropriate contraction that allows the heart to pump sufficient blood to meet the metabolic demand of the body. Impairment in cardiac pump function characterizes the pathological condition of heart failure (HF) (Karlstad et al. 2012; Kitsis and Narula 2008). Malfunction of the processes involved in Ca^{2+} handling plays an important role in the pathogenesis of HF, and this kind of alteration in myocytes is a primary defect causing contractile dysfunction in HF (Yano et al. 2005). Modifications in the expression and/or activity of Ca^{2+} channels, alongside with alterations of cardiomyocyte architecture (T-tubules), seem to have a determinant role in failing myocytes (Balke and Shorofsky 1998). The involvement of different Ca^{2+} transporters has been related to the stage and etiology of HF; indeed, studies in human failing hearts suggest that patients with ischemic cardiomyopathy are characterized by impaired Ca^{2+} uptake, while patients with idiopathic dilated cardiomyopathy exhibits mainly modifications in Ca^{2+} release (Sen et al. 2000).

Cardiac contraction is the result of isometric force (or ventricular pressure) and rapid shortening to allow ejection of the blood (Caremani et al. 2016; Colomo et al. 1994). Both of them rely on Ca^{2+}, specifically on amplitude/duration of Ca^{2+} transients, and on sensitivity of myofilaments to Ca^{2+}. To allow the generation of Ca^{2+} transients appropriate in terms of duration and amplitude, cardiac myocytes need a high – and at the same time flexible – capacity of Ca^{2+} buffering. Normally the amount of Ca^{2+} bound is in a 100:1 ratio compared to Ca^{2+} free in the cytosol, and during contraction such ratio immediately increases (about tenfold) in favor to free Ca^{2+} (MacGowan et al. 2006). Ca^{2+} buffering should ensure an optimal removal of free Ca^{2+} from cytosol in order to have an appropriate amount of Ca^{2+} available to the contraction in the next beat.

Each cycle of EC coupling needs a dynamic interplay between Ca^{2+} transient and myofilaments. The sensitivity of myofilaments to Ca^{2+} is high when the myofilaments are stretched, *i.e.* in the phase of cardiac blood filling (diastole) (Zhao et al. 2016). Therefore, right after relaxation the myofilaments are more responsive to Ca^{2+} binding. Such autoregulation is a key mechanism underlying the coordination in EC coupling. Hence, when a perfect overlap of high Ca^{2+} transient and high myofilaments sensitivity to Ca^{2+} is obtained, an appropriate force is generated, leading to an optimal contraction.

Although the exact mechanisms involved in cardiac Ca^{2+} handling are not entirely understood, it is known (Benitah et al. 2003) that EC coupling and cardiac performance are mainly based on two mechanisms: (1) Synchronized Ca^{2+} release during contraction; (2) Effective Ca^{2+} reuptake that ensure a good and robust termination of Ca^{2+} dependent contraction.

To satisfy the first point, there are systems that mediate Ca^{2+} flux towards the cytosol, from extracellular compartment or from intracellular Ca^{2+} stores, *i.e.* SR, during EC coupling (Fig. 1). For the second one, there are systems involved in retrograde Ca^{2+} flux, to terminate EC coupling (Fig. 2).

5 Ca^{2+} Fluxes during Systole

Ca^{2+} flux towards the cytosol starts with the entrance of a small amount of Ca^{2+} from extracellular space, triggering EC coupling: the depolarization wave is “transformed” in high Ca^{2+} release from intracellular store for contraction (Nanasi et al. 2017). The individual events of local Ca^{2+} release from SR are named Ca^{2+} sparks and reflect the activation of a cluster of about 6–20 Ca^{2+} channels on SR (Xie et al. 2013). Single Ca^{2+} sparks occur also at rest, and a crucial difference from Ca^{2+} sparks events during EC coupling is the synchronization; indeed, the action potential is able to synchronize several thousand of Ca^{2+} sparks within the same cell (Louch et al. 2013). Thus, individual events of local Ca^{2+} release are overlapping in time and space during EC coupling.

The main cellular complexes mediating Ca^{2+} flux towards cytosol for EC coupling are: voltage sensitive Ca^{2+} channels (T- and L-type) on the plasma membrane and RyRs on the SR.

6 Voltage-Dependent Ca^{2+} Channels

In myocytes there are two main types of voltage-dependent Ca^{2+} channels: T-type and L-type Ca^{2+} channels (Gonzalez-Rodriguez et al. 2015; Shaw and Colecraft 2013). The T-type channels are not preferentially located in the junctional region inside the diads, and the Ca^{2+} current generated by this kind of channels is negligible, with a minimal contribute to EC coupling (Zhou and January 1998). The L-type channels, also known as dihydropyridine receptors (DHPRs), are the main voltage dependent Ca^{2+} channels involved in EC coupling; they mainly localize on the T-tubule, in close proximity of Ca^{2+} channels on SR terminal cisternae (Bodi et al. 2005). DHPRs are activated by depolarization, allowing the Ca^{2+} to enter inside the cytosol and trigger CICR. A strategic auto-regulation of the CICR mechanism occurs at this level: indeed, DHPRs are inhibited by Ca^{2+} itself at the cytosolic side, limiting the amount of Ca^{2+} entry after depolarization. This local inhibitory effect on DHPRs is mediated by calmodulin, which binds the C-terminal domain on the receptor (Pott et al. 2007). Ca^{2+} released from SR in the same sarcolemmal-SR junction has also a modulatory effect on L-type receptors: when SR Ca^{2+} release occurs, the Ca^{2+} flux through DHPRs is reduced (Shiferaw et al. 2003). These events confirm that the Ca^{2+} needed for the contraction primarily derives from SR, since Ca^{2+} channels on plasma membranes are quickly inhibited after the entrance of small amount of Ca^{2+}.

As mentioned above, action potential is responsible for synchronization of Ca^{2+} release from SR. The specific organization of ion channels on the plasma membrane, and in particular on the specialized invaginations of the T-tubules, plays a pivotal role in EC coupling (Oyehaug et al. 2013; Galbiati et al. 2001). Indeed, the loss of these structures leads to aberrant Ca^{2+} handling with blunted contractility, and such alteration has been mechanistically associated to HF (Wei et al. 2010).

In humans, HF secondary to dilated, hypertrophic, and ischemic cardiomyopathy, is related to aberrant alterations of T-tubule structure and the subsequent not-appropriate organization of voltage-dependent Ca^{2+} channels (Lyon et al. 2009). These anomalies could also be related to impaired function of junctophilins, proteins that are responsible for appropriate positioning of voltage-gated Ca^{2+} channels on T- tubules (Pinali et al. 2017; Schobesberger et al. 2017).

7 Key Role of RyR2 in Cardiac EC Coupling

RyRs are intracellular release channels, deputed to Ca^{2+} release from intracellular stores; the RyR2 isoform represents the most abundant isoform of this family in cardiomyocytes (Tunwell et al. 1996). This name was attributed based on the molecule with a high binding affinity to these receptors: the ryanodine, a natural product, known to induce a paralytic effect on striated muscle (Sutko et al. 1997; Rumberger and Ahrens 1972).

These channels have a tetrameric structure, similar to a mushroom, with the stalk across the SR membrane and the cap towards the cytosol. In this large structure, it is possible to identify at least two functional domains: C-terminus, which represents the ion pore across the membrane, and N-terminus that contains numerous modulatory sites (Gao et al. 1997). Indeed, RyR activity is highly regulated by several molecules – including calmodulin, FK-506 binding protein (FKBP), sorcin, junctin, and triadin (Balshaw et al. 2001; Anthony et al. 2007) – linked to the receptor, which thus represents the scaffold of a large macromolecular complex (Santulli et al. 2017b). Calmodulin and sorcin, two small proteins with high affinity for Ca^{2+}, are able to inhibit RyR when Ca^{2+} levels in the cytosol are higher than a threshold value, preventing further Ca^{2+} release from SR. This phenomenon is involved in EC coupling termination.

RyR has also several sites modulated by Ca^{2+}, Mg^{2+}, phosphorylation, and oxidation, making this receptor also a sensor of intracellular redox state (Hain et al. 1995; Chugun et al. 2007; Xie et al. 2015). Therefore, RyR activity is the result of a multifaceted interactome specialized in Ca^{2+} handling.

Inositol-1,4,5, trisphosphate (IP3) receptors (IP3Rs) represent another example of intracellular Ca^{2+} release channel. Located on the SR as RyR, they are activated by a second messenger, IP3, involved in several pathways. These receptors are closely related to the RyR family, sharing a high structural homology (Santulli et al. 2017a, b; Maltsev et al. 2017). Although there are several stimuli that induce IP3 accumulation, the physiological depolarization of cardiac myocyte, does not seem to activate IP3Rs and their involvement seem to be limited to the regulation of transcription of important modulator of Ca^{2+} handling

machinery (*e.g.* CamKII, calcineurin), indirectly contributing to regulate the capacity of the cells to maintain Ca^{2+} homeostasis, indispensable for appropriate EC coupling and contractility (Santulli et al. 2017a; Santulli and Marks 2015). Moreover, IP3R has a different distribution in atrial and ventricular myocytes, compared to RyR2; in particular, IP3Rs are principally located in the atrial myocyte and also in Purkinje fibers (Luo et al. 2008; Mignery et al. 1990). Purkinje fibers are a specialized conduction system, and IP3Rs can modulate the transfer of depolarization wave through ventricular mass.

8 Ca^{2+} Fluxes During Diastole

To ensure muscle relaxation, mechanisms of Ca^{2+} reuptake from the cytosol actively mediate a retrograde Ca^{2+} flux. The main "cytosolic Ca^{2+} scavengers", Sarco-Endoplasmic reticulum Ca^{2+} ATPase (SerCa) and Na^{+}/Ca^{2+} exchanger, achieve this function (Fig. 2). A large portion of Ca^{2+} is pumped by SerCa from the cytosol back to the SR, but the relative contribute of different Ca^{2+} removal systems can depend on the species.

9 Functional Role of Na^{+}/Ca^{2+} Exchanger in Ca^{2+} Reuptake

Na^{+}/Ca^{2+} exchanger mediates reversibly influx or efflux of Ca^{2+}, depending on concentration of free Ca^{2+} inside the cytosol, but normally it works in Ca^{2+} efflux mode (Fujioka et al. 2000; Luongo et al. 2017). In cardiomyocytes this channel represents the major Ca^{2+} efflux system, with a critical role in the regulation of Ca^{2+} cellular content (Zhu et al. 2015; Acsai et al. 2011). Indeed, some alterations of ionic equilibrium inside the cell, that induce increase in Na^{+} intracellular levels, can trigger changes in the activity of the channel, which starts to work in reverse mode, mediating Na^{+} efflux, with influx of Ca^{2+} ions (Kang and Hilgemann 2004).

10 SerCa-ATPase

SerCa ATPase represents a fundamental pump system mediating Ca^{2+} reuptake in the SR/ER (Zima et al. 2014). In cardiomyocytes, SerCa removes the Ca^{2+} from cytosol during relaxation with an active process (ATP hydrolysis), in order to terminate the EC coupling cycle and to restore Ca^{2+} levels inside SR, necessary for the next contraction.

The correct activity of SerCa, and the indirect interplay with RyR2 that promotes Ca^{2+} flux in the opposite direction, are essential to have an EC coupling cycle with appropriate amplitude and synchronization in space and time. Ca^{2+} itself plays a pivotal role in mediating such interplay (Collins and Thomas 2001). SerCa, as well as RyR2, is highly regulated not only directly by Ca^{2+}, but also by other molecules that are sensitive (CaMKII) or not (PKA) to Ca^{2+}. These two kinases, as seen for RyR2, are able to regulate SerCa, but not via direct phosphorylation, but through phosphorylation of the most important regulator of SerCa, phospholamban. Phospholamban (PLB), is an endogenous inhibitor of SerCa that limits the affinity of the pump for Ca^{2+}. PKA can phosphorylate PLB at Ser^{16}, inhibiting PLB and therefore activating SerCa, increasing its pumping rate (Simmerman et al. 1986). CaMKII, whose activation relies also on the exchange protein directly activated by cAMP (Epac) pathway (de Rooij et al. 1998; Lymperopoulos et al. 2014; Parnell et al. 2015), is able

to phosphorylate PLB at Thr^{17}, leading also in this case to an acceleration of SR Ca^{2+} uptake (Simmerman et al. 1986). SerCa is also regulated by the metabolic state of the cell in terms of ATP/ADP ratio, and redox-status (Zima et al. 2014). Alterations in expression or activity of SerCa, strongly contribute to HF development and progression, through dysfunctional Ca^{2+} handling. In particular, several studies show that both mRNA and protein levels of SerCa pump are downregulated in HF (Currie and Smith 1999; Armoundas et al. 2007). The decrease in SerCa/PLB ratio results in impaired SR Ca^{2+} uptake (Linck et al. 2000). Moreover, the regulation of SerCa by both PKA (Schwinger et al. 1998) and CaMKII (Schwinger et al. 1999) is significantly impaired in failing hearts.

11 Intracellular Ca^{2+} Leak: Definition, Pathophysiology, and Interventions

RyR2 interactome ensures the appropriate amplitude and kinetics of Ca^{2+} cycling, indispensable for cardiac contractility. Alterations in RyR2 and/or in RyR2 interactome, are among the main identified aspects of HF (Ono et al. 2000; Kohno et al. 2003). All the events that are able to affect the opening frequency of RyR2, determining changes in amplitude or duration of Ca^{2+} release, can predispose to contractility dysfunction (Patel et al. 2000). In particular, the phenomenon of Ca^{2+} leak, defined as inappropriate release of Ca^{2+} from the SR (*e.g.* during the diastolic phase), is determinant in HF progression (Hofer et al. 1996). In pathological conditions such as HF, there is a high release of Ca^{2+} from SR during diastole, reducing the availability of SR Ca^{2+} for the subsequent contraction, thereby impairing contractility (Santulli et al. 2017b).

FKBP12.6, also known as Calstabin2, plays an important pathophysiological role in the regulation of RyR2 function. Indeed, it stabilizes a conformation of the channel that prevents Ca^{2+} leak (Timerman et al. 1996; Lam et al. 1995; Xin et al. 1999; Yuan et al. 2014). There are numerous events, both acute and chronic, that trigger instability of RyR macromolecular complex. One typical example is represented by its phosphorylation, which induces the dissociation from the receptor of its stabilizing molecule, FKBP12.6 (Yuan et al. 2014). Chronic activation of beta-adrenergic system increases PKA activity (Santulli et al. 2013), with consequent phosphorylation of RyR (Takasago et al. 1991). Phosphorylation of RyR by CaMKII has also been reported in HF (Kushnir et al. 2010). Furthermore, ROS-linked oxidation of RyR affects the normal Ca^{2+} handling, compromising the correct contraction of myocytes during HF (Santulli et al. 2015).

Several benzothiazepine derivatives, including *JTV519* (also known as *K201*, 4-[−3{1-(4-Benzyl) piperidinyl}propionyl]-7-methoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine) (Kohno et al. 2003; Hachida et al. 1999a, b; Sacherer et al. 2012) and its substructure *S107* (7-methoxy-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine) (Thevis et al. 2009; Matecki et al. 2016; Lukyanenko et al. 2017) have shown cardioprotective and antiarrhythmic properties by decreasing Ca^{2+} leak (Santulli et al. 2017a; Xie et al. 2013, 2015).

Henceforth, RyR2 represents the central target of many pathways dysregulated in cardiac pathological conditions, including adrenergic dysfunction, metabolic disorders, ROS production: all of these conditions are accompanied by alterations in Ca^{2+} handling and subsequent impairment in contractility.

12 Role of Mitochondrial Ca^{2+} in Metabolism-Contraction Coupling

Mitochondria play a strategic role in ensuring an adequate EC coupling (Miragoli and Cabassi 2017; Umanskaya et al. 2014; Gambardella et al. 2017; Torrealba et al. 2017). Indeed, cardiac myocytes are critically dependent on constant and appropriate energy supply, alongside with a finely tuned Ca^{2+} handling (Torrealba et al. 2017; Sorriento et al. 2017; Sheeran and Pepe 2017). Mitochondria and SR are functionally and structurally associated and, at the point of interaction (mitochondrial associated membranes) Ca^{2+} transits from SR to mitochondria (Min et al. 2012; Bononi et al. 2017). Ca^{2+} that enters in mitochondria is able to increase their bioenergetics, but at the same time, mitochondria, allowing Ca^{2+} entrance through the mitochondrial Ca^{2+} uniporter (De Stefani et al. 2011; Liu et al. 2017; Granatiero et al. 2017), can act as local Ca^{2+} buffers, actively participating in Ca^{2+} handling (Walsh et al. 2009; Gunter and Sheu 2009; Drago et al. 2012; Morciano et al. 2017). However, mitochondrial Ca^{2+} overload has been shown to be detrimental in various cell types (Liu et al. 2016; Kostic et al. 2015; Charles et al. 2017), and, specifically, it has been proven to play a mechanistic role in the pathogenesis of HF (Santulli et al. 2015). Therefore, our hypothesis is that whereas transient mitochondrial Ca^{2+} uptake promotes ATP production, prolonged or excessive Ca^{2+} uptake can be harmful.

The ability of mitochondria to respond to changes in Ca^{2+} levels, increasing metabolic outcome, and acting as Ca^{2+} scavenger, contributes to the adequate contractile response of cardiomyocytes. Indeed, alterations in these processes can lead to increase in cytosolic Ca^{2+} with potential activation of detrimental pathways that have been associated with HF, including CaMKII (Zhang and Brown 2004). Additionally, alterations in SR-mitochondria contacts have been found in cardiac dysfunction and HF (Lopez-Crisosto et al. 2017).

Whether mitochondrial Ca^{2+} transients exist during physiological EC coupling, in a beat-to-beat fashion, remains to be determined. Anyway, an important aspect of these phenomena is that Ca^{2+} proves once again its ability to act as a messenger, communicating to mitochondria the energetic demand of the cell, for adequate contraction.

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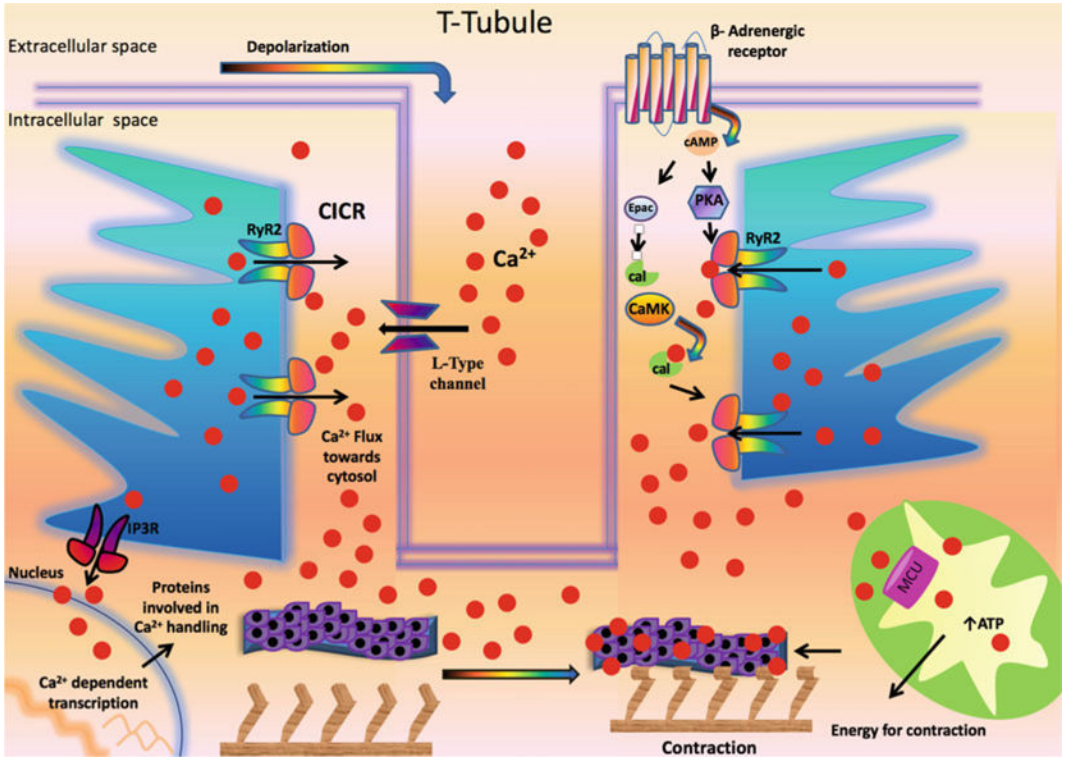

Fig. 1.

Role of Ca^{2+} in excitation-contraction coupling in cardiomyocyte. Ca^{2+}: calcium; cal: calmodulin; CaMK: Ca^{2+}/calmodulin-dependent protein kinase; CICR: Ca^{2+}-induced Ca^{2+} release; Epac: exchange protein directly activated by cAMP; IP3R: inositol 1,4,5-trisphosphate receptor; MCU: mitochondrial Ca^{2+} uniporter; PKA: Protein Kinase A; RyR2: Type 2 ryanodine receptor Ca^{2+} release channel

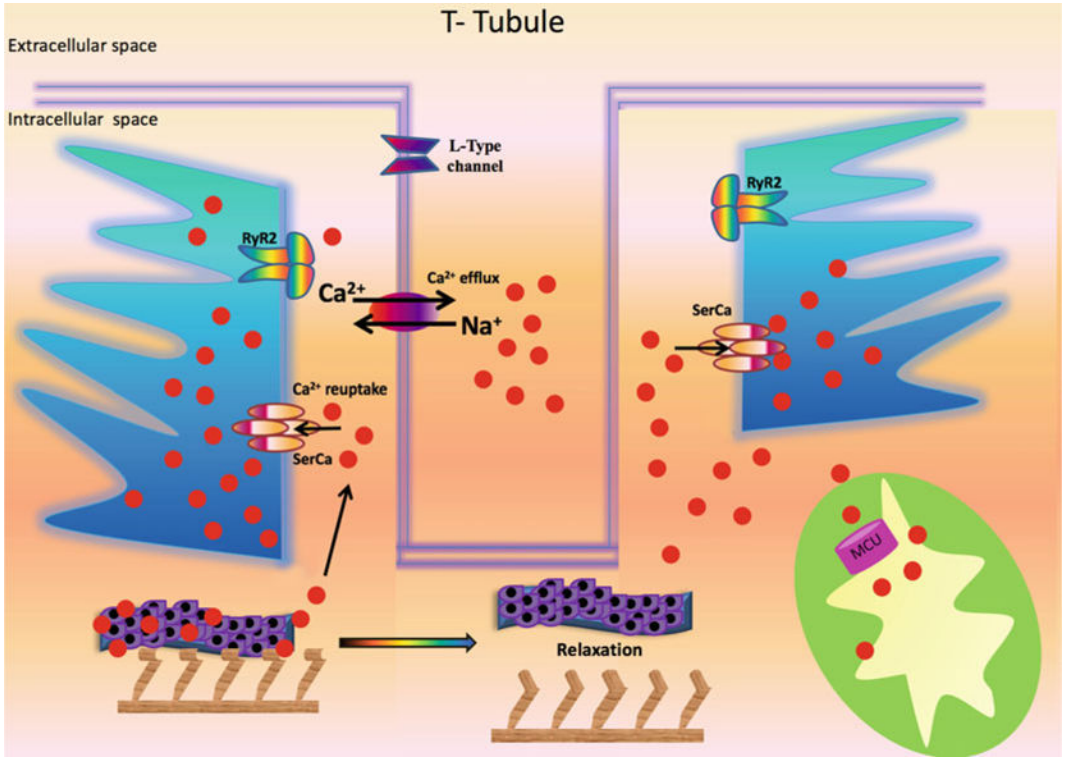

Fig. 2.

Mechanistic role of Ca^{2+} in the relaxation phase. Ca^{2+}: calcium; MCU: mitochondrial Ca^{2+} uniporter; Na^{+}: sodium; RyR2: Type 2 ryanodine receptor Ca^{2+} release channel; SERCA: sarco/endoplasmic reticulum Ca^{2+}-ATPase