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A calcium-induced calcium release mechanism mediated by calsequestrin

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ABSTRACT

Calcium (Ca^{2+})-induced Ca^{2+} release (CICR) is widely accepted as the principal mechanism linking electrical excitation and mechanical contraction in cardiac cells. The CICR mechanism has been understood mainly based on binding of cytosolic Ca^{2+} with ryanodine receptors (RyRs) and inducing Ca^{2+} release from the sarcoplasmic reticulum (SR). However, recent experiments suggest that SR lumenal Ca^{2+} may also participate in regulating RyR gating through calsequestrin (CSQ), the SR lumenal Ca^{2+} buffer. We investigate how SR Ca^{2+} release via RyR is regulated by Ca^{2+} and calsequestrin (CSQ). First, a mathematical model of RyR kinetics is derived based on experimental evidence. We assume that the RyR has three binding sites, two cytosolic sites for Ca^{2+} activation and inactivation, and one SR lumenal site for CSQ binding. The open probability (P_o) of the RyR is found by simulation under controlled cytosolic and SR lumenal Ca^{2+}. Both peak and steady-state P_o effectively increase as SR lumenal Ca^{2+} increases. Second, we incorporate the RyR model into a CICR model that has both a diadic space and the junctional SR (jSR). At low jSR Ca^{2+} loads, CSQs are more likely to bind with the RyR and act to inhibit jSR Ca^{2+} release, while at high SR loads CSQs are more likely to detach from the RyR, thereby increasing jSR Ca^{2+} release. Furthermore, this CICR model produces a nonlinear relationship between fractional jSR Ca^{2+} release and jSR load. These findings agree with experimental observations in lipid bilayers and cardiac myocytes.

1. Introduction

In cardiac myocytes, Ca^{2+}-induced Ca^{2+} release (CICR) is the process whereby Ca^{2+} influx through voltage-dependent Ca^{2+} channels induces a large Ca^{2+} release from the sarcoplasmic reticulum (SR) and consequential muscle contraction (Fabiato, 1983). It is generally accepted that a rapid local increase in Ca^{2+} concentration ($[Ca^{2+}]$) in the diadic space between the sarcolemma and the SR membrane, called a "Ca^{2+} spark" (Cheng et al., 1993), is the basic unit of CICR in cardiac myocytes (Cannell et al., 1994). Since CICR is a primary link between the electrical activity of the membrane and the mechanical contraction of the muscle, i.e., excitation–contraction (EC) coupling, its abnormality may be a cause of cardiac arrhythmia (Boyden and ter Keurs, 2001; Chudin et al., 1999; Clusin, 2003).

Because of the importance of CICR, the mechanism by which it is regulated is an area of active study. Fabiato suggested from experiments on skinned cardiac cells that CICR is regulated by time- and Ca^{2+}-dependent activation and inactivation through the SR Ca^{2+} channels or ryanodine receptors (RyRs) (Fabiato, 1985). Cytosolic Ca^{2+} binds to the activation site of the RyR and thus triggers SR Ca^{2+} release, providing a positive feedback. Although the termination mechanism of Ca^{2+} sparks remains controversial, Sham et al. (1998) suggested that the SR Ca^{2+} release is terminated by localized and Ca^{2+}-dependent inactivation in which Ca^{2+} binds to the inactivation site of the RyR, with a higher affinity at a lower rate constant than the activation site, leading to a negative feedback to terminate SR Ca^{2+} release.

Indeed, considerable attention has been paid to the cytosolic aspects of Ca^{2+} release where cytosolic Ca^{2+} alone plays a role in regulating Ca^{2+} release through the RyR. However, some experiments from lipid bilayers suggest that SR lumenal Ca^{2+} can also regulate the RyR channel gating (Sitsapesan and Williams, 1997; Gyorke and Gyorke, 1998). These studies demonstrate that Ca^{2+}-sensing sites exist in the SR lumen (Ching et al., 2000), and high (low) SR Ca^{2+} load enhances (decreases) the open probability of the RyR. Therefore, SR Ca^{2+} load can be considered not only a Ca^{2+} store for release, but also influences the RyR channel gating. Furthermore, potentiation of SR Ca^{2+} release by increased SR Ca^{2+} load can produce a nonlinear relationship between the fractional SR Ca^{2+} release and the SR Ca^{2+} load (Bassani et al., 1995; Shannon et al., 2000b). So the question arises: How does the SR lumenal Ca^{2+} regulate (or modulate) the activity of the RyR channel?

It has been suggested that the regulation occurs through either a direct Ca^{2+} binding to the RyR inside the SR or via the SR

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lumenal auxiliary proteins calsequestrin (CSQ), triadin and junctin (Gyorke and Gyorke, 1998; Ching et al., 2000; Gyorke et al., 2004). In recent experiments with a lipid bilayer, Gyorke et al. (2004) proposed that CSQ, the SR lumenal Ca^{2+} buffer, inhibits (enhances) RyR activity at low (high) SR Ca^{2+} load through its association (dissociation) with the RyR. However, the precise molecular mechanisms by which CICR via the RyR is modulated by CSQ are still elusive.

The local control theory of EC coupling (Stern, 1992) suggests that global Ca^{2+} release in the whole cell is primarily controlled by local Ca^{2+} in the junctional area between the T-tubule and the SR, where Ca^{2+} influx via L-type Ca^{2+} channels, or dihydropyridine receptors (DHPRs), triggers Ca^{2+} release through co-localized RyR channels. The junctional area is divided into two domains: diadic space and junctional SR (jSR) (see Fig. 1). The jSR is functionally separated from the network SR (NSR), which is a sparse and continuous subcompartment of the SR. Most SR Ca^{2+} pumps reside in the NSR for sequestering released Ca^{2+}. CSQ is found mostly in the jSR, not in the network SR (Jorgensen and Campbell, 1984). Furthermore, experimental studies have suggested that CSQ actively participates in the regulation of RyR activity from the jSR (Beard et al., 2002, 2004, 2005; Dulhunty et al., 2006; Gyorke et al., 2004).

Although several mathematical models of CICR incorporated the fact that the lumenal Ca^{2+} has a regulatory role in RyR gating directly (Laver, 2007; Sobie et al., 2002; Shannon et al., 2004) or indirectly mediated by CSQ (Snyder et al., 2000), none of those models take the interaction between RyR and CSQ (RyR–CSQ) in the regulation of CICR into account. Thus, our goal here is to develop a model of RyR gating that directly incorporates regulation by CSQ, and to incorporate this model into a CICR model with which to address the following questions: (a) What are the roles of CSQ in RyR channel gating and CICR? (b) How does the fractional SR Ca^{2+} release depend on the SR Ca^{2+} load? (c) What is the effect of changing the concentration of total CSQ inside the jSR?

Our CICR model shows that tight control of CICR can be obtained by a localized Ca^{2+}-dependent regulation, as well as by RyR–CSQ interaction. The description of RyR–CSQ in this model yields a good correlation with recent experimental observations, and this model produces a nonlinear relation between the fraction of jSR Ca^{2+} release and the jSR load that fits well with the experimental findings of Shannon et al. (2000b).

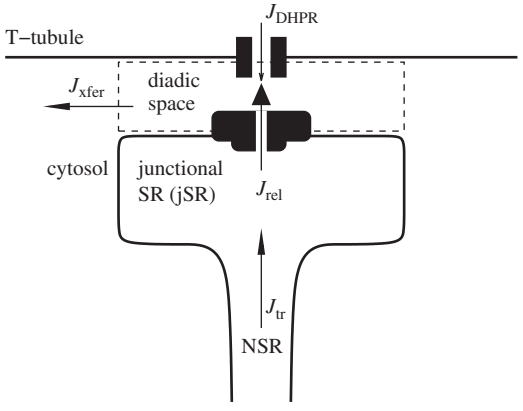

Fig. 1. A diagram of local Ca^{2+} transport at the junctional area. Ca^{2+} influx (J_{DHPR}) enters the diadic space (indicated by the box with the dotted line) and induces SR Ca^{2+} release (J_{rel}) from the junctional SR (jSR). The local Ca^{2+} is removed from the diadic space to the cytosol (J_{xfer}). Ca^{2+} is supplied to the jSR from the network SR (NSR) (J_{tr}).

2. The model

2.1. Overview

We focus on CICR regulation by CSQ, which is primarily controlled by local Ca^{2+} in the junctional area between the T-tubule and the surface of SR membrane. To describe the behavior of Ca^{2+} release and transport, we construct a model of CICR, based on that of Rice et al. (1999), with modifications as follows. First, our kinetic model of RyR is a generalization of the four state model of Stern et al. (1999) that specifically incorporates cytosolic Ca^{2+} and CSQ binding. Second, we use master equations to determine the RyR open probability rather than use a fully stochastic model. Stochastic attrition of RyR channels may be an important factor for termination of the RyR activity (Stern, 1992), but local Ca^{2+} dependent inactivation, modeled in a deterministic way (via deterministic master equations), can also terminate Ca^{2+} release (Sham et al., 1998) and is used in our model. Third, a specified L-type Ca^{2+} current is used as the Ca^{2+} influx to stimulate CICR, allowing us to focus on Ca^{2+} release dynamics of RyR channels. Because of this third feature, our CICR model does not exhibit graded response; graded response appears to result primarily from the stochastic behavior of L-type calcium channels in response to voltage stimuli.

2.2. Experimental observations

CSQ is a Ca^{2+}-binding protein with high capacity and moderate affinity, and is localized in close proximity to the RyR channel in the lumen of jSR (Jorgensen and Campbell, 1984). Each CSQ molecule has a capacity to bind about 40–50 Ca^{2+} ions (Maclennan and Wong, 1971). The equilibrium constant of CSQ binding to Ca^{2+} ($K_{D,CSQ} = 0.63$ mM) (Shannon and Bers, 1997) is known, but other kinetic constants of CSQ binding are not known yet (Gyorke et al., 2002). Donoso et al. (1995) reported that Ca^{2+} dissociation from or association to CSQ occurs on a much faster time scale than the Ca^{2+} release process.

Contact between the RyR and CSQ is mediated by two junctional SR membrane proteins triadin and junctin (Guo and Campbell, 1995; Jones et al., 1995). These four proteins, RyR, triadin, junctin, and CSQ, form a quarternary "RyR complex" as a unit of Ca^{2+} regulation in EC coupling (Zhang et al., 1997) (see Fig. 2). Triadin and junctin are anchoring proteins between CSQ and RyR, but it has also been reported that CSQ can bind directly to RyR (Cho et al., 2007).

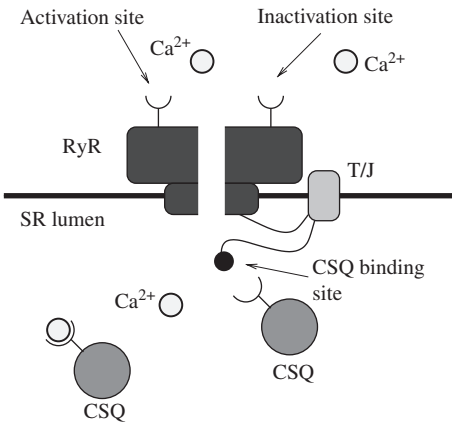

Fig. 2. Schematic description of RyR, CSQ, junctin, and triadin. The RyR has two cytosolic binding sites (activation and inactivation) and one jSR lumenal CSQ binding site. CSQ can bind either with Ca^{2+} or the RyR mediated by the linkage of triadin and junction (T/J).