Computational Study on the Cell Volume Regulation of Myocyte

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1. Introduction

A lot of experimental investigations have been made on the mechanism by which cells maintain their volume. In general sense, changes in intracellular and extracellular solutes concentrations generate a membrane osmotic gradient, resulting in the immediate flow of water into or out of the cell until osmotic equilibrium is restored. Water flow causes cell swelling or shrinkage, resulting in serious cell damage over a critical variation of cell size because animal cell membrane can't exert hydrostatic pressure gradient. To avoid excessive changes of cell volume, cells utilize volume regulatory mechanisms including transport across cell membrane[1].

For solutes transports across membrane, there have been a lot of experimental works, and also a lot of researches using computational method have been done. Though there have been several other papers of volume regulation modeling[2,3] mainly on epithelial cells, any computational model of volume regulation of cardiac myocyte is not available as far as we know. Considering, however, the physiological importance of cardiac cell model, volume regulation of cardiac myocytes combined with action potential approximation is one of the crucial parts in overall cardiac cell model.

In this paper, we present a computational model of volume regulation in cardiac myocytes. Two major ion exchange mechanisms are considered: Na^+/K^+ ion pump and Na^+-K^+-$2Cl^-$ cotransporter. Volume sensitive Cl- permeability is also considered in the present model, based on previous experimental and theoretical observations[2,3]. This model is combined with our previous ventricular cell model, named as Kyoto model[4].

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2. Computational model

We consider two compartments (intracellular and excellular ones) as displayed in Fig. 1. We assume that there are three solutes, sodium (Na^+), potassium (K^+), chloride(Cl^-) to which cell membrane is permeable. In here, we denote ion concentrations by $[Na^+]$, $[K^+]$, and $[Cl^-]$ with subscripts "i" for intracellular space, "e" for the extracellular space. $[X^-]i$, Vi denote the concentration of intracellular protein and the intracellular volume, respectively. As shown in Fig. 1, solutes transports are described by combinational ion movements including a Na^+/K^+ ion pump, and a Na^+-K^+-$2Cl^-$ cotransporter. The reaction processes of these ion transporters are described by state equations using kinetic model.

We utilize a dynamic equations of the intracellular ion quantities induced by the principle of mass conservation[1]. In these equations, the ion fluxes by Na/K ion pump and cotransporter are represented. To approximate the Na^+/K^+ ion pump, the six state model was lumped into a two-state one according to Simmons[3]. The state model of Na^+-K^+-$2Cl^-$ cotransporter is based on the theoretical study by Benjamin & Johnson[5], where 10 states

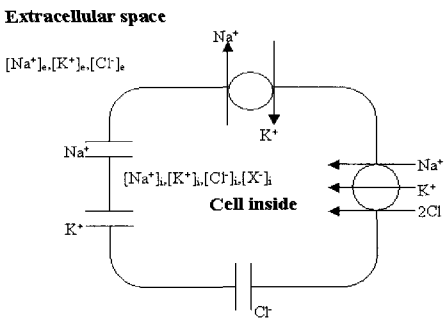


Fig. 1 Schematic representation of solutes transport across cell membrane.

description on the Na^+-K^+-2Cl^- cotransporter have been made for several types of cell.

3. Results and discussions

We simulated the cell volume change according to the extracellular osmolarity and compared the results with the experimental one[6]. As shown in Fig. 3, water came into cell in case of the hypotonic solution in extracellular part, inducing cell volume increase. As the tonicity value of extracellular fluid increases, the cell volume began to decrease and almost 50% cell shrinkage was observed in case of 200% hypertonicity solution of extracellular fluid. Numercial solutions are well matched the experimental ones in a quantitative sense, as shown in Fig. 3.

In the present model, K^+ and Cl^- permeabilities across cell membrane are assumed to be function ofcell volume, utilizing the exponential variations of the permeabilities according to cell volume. To verify

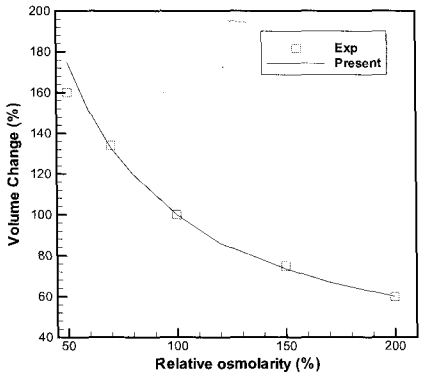
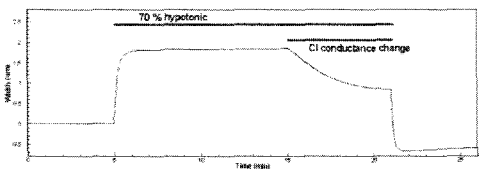
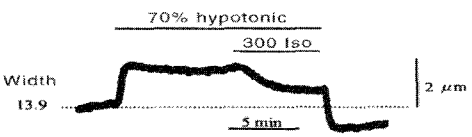


Fig. 2 Comparisons of the computed results with the experimental one[6]



(a) The present numerical solutions



(b) The previous experimental result[6]

Fig. 3 Transient simulation of isoprenaline-induced regulatory volume decrease.

this formulation, we simulated chemical inducing RVD (regulatory volume decrease). Initially 70% hypotonic solution was applied to target myocyte cell. After 10 minutes isoprenaline was added into the solution to activate volume dependent K^+ and Cl^- permeability. Abrupt volume decrease was observed by the volume-dependent K^+ and Cl^- permeability, which showed a good agreement with the previous experimental one[6].

4. Conclusions

Computational model of cell volume regulation for myocyte was proposed in this study. Na^+/K^+ ion pump and Na^+-K^+-2Cl^- cotransporter models are utilized to explain the ionic transport across cell membrane. Cell volume change according to the extracellular osmolarity was simulated and its results were compared with the experimental data. To test the model of volume dependent K^+ and Cl^- permeability, we conducted the transient simulation of isoprenaline-induced regulatory volume decrease and could successfully reproduce the previous experimental one.

References

(1) Baumgartner, C.M. & Feher, J.J. Osmosis and the regulation of cell volume. In: Cell physiology Source Book. (Sperelakis, N., ed.), Chapter 19, pp.253-292. San Diego: Academic Press, 1998.

(2) Mitchell CH, Fleischhauer JC, Stamer WD, Peterson-Yantorno K, Civan MM., Human trabecular meshwork cell volume regulation, Am J Physiol Cell Physiol. Jul;283(1):C315-26, 2002.

(3) Simmons N.L., Epithelial cell volume regulation in hypotonic fluids: studies using a model tissue culture renal epithelial cell system, Q J Exp Physiol.;69(1):83-95, 1984.

(4) 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.;53(2):105-23, 2003.

(5) Benjamin B.A., Johnson E.A., A quantitative description of the Na-K-2Cl cotransporter and its conformity to experimental data, Am J Physiol., 273(3 Pt 2):F473-82, 1997.

(6) Wang Z., Mitsuiye T., Rees S.A., Noma A., Regulatory volume decrease of cardiac myocytes induced by beta-adrenergic activation of the Cl-channel in guinea pig, J Gen Physiol., 110(1):73-82, 1997.