Contribution of Developmental Changes in Energy Metabolism to Excitation-Contraction Coupling of a Ventricular Cell: A Simulation Study

Hitomi I Sano[1,2], Tamami Toki[1,3], 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

In fetal guinea pigs, ventricular cells have higher anaerobic glycolytic capacity and lower mitochondrial enzyme activity. Here, we implemented developmental changes in glycolytic enzyme activity, concentrations of glycogen, and total creatine in late embryonic and adult ventricular cell models. We then simulated the effects of hypoxic conditions on dynamic changes in contractile force and ATP concentration. Our model demonstrates that fetal ventricular cells maintain ATP for longer periods of time than adult ventricular cells. This is consistent with reported dynamics of ventricular cells under hypoxic conditions.

1. Introduction

The heart develops and acquires new functions, all while continuously pumping blood. Meanwhile, heart abnormalities that develop early in this process progress to congenital heart malformations. Accordingly, the developmental program of the heart, including expression of genes encoding ion channels, is likely to be tightly regulated.

We previously modeled developmental changes in action potentials (AP) in rodent ventricular cells [1]. We integrated quantitative changes in ionic components of the cellular membrane and sarcoplasmic reticulum (SR) throughout the course of development using the Kyoto model, a comprehensive model of guinea pig ventricular cells [2, 3]. Using these models, we demonstrated the contribution of quantitative changes in individual ionic systems to developmental changes in electrophysiological properties of ventricular cells. Further, we predicted a sequence of regulatory changes in ionic systems [4] and showed that quantitative changes in Na^+ current (I_{Na}) and funny current (I_f), for example, contributed significantly to the wide range of basic cycle lengths of spontaneous APs. Developmental changes in APs were accurately represented, as I_{Na} increased before the disappearance of I_f, followed by a 10-fold increase in inward-rectifying K^+ current (I_{K1}). We predicted that an increase in I_{Na} density and disappearance of I_f should be observed in the early stage of embryonic development. This prediction was supported by experimental observations that I_{Na} and I_f densities change earlier than those of other components [5, 6].

Here, we simulated developmental changes in energy metabolism using mathematical models to demonstrate changes in the contribution of glycolysis and mitochondrial oxidative phosphorylation to excitation-contraction coupling in ventricular cells. Developmental changes in glycolytic enzymatic activity, glycogen concentrations, and total creatine were implemented according to the model to represent specific stages in development. We then simulated the effects of hypoxic conditions on dynamic changes in contractile force and ATP concentration. Our model shows that fetal ventricular cells maintain ATP for longer periods of time than adult ventricular cells. Our model is consistent with reported dynamics of ventricular cells under hypoxic conditions.

2. Methods

Previously, we simulated APs of rodent ventricular cells at three different developmental stages: early embryonic, late embryonic, and neonatal stages [1]. We used the Kyoto model, an electrophysiological model of guinea pig ventricular cells [2]. To summarize briefly, quantitative changes in various ionic components were represented as the densities of the components in developmental stages, relative to those in adult stage.

The parameters listed in Table 1 were modified to represent ventricular cells in the late embryonic guinea pig heart. The L-type Ca^{2+} current (I_{CaL}) density relative to that in adult stage was estimated from a current-voltage curve from ventricular cells obtained from fetal guinea

pigs 1-7 days before birth [7]. Based on findings suggesting that postnatal quantitative changes in the density of Na^+-Ca^{2+} exchange (I_{NaCa}) correspond with changes in protein production levels [8], we assumed that the relative amounts of protein directly reflected the relative ratios of ion flux of I_{NaCa}, the SR Ca^{2+} pump, and the ryanodine receptor (RyR) channel. Western blots of the NCX1 protein in rabbit [9] and mouse [10], SR Ca^{2+} pump proteins in rabbit [11] and mouse [10], and the RyR channel in mouse [10] were used to quantify the relative amount of ion flux. The level of Ca^{2+}-induced Ca^{2+} release (CICR) factor in the late embryonic stage was determined based on the average relative density values for SR Ca^{2+} kinetics [12].

Table 1. The model components modified to represent the guinea pig late ventricular cell.

	Late Embryonic	Adult
L-type Ca^{2+} channel	0.78	1.0
Na^+/Ca^{2+}exchange	2.0	1.0
SR Ca^{2+} pump	0.21	1.0
RyR channel	0.40	1.0
CICR factor	-60	-150

In addition to the use of ionic systems to reproduce APs and changes in intracellular ion concentrations, the Kyoto model also accounts for ATP consumption by Na^+-K^+ ATPase, SR Ca^{2+} ATPase, and myosin ATPase, as well as ATP production by mitochondrial oxidative phosphorylation [3]. Recently, a dynamic model of the glycolytic pathway [13] was incorporated into the Kyoto model to reproduce a hypoxic reaction in a myocardial cell.

Developmental changes in enzymatic activity in fetal ventricular cells [14] were modeled by modifying enzyme activity relative to adult ventricular cells, as summarized in Table 2. Specifically, the activities of L-lactate dehydrogenase (LDH), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), 6-phosphofructokinase (PFK), and glycogen phosphates (GP) were multiplied by 2.1, 1.5, 1.28, and 0.825, respectively, relative to the normalized adult values.

Table 2. Relative activities of glycolytic enzymes

Enzyme	Late Embryonic	Adult
LDH	2.1	1.0
GAPDH	1.5	1.0
PFK	1.28	1.0
GP	0.825	1.0

The modified models were first simulated for 20 hours in order for all glycolytic intermediates to reach a quasi-steady state, and then externally stimulated by potassium ions at a frequency of 2.5 Hz for 600 s to pace the model. All simulations were based on the Dormand–Prince method, as implemented in E-Cell Simulation Environment (SE) version 3 [15].

3. Results and discussion

We simulated developmental changes in energy metabolism in late embryonic and adult cells to compare with values from previous research [14]. As illustrated in Figure 1, qualitative characteristics of the simulated concentrations of glycolytic intermediates are well in agreement with the experimental results.

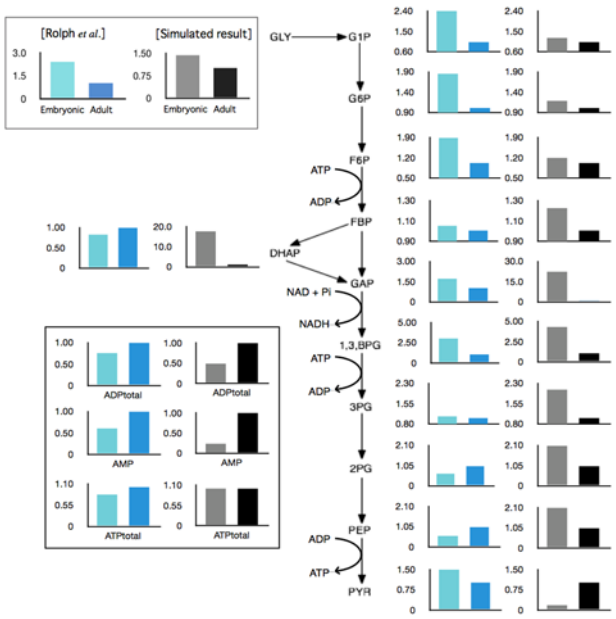

Figure 1. Simulation of developmental changes in concentrations of glycolytic intermediates. Light and dark bars indicate the concentrations of the corresponding intermediates at late embryonic and adult ventricular cells, respectively. Numerical values on the y-axis show relative concentration of embryonic to adult.

We then simulated the effect of hypoxic conditions on dynamic changes in ATP concentration. As illustrated in Figure 2, the intracellular concentration of ATP is maintained for a longer period of time in late embryonic ventricular cells (light line) than in adult ventricular cells (dark line) in response to hypoxia.

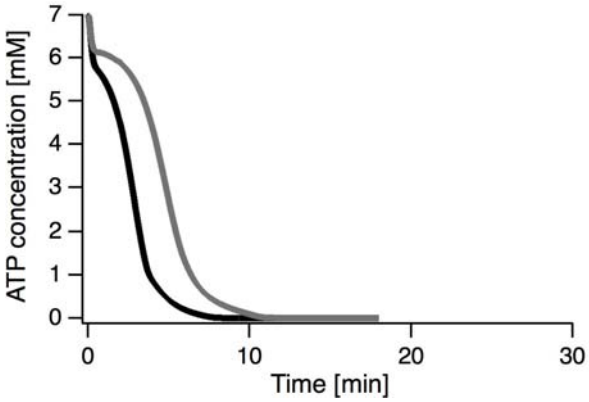

Figure 2. Simulation of dynamic changes in ATP concentration under hypoxic condition in late embryonic ventricular cell (light line) and adult ventricular cell (dark line).

In order to determine which characteristics of late embryonic ventricular cell contribute to further maintenance of ATP concentration under hypoxic conditions, we constructed a model to represent a late embryonic ventricular cell with modified enzyme activity (Figure 3) or a concentration of total creatine decreased by 50% (Figure 4). As a result, modification of enzyme activities had a negative impact on maintenance of ATP concentration under hypoxic conditions, while decreasing the concentration of total creatine contributed to ATP concentration maintenance over a longer period of time.

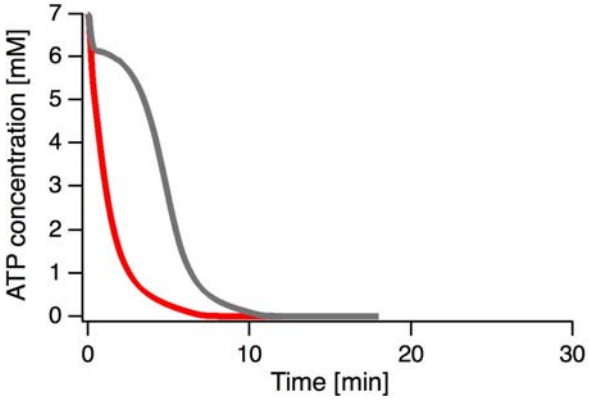

Figure 3. Simulation of dynamic changes in ATP concentration under hypoxic conditions in a late embryonic ventricular cell (light line) and a late embryonic ventricular cell with modified enzyme activities (red line).

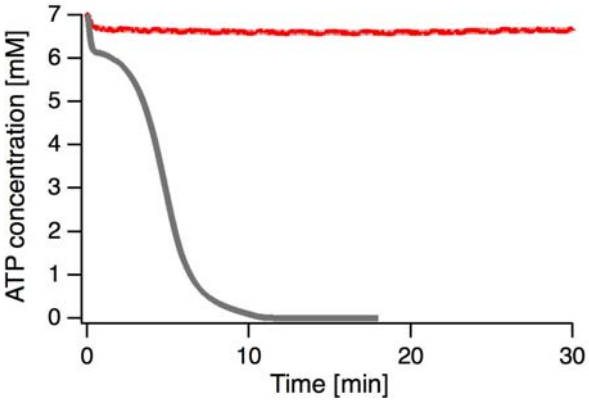

Figure 4. Simulation of dynamic changes in ATP concentration in a late embryonic ventricular cell under hypoxic conditions (light line) and with the amount of total creatine decreased by 50% (dark line).

4. Conclusion

Simulation results show that intracellular ATP concentration is maintained for a shorter period of time when enzyme activity is modified (Figure 3). On the other hand, intracellular ATP concentration is maintained for a longer period of time when the amount of total creatine is decreased by 50%.

Acknowledgements

This work was supported by funds from the Yamagata Prefectural Government and Tsuruoka City and Keio Gijuku Academic Development Funds. We would like to thank the members of E-Cell Project at the Institute for Advanced Bioscience, Keio University, for critical suggestions.

References

[1] Itoh H, Naito Y, Tomita M. Simulation of developmental changes in action potentials with ventricular cell models. Syst Synth Biol, 2007;1:11-23.
[2] Matsuoka S, et al. Role of individual ionic current systems in ventricular cells hypothesized by a model study. Jpn J Physiol 2003;53:105-23.
[3] Kuzumoto M, et al. Simulation analysis of intracellular Na+ and Cl- homeostasis during beta 1-adrenergic stimulation of cardiac myocyte. Prog Biophys Mol Biol 2008;96:171-86.
[4] Okubo C, et al. Contribution of quantitative changes in individual ionic current systems to the embryonic development of ventricular myocytes: a simulation study. J Physiol Sci 2013;63:355-67.
[5] Davies MP, et al. Developmental changes in ionic channel activity in the embryonic murine heart. Circ Res 1996;78:15-25.

[6] Yasui K, et al. I(f) current and spontaneous activity in mouse embryonic ventricular myocytes. Circ Res 2001;88:536-42.
[7] Kato Y, et al. Developmental changes in action potential and membrane currents in fetal, neonatal and adult guinea-pig ventricular myocytes. J Mol Cell Cardiol 1996;28:1515-22.
[8] Artman M, et al. Na+/Ca2+ exchange current density in cardiac myocytes from rabbits and guinea pigs during postnatal development. Am J Physiol 1995;268: 1714-22.
[9] Artman M. Sarcolemmal Na(+)-Ca2+ exchange activity and exchanger immunoreactivity in developing rabbit hearts. Am J Physiol 1992;263:1506-13.
[10] Liu W, et al. Developmental changes of Ca(2+) handling in mouse ventricular cells from early embryo to adulthood. Life Sci 2002;71:1279-92.
[11] Chen F, et al. Sarcoplasmic reticulum Ca(2+)ATPase and cell contraction in developing rabbit heart. J Mol Cell Cardiol 2000;32:745-55.
[12] Tohse N, et al. Development of excitation-contraction coupling in cardiomyocytes. Jpn J Physiol 2004;54:1-6.
[13] Lambeth MJ, Kushmerick MJ. A computational model for glycogenolysis in skeletal muscle. Ann Biomed Eng 2002;30:808-27.
[14] Rolph TP, Jones CT. Regulation of glycolytic flux in the heart of the fetal guinea pig. J Dev Physiol 1983;5:31-49.
[15] Takahashi K, et al. 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