Role of Na^+-Ca^{2+} Exchange in Neonatal and Adult Ventricular Cells: A Simulation Study

Hitomi I Sano[1,2], Yasuhiro Naito[1,2,3], Masaru Tomita[1,2,3]

[1]Institute for Advanced Biosciences, Keio University, Kanagawa, Japan
[2]Department of Environment and Information Studies, Keio University, Kanagawa, Japan
[3]Systems Biology Program, Graduate School of Media and Governance, Keio University, Kanagawa, Japan

Abstract

The Na^+-Ca^{2+} exchange assumes considerable importance in neonatal cells with a morphologically sparse sarcoplasmic reticulum. Our simulation shows that the neonatal ventricular cell consumed larger amount of ATP than the adult ventricular cell, owing to a long relaxation time. The amount of ATP consumed per beat was reduced to the amount equivalent to the adult ventricular cells, thus increasing the relative current density of Na^+-Ca^{2+} exchange by 4-fold, which is consistent with the observed current density in the neonatal rabbit ventricular cells.

1. Introduction

The relative significance of Ca^{2+} release from sarcoplasmic reticulum (SR) changes during the postnatal maturation of ventricular cells. Electron microscopic observation of rat ventricular cells has shown that SR increases rapidly by 5-fold during early postnatal maturation and that the SR to sarcolemma (SL) ratio reaches the level of adult in a 22-day-old rat [1]. The relative extent of SR maturation is highly correlated with the gestational age; guinea pig hearts exhibit more extensive SR at birth than rabbit hearts do [2], and postnatal development increases the immature SR of rabbit hearts by approximately 3-fold [3]. Quantitative changes in the levels of SR-related proteins [4-6] are roughly proportional to the changes in the SR volume [1], indicating that SR expands its functional significance in cardiac Ca^{2+} regulation by morphological maturation as well as by increasing the levels of SR-related proteins. The developmental changes in Na^+-Ca^{2+} exchange, SR-related components, and structural components are summarized in the schematic diagram (Figure 1).

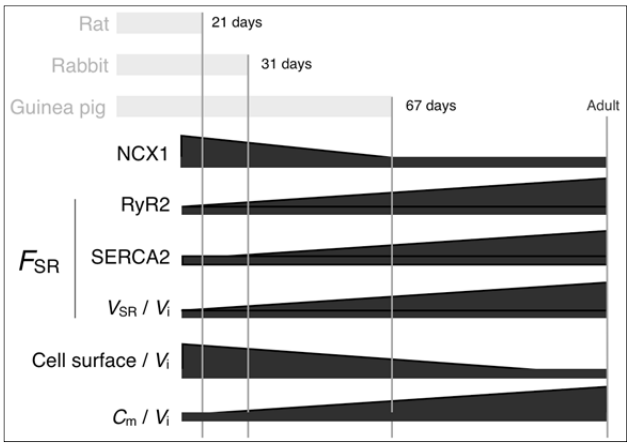

Figure 1. Developmental changes in Na^+-Ca^{2+} exchange current density, SR-related components, and structural components

Two research groups have independently reported reciprocal changes in the postnatal production of Na^+-Ca^{2+} exchange and SR Ca^{2+}-ATPase (SERCA). Vetter *et al*. (1995) analyzed postnatal steady-state protein levels in rat ventricular cells by immunoblot analysis [6], and found that the level of the Na^+-Ca^{2+} exchange protein declined by approximately 4-fold within the first 12 days of postnatal development, which is in good reciprocal agreement with the extent of postnatal SR maturation [1] as well as with changes in the level of SERCA [4]. Moreover, the Na^+-Ca^{2+} exchange proteins are shown to be abundant in the peripheral SR in neonatal rabbits [7]. In addition, Artman (1995) compared the current density of Na^+-Ca^{2+} exchange in neonatal ventricular cells of both rabbit and guinea pig hearts [2], and found that the current density of Na^+-Ca^{2+} exchange is approximately 4-fold greater in neonatal ventricular cells than in adult ventricular cells in rabbits, but did not detect significant

changes in guinea pigs. These studies led to the conclusion that Na^+-Ca^{2+} exchange activity is reciprocally regulated with the morphological maturation of SR.

The functional importance of Na^+-Ca^{2+} exchange in the neonatal ventricular cell is a matter of debate. Haddock *et al*. (1999) have shown that transsarcolemmal Ca^{2+} flux via the reversal of Na^+-Ca^{2+} exchange are sufficient to account for the Ca^{2+} transient observed in neonatal rabbits [8]. Moreover, while the inhibition of I_{CaL} with nifedipine did not affect the maximal contraction amplitudes in neonatal rabbit myocytes, contractions of adult rabbit myocytes are almost completely abolished by the application of nifedipine [9]. On the other hand, Artman (1995) proposed that relaxation of myocytes occurs predominantly by transsarcolemmal Na^+-Ca^{2+} exchange rather than by Ca^{2+} reuptake into the SR.

Here, we aim to address the functional role of large current density of Na^+-Ca^{2+} exchange in neonatal ventricular cell in terms of 2 indices: sarcomere relaxation velocity and ATP consumption rate.

2. Methods

We have previously modeled the developmental changes in the action potentials of rodent ventricular cells [10]. We integrated the quantitative changes in the ionic components in both cell membrane and SR during the course of rodent development into a comprehensive model of guinea pig ventricular cell—the Kyoto model [11]. The Kyoto model incorporates a contraction model referred to as the Negroni-Lascano (NL) model [12] that effectively reconstructed the force-length and force-velocity relationships of sarcomere shortening. As such, the relaxation velocity of ventricular cell was computed on the basis of the simulated dynamics of changes in the sarcomere length.

In order to represent the ventricular cell in the neonatal guinea pig heart, the parameters listed in Table 1 were modified accordingly. P_x represents conversion factors (pA/mM) for the current and G_x represents conductance (pA/mV). C_m is cell capacitance and volumes of cell cytoplasm, SR release site, and SR uptake sites are represented as V_i, V_{rel}, and V_{up}, respectively. In addition, the relative current density of Na^+-Ca^{2+} exchange was varied from 1.0 to 4.0 by increments of 0.4, in order to observe the changes in the relaxing velocity and ATP consumption rate per beat as changes in the Na^+-Ca^{2+} exchange density.

The modified models were simulated for 600 s to reach the quasi-steady state and then externally stimulated by using potassium ions, at a frequency of 2.5 Hz for 600 s to pace the model. All the simulations were based on the Dormand–Prince method, as implemented in the E-Cell Simulation Environment (SE) version 3 [13].

Table 1. The expanded components in the model to represent the guinea pig neonatal ventricular cell.

Parameter	Neonate	Adult
P_{CaL}	13 590	17 424
G_{Kr}	0.0432	0.0864
P_{Ks}	6.30	5.04
$I_{SR,uptake,max}$	843	4 013
P_{RyR}	16 896	42 240
$P_{SR,leak}$	317	1 056
$P_{SR,transfer}$	19	63
V_i (μL)	2.42×10^{-3}	8.0×10^{-3}
V_{rel} (μL)	1.45×10^{-5}	1.6×10^{-4}
V_{up} (μL)	3.64×10^{-5}	4.0×10^{-4}
C_m (pF)	40	132
Diadic Factor	-60	-150

3. Results and discussion

Over-representation of Na^+-Ca^{2+} exchange by 4-fold accelerated the relaxation of sarcomere without changing the amplitude of the sarcomere shortening in the neonatal ventricular cells (Figure 2, left). The Ca^{2+} transient lasted longer in the neonatal cell than in the adult ventricular cell, thereby increasing the time required for the sarcomere to both shorten and relax. On the other hand, the 4-fold increase in Na^+-Ca^{2+} exchange decreased the amplitude of the Ca^{2+} transient, which subsequently caused a decrease in the amplitude of the sarcomere shortening (Figure 2, right).

While the neonatal ventricular cell maintained the amplitude of the sarcomere shortening, the adult ventricular cell substantially reduced the amplitude of the shortening because of the increase in Ca^{2+} efflux, since the Na^+-Ca^{2+} exchange is quickly flipped back to a forward mode that excludes Ca^{2+} from the myoplasm (data not shown). These differences consequently resulted in the acceleration of relaxing velocity by increasing Na^+-Ca^{2+} exchange current density in the neonatal ventricular cell (Figure 3).

The ATP consumption rate was greater in the neonatal (302 μM per beat) than in the adult ventricular cell (243 μM per beat). Admittedly, the computed amount of ATP consumption may not be quantitatively accurate, since differences in the metabolic pathway, glycogen content, and expression of myosin genes between neonatal and adult ventricular cells were not considered. The total amount of ATP consumed per beat in neonatal ventricular cell was substantially reduced to the amount equivalent to

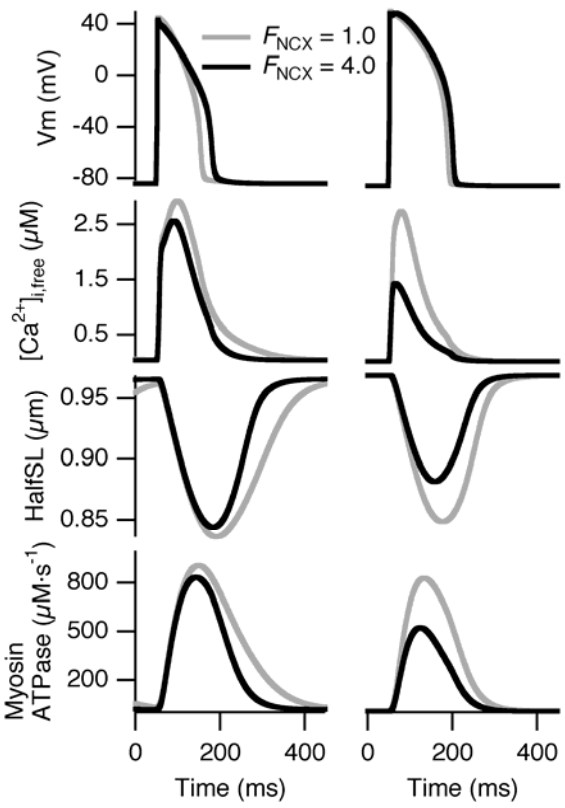

Figure 2. Changes in the dynamics of the action potential, Ca^{2+} transient, contraction (half sarcomere length), and ATP consumption via myosin ATPase in neonatal (left) and adult (right) ventricular cell models. Light lines represent simulated traces with the control model (F_{NCX} = 1.0) and dark lines represent those with over-represented Na^+-Ca^{2+} exchange (F_{NCX} = 4.0).

adult ventricular cell by over-representing Na^+-Ca^{2+} exchange by 4-fold (Figure 3).

The 4-fold increase in the Na^+-Ca^{2+} exchange current density is approximately equivalent to the relative Na^+-Ca^{2+} exchange current density in the neonatal ventricular cell [2]. Since the over-representation of the current led to reduction of the total ATP consumption rate to a level equivalent to that in the adult ventricular cell, the large Na^+-Ca^{2+} exchange current density may account for the reduction in the amount of ATP consumed per beat as a substitute for immature SR, which consumes ATP to uptake Ca^{2+}.

4. Conclusion

The role of large Na^+-Ca^{2+} exchange current density in the neonatal ventricular cell is to accelerate the relaxation of sarcomere by increasing the transsarcolemmal Ca^{2+} efflux and shortening the Ca^{2+} transient lasting time. The over-representation of Na^+-Ca^{2+} exchange in the neonatal ventricular cell therefore plays an important role as a substitute for immature SERCA that mediates reuptake of Ca^{2+}.

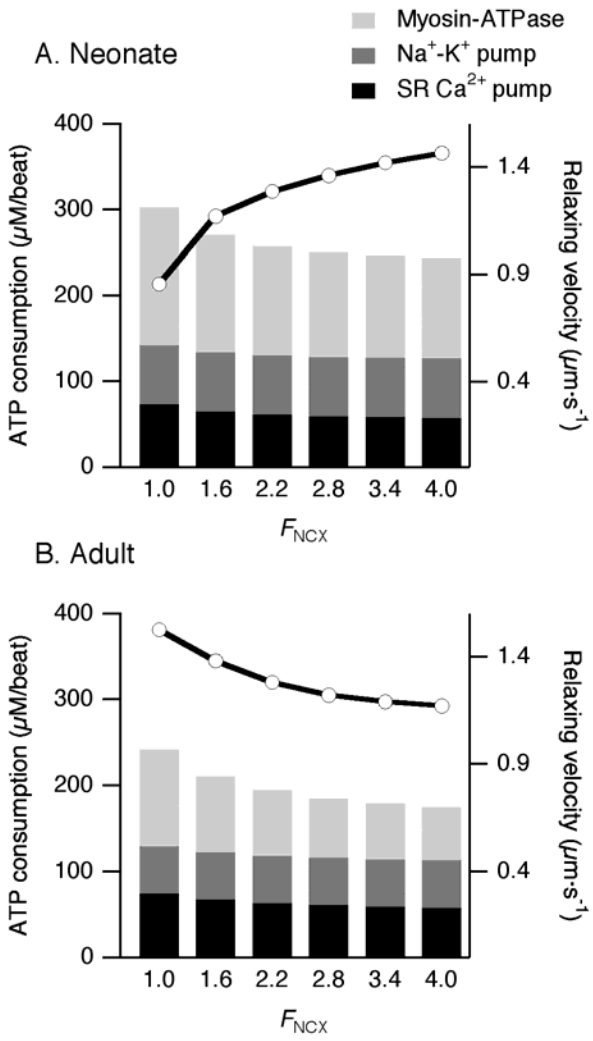

Figure 3. Changes in the ATP consumption per beat and relaxing velocity with increasing Na^+-Ca^{2+} exchange current density in neonatal (A) and adult (B) ventricular cells.

References

[1] Olivetti G, Anversa P, Loud AV. Morphometric study of early postnatal development in the left and right ventricular myocardium of the rat. II. Tissue composition, capillary

growth, and sarcoplasmic alterations. Circ Res 1980; 46: 503-12.
[2] Artman M, Ichikawa H, Avkiran M, Coetzee WA. Na^{+}-Ca^{2+} exchange current density in cardiac myocytes from rabbits and guinea pigs during postnatal development. Am J Physiol 1995; 268: 1714-22.
[3] Chen F, Ding S, Lee BS, Wetzel GT. Sarcoplasmic reticulum Ca^{2+}-ATPase and cell contraction in developing rabbit heart. J Mol Cell Cardiol 2000; 32: 745-55.
[4] Liu W, Yasui K, Opthof T, Ishiki R, Lee JK, Kamiya K, Yokota M, Kodama I. Developmental changes of Ca^{2+} handling in mouse ventricular cells from early embryo to adulthood. Life Sci 2002;71: 1279-92.
[5] Harrer JM, Haghighi K, Kim HW, Ferguson DG, Kranias EG. Coordinate regulation of SR Ca^{2+}-ATPase and phospholamban expression in developing murine heart. Am J Physiol. 1997; 272: 57-66.
[6] Vetter R, Studer R, Reinecke H, Kolar F, Ostadalova I, Drexler H. Reciprocal changes in the postnatal expression of the sarcolemmal Na^{+}-Ca^{2+}-exchanger and SERCA2 in rat heart. J Mol Cell Cardiol 1995;27: 1689-701.
[7] Chen F, Mottino G, Klitzner TS, Philipson KD, Frank JS. Distribution of the Na^{+}-Ca^{2+} exchange protein in developing rabbit myocytes. Am J Physiol 1995;268: 1126-32.
[8]Haddock PS, Coetzee WA, Cho E, Porter L, Katoh H, Bers DM, Jafri MS, Artman M. Subcellular $[Ca^{2+}]_i$ gradients during excitation-contraction coupling in newborn rabbit ventricular myocytes. Circ Res 1999;85: 415-27.
[9] Wetzel GT, Chen F, Klitzner TS. Na^{+}-Ca^{2+} exchange and cell contraction in isolated neonatal and adult rabbit cardiac myocytes. Am J Physiol 1995;268: 1723-33.
[10] Itoh H, Naito Y, Tomita M. Simulation of developmental changes in action potentials with ventricular cell models. Syst Synth Biol 2007;1:11-23.
[11] Matsuoka S, Sarai N, Kuratomi S, Ono K, Noma A. Role of individual ionic current systems in ventricular cells hypothesized by a model study. Jpn J Physiol 2003;53: 105-123.
[12] Negroni JA, Lascano EC. A cardiac muscle model relating sarcomere dynamics to calcium kinetics. J Mol Cell Cardiol 1996;28: 915-29.
[13] Takahashi K, Kaizu K, Hu B, Tomita M. A multi-algorithm, multi-timescale method for cell simulation. Bioinformatics 2004;20: 538-46.

Address for correspondence.

Hitomi I. Sano
5322 Endo, Fujisawa, Kanagawa 252-0882, Japan.
ducky@sfc.keio.ac.jp