

Ca²⁺-induced Calcium-Release in a Rat Ventricular Cell

---- A Model Study

L. Sun¹, J. W. Clark¹, J-S. Fan², P. T. Palade²

¹Dept. of Electrical and Computer Engineering, Rice University, Houston, TX 77005-1892. USA

²Dept. of Physiology and Biophysics, University of Texas Medical Branch, Galveston TX 77555. USA

Abstract—A computer model is developed for the characterization of Ca²⁺-induced calcium release (CICR) from the sarcoplasmic reticulum (SR) in the rat ventricular cell. The fluid compartment model is configured to describe the trigger Ca²⁺ influx ($I_{Ca,L}$) through the membrane of the sarcolemma (SL); the diffusion of Ca²⁺ throughout a small cleft space, which is located between the SL and the junctional sarcoplasmic reticulum (jSR); and a distribution of five ryanodine (Ry)-sensitive Ca²⁺ release channels called the "Ca²⁺-release complex". Each Ry-receptor controlled channel (or RyR channel) is characterized by a 4-state Markovian kinetic scheme. Two Ca²⁺ ions are required to bind to RyR for channel activation, and one Ca²⁺ ion is required for channel inactivation. The model provides both sufficient Ca²⁺-release gain and graded release behavior. The complete model is used to simulate the whole-cell Ca²⁺ transient data, evoked in voltage clamp test. We also studied the linear relationship between the rising rate of the Ca²⁺ transients and the peak trigger $I_{Ca,L}$. The model results suggest that this relationship is the indirect result of 2nd-order RyR activation dynamics, filtered by fluorescent indicator dye.

Keywords – CICR, Ca²⁺ graded release, Computer model.

I. INTRODUCTION

A transient rise in intracellular Ca²⁺ concentration results in contraction of cardiac muscle. An important characteristic of Ca²⁺ release in cardiac muscle is that it is not directly dependent upon voltage depolarization. Rather, it is the local Ca²⁺ concentration around the RyR channels of the jSR membrane that causes the opening of the RyR channel and subsequent Ca²⁺ release [1]. The jSR stores large amounts of Ca²⁺ in the resting state. This phenomenon is commonly called "calcium-induced calcium release" or CICR [2]. Two fundamental properties are related to CICR, namely graded behavior and high gain [1]. Graded behavior refers to the experimental fact that SR Ca²⁺ release is proportional to the amplitude of trigger $I_{Ca,L}$ influx, and high gain relates to the fact that cytosolic Ca²⁺ concentration is much larger when Ca²⁺ release from the jSR occurs, compared to the case that Ca²⁺ release from the jSR is inhibited.

II. MODEL DEVELOPMENT

Figure 1 shows the structure of the fluid compartment model. We model the diffusion of Ca²⁺ throughout a cylindrical cleft space using partial differential equations

(PDEs). Ca²⁺ enters the cell and diffuses within the cleft space and reaches the receptors on the other side of the cleft, the cluster of RyR channels distributed on the jSR. Ca²⁺ then accumulates at the "mouths" of the RyRs and activates the jSR release channels. Ca²⁺ diffuses from the cleft space into the bulk myoplasm. All major Ca²⁺ buffers are considered in the fluid compartment model (not shown in the figure), including fluorescent dye and calmodulin distributed both in the myoplasm and in the cleft space, troponin in the bulk myoplasm, and calsequestrin in the jSR. Active and passive Ca²⁺ pumps and exchangers, which are embedded either in the SL membrane or in the SR, are also considered in the model.

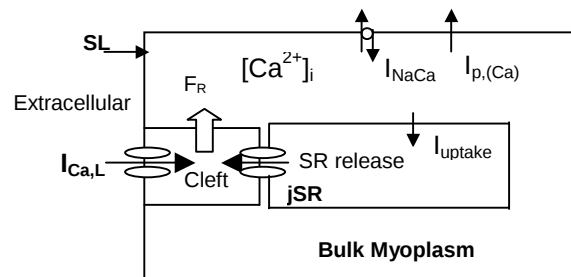


Fig 1. Illustration of the Ca²⁺ release model

Morphological studies indicate that a single DHP-sensitive $I_{Ca,L}$ channel is coupled with multiple RyRs [3]. We therefore configure one $I_{Ca,L}$ channel facing a distribution of RyRs on the jSR surface membrane. Specifically, the central RyR sensing site is surrounded by other 4 identical RyRs in a circular pattern (i.e., 5:1 RyR/DHPR stoichiometry). The 4-state gating scheme for each RyR channel is illustrated in Fig 2. The activation gate (P_O) is opened by the binding of two Ca²⁺ ions, and the inactivation gate (P_I) is controlled by the binding of a single Ca²⁺ ion.

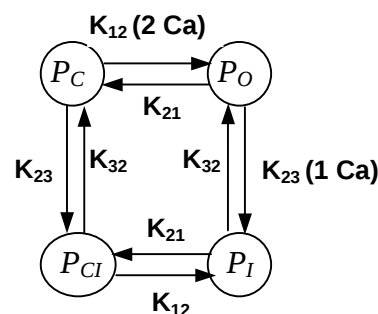


Fig 2. Schematic diagram for the 4-state Ry-sensitive Ca²⁺ release channel. K_{12} : RyR Ca-dependent activation rate, K_{21} : RyR deactivation rate, K_{23} : RyR Ca-dependent inactivation rate, K_{32} : RyR repriming rate.

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III. RESULTS

We have previously modeled the L-type Ca^{2+} current channel [4]. Our current study is focused on the response of the RyR channel model to measured $I_{\text{Ca,L}}$ data.

A. Graded Ca^{2+} Release

A simulation of cytosolic Ca^{2+} transient at the 10 mV depolarization level is shown in Fig 3A. The model provides excellent fit to measured calcium transient data at this voltage level. Quantitatively, graded Ca^{2+} release is illustrated in Fig 3B. From the I-V relationship between peak amplitude of $I_{\text{Ca,L}}$ and depolarization voltage, it is clear that peak $I_{\text{Ca,L}}$ current is largest near 10 mV and decreases with more positive depolarizations. Correspondingly, peak amplitudes of model-generated $[\text{Ca}^{2+}]_i$ over a wide range of depolarizations ($10 \leq V \leq 60$ mV) show a similar behavior, i.e., maximum values of $[\text{Ca}^{2+}]_i$ decrease from $1.0 \mu\text{M}$ to $0.25 \mu\text{M}$, as potential is made more positive. The "mirror-image" behavior of $[\text{Ca}^{2+}]_i$ to the trigger $I_{\text{Ca,L}}$ in the I-V plots confirms the graded Ca^{2+} release characterized by the computer model.

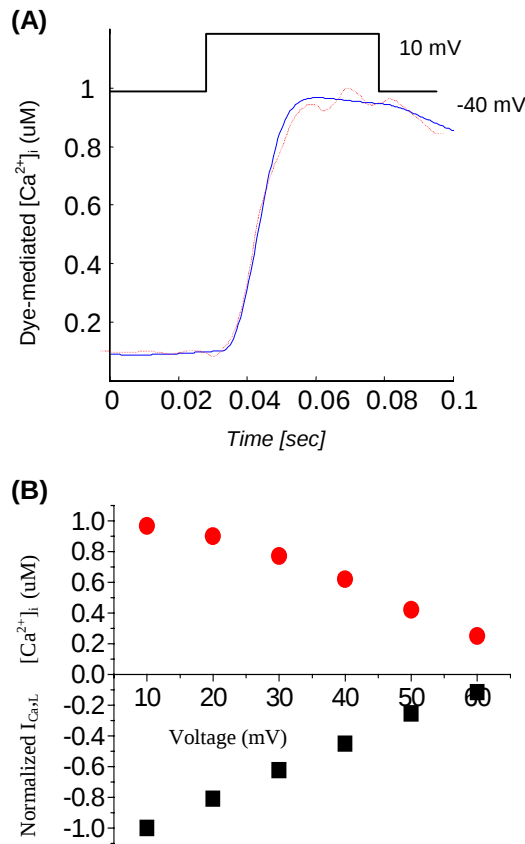


Fig 3. (A). Model simulation (solid) and data (dotted) of cytosolic Ca^{2+} transients at simple depolarization protocol of 10 mV; (B). $I_{\text{Ca,L}}$ -V and $[\text{Ca}^{2+}]_i$ -V mirrored curves representing graded Ca^{2+} release.

B. High Gain of Ca^{2+} Release

The gain or amplification factor due to CICR can be obtained by calculating the ratio of the average integrated RyR flux to the average integrated DHPR flux. Alternatively, the gain of Ca^{2+} release by opening of RyRs can be computed as the ratio of the peak $[\text{Ca}^{2+}]_i$ in the presence of CICR to the peak $[\text{Ca}^{2+}]_i$ which resulted from the trigger $I_{\text{Ca,L}}$ alone.

We used both definitions to examine CICR resulting from the opening of RyRs and Ca^{2+} release from the jSR. The first method yields a RyR/DHPR flux ratio of 7.98, whereas the second method provides a gain factor of 8.04. By either method, the calculated CICR amplitude of approximately 8 is sufficient and is similar to that reported by Stern [1].

C. Systematic Study of Ca^{2+} Release

We have also studied the input-output relationship of the Ca^{2+} release system. The maximum rate of rise of the cytosolic Ca^{2+} transient and the peak amplitude of $I_{\text{Ca,L}}$ input current are used as global measure of the output and input variables of the SR Ca^{2+} release system respectively [5]. Our model predicts a linear relationship as well, but only when Ca^{2+} indicator dyes are present. However, it is not safe to conclude that a single Ca^{2+} ion is enough to activate RyR in terms of such relationship. In fact, our input-output linear relationship was achieved by the RyR model of 2nd order Ca^{2+} -binding activation (Fig 2). Further model studies indicate that Ca^{2+} -buffering by the fluorescent indicator dye has a very important effect, namely, it distorts the quadratic relationship from the RyR model and makes the overall dye-mediated Ca^{2+} transient appear linearly related to the input $I_{\text{Ca,L}}$.

REFERENCES

- [1]. M.D. Stern, "Theory of excitation-contraction coupling in cardiac muscle." *Biophys. J.* **63**, 497-517, 1992.
- [2]. A. Fabiato, "Simulated calcium current can both cause calcium loading in and trigger calcium release from the sarcoplasmic reticulum of a skinned cardiac Purkinje cell." *J. Gen. Physiol.* **85**, 291-320, 1985.
- [3]. D.M. Bers & V.M. Stiffel, "The ratio of ryanodine: dihydropyridine receptors (RyR:DHPR) in cardiac and skeletal muscle and implication for E-C coupling." *J. Mol. Cell. Cardiol.* **24**:s.82, 1992.
- [4]. L. Sun, J-S. Fan, J.W. Clark & P. T. Palade, "A model of the L-type Ca^{2+} channel in rat ventricular myocytes: ion selectivity and inactivation mechanisms." *Journal of Physiology (London)* **529**, 139-158, 2000.
- [5]. J-S. Fan & P.T. Palade, "One calcium ion may suffice to open the tetrameric cardiac ryanodine receptor in rat ventricular myocytes." *Journal of Physiology (London)* **516**, 769-780, 1999.