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

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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\textsuperscript{+} current (\(I_{\text{Na}}\)) 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 \(I_{\text{Na}}\) increased before the disappearance of \(I_f\), followed by a 10-fold increase in inward-rectifying K\textsuperscript{+} current (\(I_{\text{K1}}\)). We predicted that an increase in \(I_{\text{Na}}\) density and disappearance of \(I_f\) should be observed in the early stage of embryonic development. This prediction was supported by experimental observations that \(I_{\text{Na}}\) 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\textsuperscript{2+} current (\(I_{\text{CaL}}\)) 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 $\text{Na}^+-\text{Ca}^{2+}$ exchange ($I_{\text{NaCa}}$) 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 $I_{\text{NaCa}}$, 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.

<table>
<thead>
<tr>
<th>Component</th>
<th>Late Embryonic</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-type Ca$^{2+}$ channel</td>
<td>0.78</td>
<td>1.0</td>
</tr>
<tr>
<td>Na$^+$/Ca$^{2+}$ exchange</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SR Ca$^{2+}$ pump</td>
<td>0.21</td>
<td>1.0</td>
</tr>
<tr>
<td>RyR channel</td>
<td>0.40</td>
<td>1.0</td>
</tr>
<tr>
<td>CICR factor</td>
<td>-60</td>
<td>-150</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Late Embryonic</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>GAPDH</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>PFK</td>
<td>1.28</td>
<td>1.0</td>
</tr>
<tr>
<td>GP</td>
<td>0.825</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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.](image)

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.
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%.

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References


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