MODELING THE TEMPERATURE EFFECT ON THE CARDIAC RYANODINE RECEPTOR GATING

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Temperature is one of the most important factors affecting all physiological processes, in particular, cardiac excitation-contraction coupling. There is a growing evidence that the thermosensitivity of the ryanodine receptors (RyRs) gating can be responsible for the temperature effects on cardiac contractility. However, to the best of our knowledge, no theoretical models are available for that effect for these giant channels whose abnormal gating is one of the main reasons of cardiac arrhythmias and heart failure. Traditional Markov chain models do not provide a reasonable molecular mechanistic insight on the origin of the temperature effects.
We address a simple physically clear electron-conformational model [1] to describe the RyR gating. The model starts with the RyR energy depending on its electronic and conformational state. The RyR dynamics includes fast electronic transitions triggered by *cis*-Ca^{2+}, tunneling effects and slow conformational Langevin dynamics which does not obey the fluctuation-dissipation theorem and implies both internal friction [2] and conventional thermal fluctuation forces (Gaussian–Markovian noise). We argue that a synergetic effect of external thermal fluctuation forces and internal friction via the temperature stimulation/suppression of the open-close RyR tunneling probability can be considered as a main contributor to the temperature effects on the RyR gating [3]. Results of computer modeling and parametric analysis allowed us to reproduce all the temperature effects observed for an isolated RyR gating *in vitro* under hypothermia[4]: i) increased open probability P_{open}; ii) increased mean open time; iii) marginal change of the mean closed time; iv) reduced maximal conductance.

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References

1. *Moskvin A.S., Philipiev M.P., Solovyova O.E. et al.* Electron-conformational model of ryanodine receptor lattice dynamics.// Progress in Biophysics and Molecular Biology**,** Vol. **90,** 2006. Pp. 88-103.
2. *Hagen S.G.* Solvent viscosity and friction in Protein Folding Dynamics.//Curr. Protein Pept. Sci. Vol. **11**, No. 5, 2010. Pp.385– 395
3. *Moskvin A.S., Iaparov B.I. et al.* Electron-conformational transformations govern the temperature dependence of cardiac ryanodine receptor gating // JETP Letters Vol. **102**, No. 1, 2015. Pp. 67-73.
4. *Sitsapesan, R. et al*. Sheep cardiac sarcoplasmic reticulum calcium-release channels: modification of conductance and gating by temperature.// J. Physiol. Vol. **434**, 1991. Pp.469– 488