Physiological Role of Transverse-Axial Tubular System in Cardiac Ventricular Myocytes: A Simulation Study

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Abstract

Experimental data related to the transverse – axial tubular system of guinea pig and rat ventricular myocytes were incorporated into quantitative models of their electrical activity. The results of simulations suggest that activity-dependent depletion of Ca^{2+} within the tubular lumen decreases the intracellular Ca^{2+} load and intracellular Ca^{2+} transients in both species. However, considerable species differences in the magnitude of the depletion, its frequency dependence and the resulting effect on cellular activity were observed.

1. Introduction

The transverse-axial tubular system (TATS) of cardiac ventricular myocytes comprises a large number of invaginations extending from the surface membrane into the cell interior. The periodic activation of ion transporters in the tubular membrane results in repetitive changes of ion concentrations in the restricted tubular space. Their magnitude and effect on the electrical activity of myocytes from different species have been studied in our recent work [1, 2] based on quantitative modelling. In this paper, we summarize the results of our latest exploration of the role of TATS in modulating the intracellular Ca^{2+} homeostasis and intracellular Ca^{2+} transients in ventricular cardiomyocytes.

2. Methods

To explore the extent of ionic concentration changes in TATS and their physiological consequences in different species, we designed quantitative models of the electrical activity of guinea pig [3] and rat [2] ventricular cardiomyocytes incorporating a quantitative description of TATS. The geometrical parameters of guinea pig and rat TATS were determined to conform with the results of recent microscopic analyses of ventricular cell ultra-structure [4, 5]. Their values are summarized in Tab. 1.

Table 1. Geometrical parameters of guinea pig and rat TATS in the model. The symbols d_t, l_t, ρ_t, fS_t and fV_t stand, respectively, for mean diameter of tubules, mean length of tubules, density of tubular mouths in surface membrane, fractional area of tubular membrane, and fractional volume of tubular system.

Parameter	Guinea pig	Rat
d_t	0.148 µm	0.15 µm
l_t	5.9 µm	4.5 µm
ρ_t	0.21 tubules/µm^2	0.3 tubules/µm^2
fS_t	53 %	56 %
fV_t	2.9 %	3.3 %

The distribution of ion transporters between the TATS and peripheral membranes exhibits significant interspecies differences. For the guinea pig and rat models, the fractions of ionic currents within the TATS as estimated in our recent work [2, 3] are summarized in Tab. 2.

Table 2. Fractions of ionic currents in guinea pig and rat TATS.

Guinea pig		Rat	
Current	TATS-fraction	Current	TATS-fraction
I_{Na}	64 %	I_{Na}	56 %
I_{Ca}	64 %	I_{Ca}	87 %
I_{Kr}	53 %	I_{Kto}	56 %
I_{Ks}	53 %	I_{Kss}	76 %
I_{Kp}	53 %	I_{K1}	56 %
I_{K1}	80 %	I_f	56 %
I_{NaCa}	70 %	I_{NaCa}	81 %
I_{NaK}	53 %	I_{NaK}	59 %
I_{pCa}	20 %	I_{pCa}	56 %

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All simulations presented in this work were obtained after a long period of regular stimulation (1200 s) when a dynamic steady state was achieved.

3. Results

The role of TATS in the models of guinea pig and rat ventricular cardiomyocytes was explored at stimulation frequencies approximately corresponding with the resting heart rates of each species, i.e. at 4 Hz in the guinea pig model and 5 Hz in the rat model (in accordance with the range of physiological frequencies recorded in guinea pig (230-380 beats per minute) and rat (320-480 beats per minute)). Fig. 1 shows simulation of steady state action potentials and changes of Ca^{2+} and K^+ concentration in TATS ($[Ca^{2+}]_t$ and $[K^+]_t$) during a cycle. In the guinea pig model, the changes of $[Ca^{2+}]_t$ alternated between accumulation (max 3.3 %, related to external ion concentration) and depletion (max 7.2 %) whereas $[K^+]_t$ exhibited persistent accumulation (max 3 %). In the rat model, the situation was different: $[Ca^{2+}]_t$ exhibited persistent depletion (max 13.13 %) whereas $[K^+]_t$ alternated between accumulation (max 2.7 %) and depletion (max 1 %).

To determine the dependence of ion concentration changes in TATS on the rate of stimulation, we explored their magnitudes in the range of stimulation frequencies between 1 Hz and 6 Hz. In the guinea pig model (Fig. 2, left), the maximal depletion of tubular Ca^{2+} during a cycle at 1 Hz was 13.7 % and maximal accumulation at the end of diastole was 4.8 %. With increased frequency, the changes of $[Ca^{2+}]_t$ decreased to produce maximal depletion of 6.1 % and maximal accumulation of 1.3 % at 6 Hz. $[K^+]_t$ exhibited accumulation at all stimulation frequencies with maximal magnitudes between 2.9 % and 4 %. In the rat model (Fig. 2, right), the maximal depletion of tubular Ca^{2+} progressively increased from 7 % at 1 Hz to 14.5 % at 6 Hz while maximal Ca^{2+} accumulation decreased from 1.9 % to almost zero at 4 Hz. At the same time, tubular K^+ oscillated between accumulation and depletion with maximal magnitudes 2.7 - 4.1 % and 0.4 - 1.3 %, respectively.

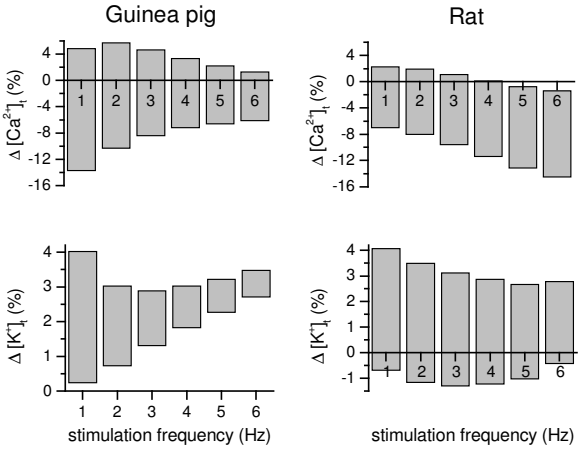

Figure 2. Frequency dependence of dynamic steady state variations of $[Ca^{2+}]_t$ and $[K^+]_t$ in the models of guinea pig and rat ventricular myocytes. The values are related to the external concentration of Ca^{2+} (1.8 mM for guinea pig and 1.2 mM for rat) and K^+ (5.4 mM for both species).

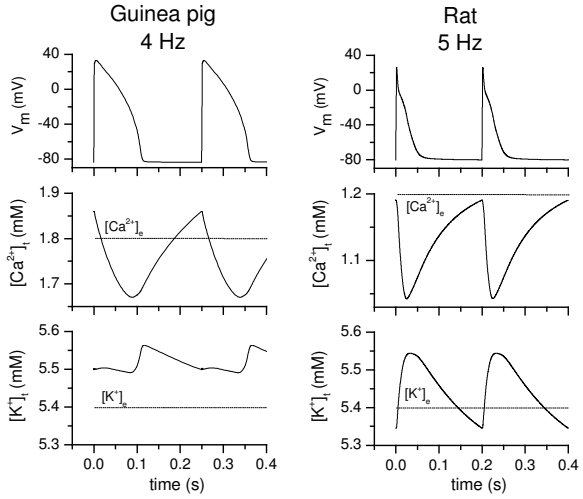

Figure 1. Steady state action potentials (V_m) and changes of ion concentrations in TATS ($[Ca^{2+}]_t$ and $[K^{2+}]_t$) during stimulation corresponding to resting hart rate of guinea pig (4 Hz) and rat (5Hz). The dotted lines denote external ion concentrations.

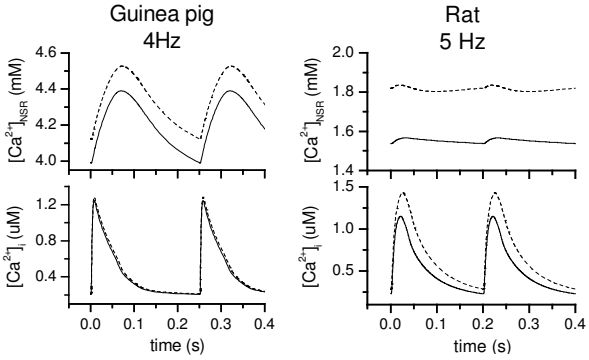

Figure 3. Dynamic steady state concentration changes in the network compartment of the sarcoplasmic reticulum ($[Ca^{2+}]_{NSR}$) and Ca^{2+} transients ($[Ca^{2+}]_i$) in the models of guinea pig and rat ventricular myocytes with ion concentration changes in TATS included (solid traces) and fixed at extracellular levels (dashed traces). The increase of intracellular Ca^{2+}load was mainly caused by the fixed tubular Ca^{2+} concentration indicating that the variations of tubular K^+ concentration played a minor role.

To assess the effect of ion concentration changes in TATS on intracellular ionic homeostasis and intracellular Ca^{2+} transients, we performed comparative simulations with models in which the tubular ion concentrations were fixed at external levels. Fig. 3 shows that maintaining tubular ion concentrations constant led to an increase of intracellular Ca^{2+} load in both models but that the size of the increase was different: the Ca^{2+} concentration in the network compartment of sarcoplasmic reticulum ($[Ca^{2+}]_{NSR}$) and the intracellular Ca^{2+} transients increased significantly in the rat model (18.34 % and 24.5 %, respectively; Fig. 3, right) but only slightly in the guinea pig model (3.1 % and 1.6 %, respectively; Fig. 3, left). The observed changes were mainly caused by fixed tubular Ca^{2+} concentration indicating that the variations of tubular K^+ concentration played a minor role.

4. Discussion and conclusions

- In the present models of guinea pig and rat ventricular cardiomyocytes, the electrical activity induced significant changes of ion concentrations in the lumen of TATS. The frequency dependence of these concentration changes exhibited species differences related to the specific features of membrane transport systems of guinea pig and rat cardiomyocytes.
- In both models, the maximal relative changes of tubular Ca^{2+} concentration (6.1-14.5 % depletion) were significantly greater than the maximal relative changes of tubular K^+ (2.7-4.1 % accumulation). Relative variations of tubular Na^+ were negligible.
- At resting heart rate, the effect of tubular Ca^{2+} depletion on $[Ca^{2+}]_{NSR}$ and systolic $[Ca^{2+}]_i$ appeared to be more profound in the rat model ($[Ca^{2+}]_{NSR}$ and systolic $[Ca^{2+}]_i$ increased by 18.34 % and 24.5 %, respectively, if concentration changes in TATS were prevented) than in the guinea pig model (3.34 % and 1.6 %, respectively). The main reason for the substantially smaller effect of guinea pig TATS in reducing intracellular Ca^{2+} load was the significant accumulation of tubular Ca^{2+} at the beginning of each cycle, smaller depletion of tubular Ca^{2+} and lower fraction of tubular I_{Ca} in guinea pig cardiomyocytes, compared with rat.
- With increasing stimulation frequency, the effect of TATS on systolic $[Ca^{2+}]_i$ becomes more marked in rat myocytes due to the increase of tubular Ca^{2+} depletion. The opposite effect is expected in guinea pig myocytes where the changes of tubular Ca^{2+} are reduced.

In conclusion, the activity-dependent depletion of Ca^{2+} within the lumen of mammalian TATS appears to decrease the intracellular Ca^{2+} load and consequently the inotropic status of ventricular myocytes. However, the extent of the depletion as well as its resulting effect on cellular activity seems to exhibit considerable species differences.

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References

[1] Pásek M, Christé G, Šimurda J. A Quantitative model of the cardiac ventricular cell incorporating the transverse-axial tubular system. Gen. Physiol. Biophys. 2003;22:355-368.

[2] Pásek M, Christé G, Šimurda J. The functional role of cardiac T-tubules explored in a model of rat ventricular myocytes. Phil. Trans. R. Soc. Lond. A. 2006, in press.

[3] Christé G, Šimurda J, Orchard CH and Pásek M. Cycling of cations between T-tubular and surface membranes in a model of guinea pig ventricular cardiomyocytes (abstract). J. Mol. Cell. Cardiol. 2005;39:174.

[4] Amsellem J, Delorme R, Souchier C & Ojeda C. Transverse-axial tubular system in guinea pig ventricular cardiomyocyte: 3D reconstruction, quantification and its possible role in K^+ accumulation-depletion phenomenon in single cells. Biol. Cell. 1995;85:43-54.

[5] Soeller C & Cannell MB. Examination of the transverse tubular system in living cardiac rat myocytes by 2-photon microscopy and digital image-processing techniques. Circ. Res. 1999;84:266-275.

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