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Calcium dynamics in cardiac excitatory and non-excitatory cells and the role of gap junction

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ABSTRACT

Calcium ions aid in the generation of action potential in myocytes and are responsible for the excitation-contraction coupling of heart. The heart muscle has specialized patches of cells, called excitatory cells (EC) such as the Sino-atrial node cells capable of auto-generation of action potential and cells which receive signals from the excitatory cells, called non-excitatory cells (NEC) such as cells of the ventricular and auricular walls. In order to understand cardiac calcium homeostasis, it is, therefore, important to study the calcium dynamics taking into account both types of cardiac cells. Here we have developed a model to capture the calcium dynamics in excitatory and non-excitatory cells taking into consideration the gap junction mediated calcium ion transfer from excitatory cell to non-excitatory cell. Our study revealed that the gap junctional coupling between excitatory and non-excitatory cells plays important role in the calcium dynamics. It is observed that any reduction in the functioning of gap junction may result in abnormal calcium oscillations in NEC, even when the calcium dynamics is normal in EC cell. Sensitivity of gap junction is observed to be independent of the pacing rate and hence a careful monitoring is required to maintain normal cardiomyocyte condition. It also highlights that sarcoplasmic reticulum may not be always able to control the amount of cytoplasmic calcium under the condition of calcium overload.

1. Introduction

The automaticity of the heart muscle is attributed to the existence of specialized groups of cells which are capable of generating a self-sustained action potential (AP) (excitatory cells, henceforth referred to as EC), the most crucial being the Sinoatrial node (SAN). The AP generated in the SAN spreads over the cells of the atrial wall and passes via the Atrioventricular node (AVN) through the bundle of His and Purkinjee fibres to the ventricular wall. AP arises from the flow of ions from extracellular region to cytoplasm as well as by ion channels. The spread of AP from excitatory to non-excitatory cells (NEC) is essentially the phenomenon of ion transfer between these sets of cells via gap junctions [1]. Gap junctions are mainly an assembles of various protein connexins, which communicate among the cells by means of cell-to-cell pathways for propagation of the precisely orchestrated patterns of current flow that govern the regular rhythm of the healthy heart [2]. Calcium, sodium and potassium ions are primarily involved in the generation and propagation of AP. Propagation of AP across cardiomyocytes is inherently dependent on the properties of ion channels involved in the generation of AP in individual cells and on the properties of the gap junctional channel proteins. Mutations in ion channel proteins have long been implied in cardiac arrhythmias such as the long-QT syndrome [3–5]. Abberations in gap junctional channel proteins- connexins cause atrial fibrillations [6,7]. These abnormalities underline the utmost importance of ion currents for normal heart functionality. Owing to the importance of ion currents, numerous mathematical models have been proposed to describe the phenomenon of SAN, AVN, purkinjee fibers etc.[8–10].

Calcium ion plays an extremely crucial role in the generation of AP and is believed to be involved in the propagation of AP [11]. It is crucial to the very process that enables the chambers of the heart to contract and relax, a process called excitation-contraction coupling. Calcium ions inside myocytes are dynamic

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entities whose oscillations and concentrations are governed by ion flow from and into (a) the extracellular milieu by means of exchangers such as sodium-calcium exchanger, L-type channels and T-type calcium channels, (b) the sarcoplasmic reticulum (SR) by means of ryanodine receptors which release calcium from SR into the cytoplasm and (c) SERCA2a pumps which remove cytosolic calcium [12]. The release of calcium from the SR is referred to as calcium induced calcium release (CICR), since it is the increase in the cytosolic calcium to certain threshold values that induces the ryanodine receptors to release calcium [12–14].

A brief description of action potential can be found in the work by Nattel et al. [15]. Initiation of AP occurs with the movement of Na^+/K^+ ion through the cell membrane. Combined effect of these two ions initiate primary depolarization of the cell and contribute phase 0 and phase 1 among the all five phases of AP of a cardiomyocyte. L-type channels open due to membrane depolarization and calcium enters into cytoplasm through this channels which corresponds to phase 2 (plateau phase) of AP. In phase 3, a rapid repolarisation happens and a slow input of calcium through L-type channels is also observed. In the plateau phase, calcium induced calcium release (CICR) has been observed. Due to Na^+ - Ca^{2+} exchanger (NCX), the last phase 4 is observed and, at the end of this phase, the cell again goes to start the new AP through phase 0.

A number of experimental as well as theoretical models have been proposed to simulate and capture the dynamics of calcium ions. From the beginning of the study of mathematical modeling for calcium dynamics in various cells, including cardiac muscle cells, people confined themselves mainly to construct models of AP. These models include the study of AP for cardiac SAN [16,17], AVN [18] and Purkinje fiber cells [10,19,20]. Recently, Podziemski et al. [21] studied a model of the right atrium, incorporating the SAN and AVN, to understand the AP of two different types of cells of heart. They constructed a model from geometric point of view to reproduce the AP in different types of cells of heart. Though they did not consider some basic components like various types of ionic currents or ionic movements across the cell membrane. Besides the AP model in SAN, AVN and Purkinje fibres in the cardiac myocyte, people also proposed different types of mathematical models for calcium dynamics in cardiac cells. Most of these models describe the CICR in cardiac myocytes as well as in other muscle cells of various animals including human [22–25]. All these studies were based on single cell only or same group of cells, i.e. SAN, AVN and Purkinje fibers cells. Kummer et al. [26] studied a mathematical model of calcium dynamics for a single cell, though it was not specifically for cardiac cells, to show regular and irregular oscillations in calcium concentration. It is a reality that there is no single mathematical model that describes the calcium dynamics considering both EC and NEC.

In this paper, we proposed and analyzed a mathematical model that encapsulates the interdependency of calcium oscillations between EC (cells of the SAN which are capable of generating a self-sustained AP) and NEC (cells of the atrial wall which are incapable of generating a self-sustained AP) groups of cells. The main objective of the present study is to understand the overall role of calcium concentration in maintaining homeostasis within and between EC and NEC cells. Here we have studied the dynamics between different calcium sources in a cell and their corresponding triggering parameters to capture the most influential factors that regulate the calcium dynamics in the cardiovascular cells.

2. Construction of mathematical model

To have a overall view of calcium fluxes, we presented a schematic diagram of the model system in Fig. 1.

2.1. Important assumptions

A1. The contraction and relaxation in the cardiomyocyte is mainly regulated by the concentration of cytoplasmic calcium [27], primarily due to the cyclical release and sequestration of calcium by the sarcoplasmic reticulum (SR) [12]. To built a simple model, we consider cytoplsamic calcium concentrations in excitatory and non-excitatory cells as our state variables. It is assumed that there is no depletion in the extracellular calcium and so did not consider any term for the extracellular calcium concentration.

A2. The effect of K^+ and Na^+ in initiating the action potential and hence regulating the calcium dynamics is implicitly considered in the model through a time dependent periodic function. This assumption is based on the fact that periodic dynamics of potassium ions permeability in NEC and sodium ions in the EC cells, influences the activity of calcium transporters, leading to the initiation of action potential. To exemplify in the SA node, the aromaticity is attributed the spontaneous decrease in membrane permeability to potassium which induces the activation of T-type calcium channels and an increased sodium current. Similarly in the non-excitatory cells,the during phase 1 of depolarisation, there is a decline in sodium permeability which induces calcium increase during phase 2 [28,29]

A3. NEC are electrically coupled to EC through gap junctions [30]. This gap junctional coupling not only propagate impulse in cardiac tissue, but also determine current passes from excitatory to non-excitatory cells [31]. AP generated in EC is propagated to its neighbouring cells (NEC) by transfer of calcium ions through gap junction [32]. The calcium flow through gap junction from EC to NEC is therefore assumed to be uni-directional.

A4. Calcium movement from the cytoplasm to the SR and through the gap junction is considered to be quadratic in calcium concentration. This is a mathematical assumption following [33], where the efflux from cytoplasm to SR due SERCA2a pump is considered quadratic. The calcium flux through gap junction is not well defined and so here also we considered quadratic in calcium concentration.

2.2. Model formulation

Let the concentrations of cytoplasmic calcium in EC and NEC to be denoted by $[C_{EC}]$ and $[C_{NEC}]$, respectively. In EC, both influxes and effluxes of the calcium are observed. The influxes are mainly the movement of the calcium from the outside of the cell to the inside, as well as from the SR to the cytoplasm. The effluxes are movements of the calcium from the cytoplasm to the SR and outside of the cell. L-type channels are the main sources of calcium influx from the extracellular space to the cytoplasm. The effect of Na^+/K^+ ion plays an important role on the calcium concentration in EC. Na^+ and K^+ channels operates and L-type channels open up, which allow the calcium ion to enter into the cytoplasm of EC. A single term for this whole process has been considered here by $\frac{k_1[C_{EC}]f(t)}{1+[C_{EC}]^p}$. As we intend to make a minimal model with two variables, we do not consider Na^+/K^+ explicitly in the model, but implicitly assume their impact on the calcium concentration as a periodic function $f(t)$. Combined effect of Na^+/K^+ ion channels and L-type channels is represented by $k_1[C_{EC}]f(t)$, where k_1 ia a rate constant. In reality, the calcium influx through L-type channels stops as the concentration of cytoplasmic calcium increases. It is, however, difficult to represent such type of on-off mechanism within a continuous differential equation system. To justify this phenomenon, we included an inhibitory effect by multiplying $\frac{1}{1+[C_{EC}]^p}$ with $k_1[C_{EC}]f(t)$, where $p(>>1)$ is an integer. Thus, the