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Sarcoplasmic reticulum Ca^{2+}, Mg^{2+}, K^+, and Cl^- concentrations adjust quickly as heart rate changes

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ABSTRACT

During systole, Ca^{2+} is released from the sarcoplasmic reticulum (SR) through ryanodine receptors (RyRs) while, simultaneously, other ions (specifically K^+, Mg^{2+}, and Cl^-) provide counter-ion flux. These ions move back into the SR during diastole through the SERCA pump and SR K^+ and Cl^- channels. In homeostasis, all ion concentrations in different cellular regions (e.g., junctional and non-junctional SR, dyadic cleft, and cytosol) are the same at the beginning and end of the cardiac cycle. Here, we used an equivalent circuit compartment model of the SR and the surrounding cytoplasm to understand the heart rate dependence of SR ion homeostasis. We found that the Ca^{2+}, Mg^{2+}, K^+, and Cl^- concentrations in the SR and the cytoplasm self-adjust within just a few heartbeats with only very small changes in Mg^{2+}, K^+, and Cl^- concentrations and membrane voltages (just a few percent). However, those small changes were enough to compensate for the large heart-rate-dependent changes in SR and cytoplasmic Ca^{2+} concentrations in the new steady state. The modeling suggests that ion adaptation to increases in heart rate is inherent to the system and that physiological changes that increase contractility and cardiac output are accommodated by the same self-adjusting mechanism of producing small changes in ion driving forces. Our findings also support the long-held hypothesis that SR membrane potentials are small (~1–2 mV).

1. Introduction

Heart rate can vary dramatically with physical activity or stress levels. Doing that requires rapid adaptation from the tissue level down to the single protein level to maintain excitation-contraction (EC) coupling. For example, Ca^{2+} is released from the sarcoplasmic reticulum (SR) through ryanodine receptors (RyRs) each time the heart beats. After the RyRs close, the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump works to restore the Ca^{2+} concentration inside the SR back to its pre-release level. The time SERCA has to accomplish this task decreases as the heart rate increases, and therefore SR Ca^{2+} load changes with heart rate.

This variation in SR Ca^{2+} homeostasis with heart rate is well-established and has been thoroughly studied [1,2]. During and between Ca^{2+} release events, other ions (specifically K^+, Mg^{2+}, and Cl^-) also move across the SR membrane. These ions provide the counter-ion flux during Ca^{2+} release required to maintain the trans-SR Ca^{2+} driving force. Currently, little is known about the heart rate dependence of the SR K^+, Mg^{2+}, or Cl^- homeostasis.

The K^+, Mg^{2+} or Cl^- move into and out of the SR through ion channels. These include the SR K^+ and Cl^- channels [3,4], as well as the RyR which conducts Ca^{2+}, Mg^{2+}, and K^+ [5,6]. Homeostasis requires that the number of K^+, Mg^{2+}, and Cl^- ions that flow out of (or into) the SR during Ca^{2+} release must go back in (out) between release events. Failure to achieve homeostasis for all ions from heartbeat to heartbeat would result in the SR steadily accumulating or losing K^+, Mg^{2+}, or Cl^-, compromising SR membrane potential stability, counter-ion availability, and/or EC coupling with potentially pathological consequences (e.g., as in K^+ channel-knockout mice [7]).

To better understand the heart rate dependence of SR ion homeostasis, we developed an equivalent circuit compartment model of the SR and the surrounding cytoplasm. This model permits us to quantify how Ca^{2+}, Mg^{2+}, K^+, and Cl^- concentrations and electrochemical potentials between various compartments change and adapt with heart rate. We found that Mg^{2+}, K^+, and Cl^- concentrations in the SR and the cytoplasm self-adjust to achieve homeostasis within just a few heartbeats, consistent with recent experiments [2]. All the ion concentrations are interdependent on each other; Ca^{2+} concentrations changes affect Mg^{2+}, K^+, and Cl^- concentrations. The net result, from a cardiac function point of view, is large, heart-rate-dependent effects on SR and cytoplasmic Ca^{2+} concentrations.

The capacity of the SR to achieve Mg^{2+}, K^+, and Cl^- homeostasis was remarkably robust; even with very large parameter changes, Ca^{2+} release and ion homeostasis was always achieved, indicating it is something inherent to the simplified system we study and probably to the physiological system as well. It also suggests that physiological changes designed to increase contractility and cardiac output (e.g.,

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phosphorylation of RyR or regulation of the SERCA pump by phospholamban) are accommodated by the same self-adjusting mechanism of producing small changes in ion driving forces.

2. Theory and methods

2.1. Equivalent circuit

To build our compartment model we considered a 32 pL cell with ~20,000 SR Ca^{2+} release units (CRUs), where cytosol, mitochondria, and the endo/sarcoplasmic reticulum occupy 66%, 30.3%, and 3.7% of the cell volume, respectively [8,9]. We modeled the space around a single CRU using five compartments: junctional SR (JSR), non-junctional SR (NSR), endoplasmic reticulum (ER), junctional cleft subspace (SUB) and the surrounding cytosol (CYT) (Fig. 1, left panel). We used the abbreviations in parentheses in mathematical symbols. Each compartment was a cylinder with dimensions based on experimental data [8] (Table 1).

For each ion species (Ca^{2+}, Mg^{2+}, K^+ and Cl^-), the total number of ions was fixed in the system as a whole. However, the concentrations of each ion type fluctuated independently in the various compartments as ions moved between compartments. Ca^{2+} buffering was modeled as an increase in the effective compartment volume "seen" by Ca^{2+} (Table 1). We also included non-Cl^- anions in each compartment as an additional ionic species, X^-. These represent all the charge neutralizing anions that must exist in each compartment (e.g., proteins and phosphates). Their concentration in the cytosol and ER always neutralized those compartments and flowed between the others (see below).

Ions flowed from compartment to compartment down electrochemical potential gradients produced by differences in concentration and/or voltage. Ions moved either through ion channels across capacitive membranes (the JSR-SUB, CYT-NSR, and CYT-ER membranes with capacitance per area 0.01 pF/μm^2 [10]) or via bulk electrodiffusion between contiguous compartments (the CYT-SUB, NSR-JSR, and ER-NSR interfaces). Ca^{2+} also crossed the NSR-CYT membrane through SERCA pumps, for which we use the model of Shannon et al. [9]. At high heart rates, the SERCA pump rate increases due to dissociation of phospholamban [11,12]. The role of this phenomenon was explored by doubling SERCA pump rate while keeping all other parameters the same.

K^+ and Cl^- currents carried by SR K^+ and Cl^- channels followed Ohm's law:

$$I_i^{1,2} = g_i^{1,2}\left(V^{1,2} - \frac{kT}{z_i e}\ln\left(\frac{c_i^1}{c_i^2}\right)\right) \quad (1)$$

where the current of ion species i between compartments 1 and 2 ($I_i^{1,2}$) depends on the conductance $g_i^{1,2}$, the potential difference between compartments 1 and 2 ($V^{1,2}$), and the concentration in each compartment (c_i^1 and c_i^2). z_i is the valence of ion species i, and k, T, and e are the Boltzmann constant, absolute temperature, and elementary charge, respectively. The SR K^+ and Cl^- channels both had conductances of 100 pS. The Ca^{2+}, Mg^{2+}, and K^+ currents through the RyR followed the Goldman-Hodgkin-Katz current formula [13]. The permeabilities were chosen to reproduce the individual ionic currents at 0 mV in physiological ion conditions, as calculated using the Gillespie ion permeation model [14]. The salient ion current/voltage curves were previously published [5].

Bulk electrodiffusion currents followed Eq. (1). We used 10 nS for all X^- bulk conductances so that they could move quickly to provide electroneutrality, since they are all the charge neutralizing anions already in each compartment and those that move with the cations. The particular choice of the X^- conductances did not significantly affect our results (data not shown). For all other ions, the SUB-CYT conductance was

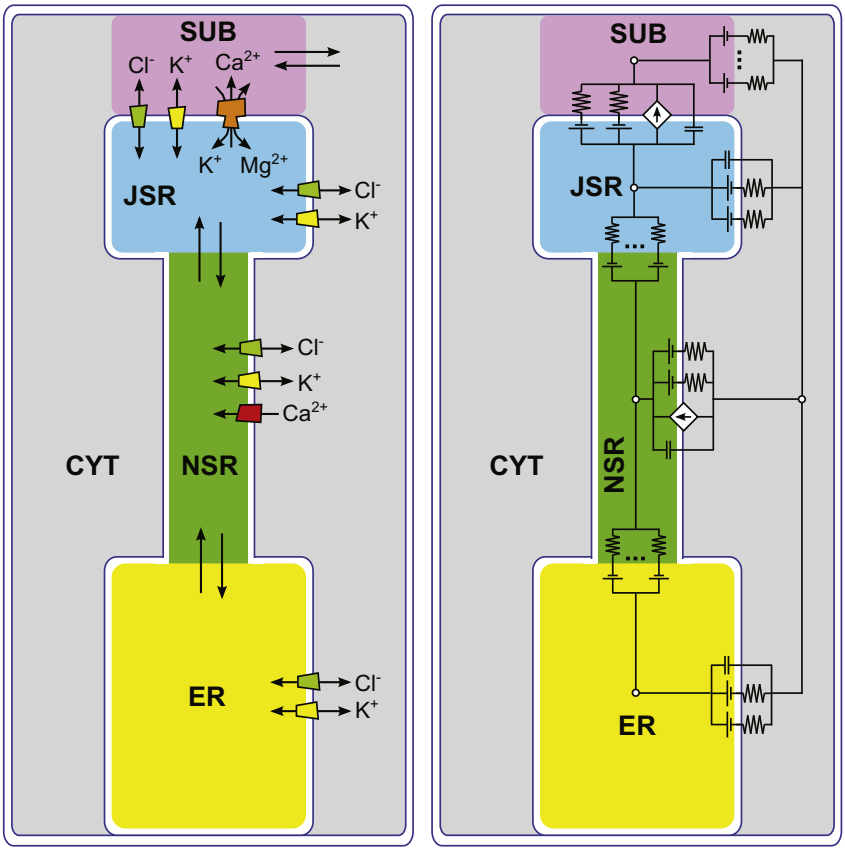

Fig. 1. (Color online) (left) Sketch of the compartment model. Ion fluxes between compartments are indicated by the arrows. (right) Equivalent circuit of the compartment model.