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Modeling of stochastic behavior of pacemaker potential in interstitial cells of Cajal

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ABSTRACT

It is widely accepted that interstitial cells of Cajal (ICCs) generate pacemaker potentials to propagate slow waves along the whole gastrointestinal tract. Previously, we constructed a biophysically based model of ICCs in mouse small intestine to explain the pacemaker mechanism. Our previous model, however, could not explain non-uniformity of pacemaker potentials and random occurrence of unitary potentials, thus we updated our model. The inositol 1,4,5-trisphosphate (IP_3)-mediated Ca^{2+} mobilization is a key event to drive the cycle of pacemaker activity and was updated to reproduce its stochastic behavior. The stochasticity was embodied by simulating random opening and closing of individual IP_3-mediated Ca^{2+} channel. The updated model reproduces the stochastic features of pacemaker potentials in ICCs. Reproduced pacemaker potentials are not uniform in duration and interval. The resting and peak potentials are -75.5 ± 1.1 mV and -0.8 ± 0.5 mV, respectively ($n = 55$). Frequency of pacemaker potential is 14.3 ± 0.4 min^{-1} ($n = 10$). Width at half-maximal amplitude of pacemaker potential is 902 ± 6 ms ($n = 55$). There are random events of unitary potential-like depolarization. Finally, we compared our updated model with a recently published model to speculate which ion channel is the best candidate to drive pacemaker depolarization. In conclusion, our updated mathematical model could now reproduce stochastic features of pacemaker activity in ICCs.

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1. Introduction

Isolated gastrointestinal (GI) tract is able to contract without any extrinsic stimulatory input, which indicates there are primary pacemaker regions in the GI tract driving phasic slow waves and contractions in smooth muscle cells. The interstitial cells of Cajal (ICCs) have been suggested to be the pacemakers in the GI tract reminiscent of sino-atrial node cells in the heart (Sanders, 1996; Thuneberg, 1982; Ward et al., 1994). ICCs are intercalated between nerves and smooth muscle cells and their ultrastructure is myoid with several fibroblast-like traits (Streutker et al., 2007). As an analogy to cardiac arrhythmias, GI arrhythmias are believed to arise from ion channelopathies. Indeed, a mutation of SCN5A in ICCs was identified from the subjects with irritable bowel syndrome (Saito et al., 2009).

As for the mechanism how ICCs generate pacemaker activity, cyclic release and uptake of Ca^{2+} through endoplasmic reticulum (ER) have been suggested to play a key role in driving phasic depolarization. In support of this idea, inhibition of inositol 1,4,5-trisphosphate (IP_3)-mediated Ca^{2+} release using 2-aminoethoxydiphenyl borate was found to abolish pacemaker potential (Yoneda et al., 2002). Inhibition of ER Ca^{2+} pumps using cyclopiazonic acid decreased pacemaker activity (Liu et al., 1995). Furthermore, chelating cytosolic Ca^{2+} using bis-(o-aminophenoxy)-ethane-N,N,N′,N′-tetra-acetic acid (BAPTA) or inhibition of IP_3 synthesis using neomycin, a phospholipase C inhibitor, also decreased the pacemaker activity (Liu et al., 1995; Malysz et al., 2001; Suzuki

Abbreviations: ER, endoplasmic reticulum; ODEs, ordinary differential equations; ICCs, interstitial cells of Cajal; IP_3, inositol 1,4,5-trisphosphate; SOCE, store-operated Ca^{2+} entry.

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and Hirst, 1999; Yoneda et al., 2002) suggesting Ca^{2+} is the biochemical clock which initiates pacemaker activity. Cyclic change in Ca^{2+} is somehow related with Ca^{2+}-associated processes which eventually depolarize cell membrane resulting in the upstroke phase of pacemaker potential. Ca^{2+}-activated non-selective cation channel (Goto et al., 2004; Kim et al., 2005), Ca^{2+}-inhibited non-selective cation channel (Koh et al., 2002), and Ca^{2+}-activated Cl^- channel (Hwang et al., 2009; Zhu et al., 2009) have been proposed as possible candidates of the Ca^{2+}-associated processes in ICCs.

After the first biophysically based model of ICCs (Youm et al., 2006), several models with their own hypotheses have been developed. One of the model (Corrias and Buist, 2008) was based on the non-selective cation conductance (NSCC) hypothesis (Sanders et al., 2006). The model by Faville et al. is also based on the NSCC hypothesis (Faville et al., 2008), but multiple pacemaker units were additionally implemented into the model to reproduce the occurrence of unitary potential. Recently, a model of store-operated Ca^{2+} entry (SOCE)-coupled Ca^{2+}-activated Cl^- channel was developed to elucidate the results of anoctamin 1 (Ano1) knockout mice (Lees-Green et al., 2014). The model was able to demonstrate that cyclic Ca^{2+} release and pacemaker depolarization could possibly be driven by SOCE-coupled Ca^{2+}-activated Cl^- channel. However, a model reproducing non-uniformity of pacemaker potential in duration and interval has not been proposed yet.

In this work, we further implemented the stochastic feature of IP_3-mediated Ca^{2+} release to reproduce the non-uniformity of pacemaker potential and associated observations of unitary potential. In order to achieve this aim, we adopted a stochastic approach instead of deterministic approach to the model of IP_3-mediated Ca^{2+} release as a numerical integration. Stochastic models of IP_3-mediated Ca^{2+} release have already been used in modeling of intracellular Ca^{2+} oscillation in neurons (Diambra and Guisoni, 2005; Falcke, 2003; Gin et al., 2009) but have never been used in modeling of intracellular Ca^{2+} oscillation in ICCs to our knowledge. We also present a simple linear 4-state model with Ca^{2+}-inhibitory step to reproduce a typical bell-shaped relation between $[Ca^{2+}]_i$ and open probability of IP_3 receptor channel. Na^+-leak channel (NaLCN), which is known to form a background Na^+ conductance in neurons (Kim et al., 2012), was also included in our model to better approximate experimentally obtained resting membrane potential (−71.5 mV). Finally, we compared our current model in the view of characteristics of pacemaker potentials, pacemaker currents, and calcium transients with the previous published model by Lees-Green et al. (2014). A hybrid between two models is also presented.

2. Methods

2.1. General

This work is based on a previously published model (Youm et al., 2006) and further updated and newly employed components are described. All the components included in this updated model are schematically represented in Fig. 1. Detailed descriptions and formulations are presented in Tables 1–6 and Appendix A, respectively. Numerical integration of variables such as ion concentrations and membrane potential was carried out by a simple Euler method. For calculation of state variables of most ion channels, pumps, and exchanger, an alternative method (Youm et al., 2004) was employed to prevent critical errors arising from the very rapid rate constants. For numerical integration of IP_3 receptor channel, a stochastic approach was applied to reproduce its random opening and closing.

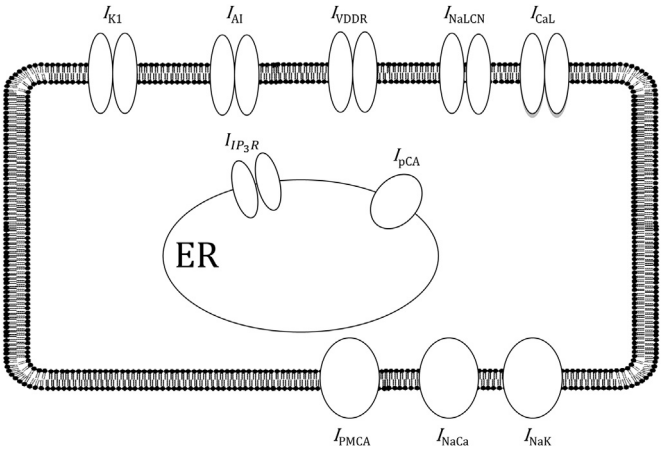

Fig. 1. Schematic representation of ion channels, pumps, and exchangers on cell membrane and endoplasmic reticulum (ER) in the model. See Table 1 for detailed descriptions.

2.2. Modeling of IP_3 receptor channel

There is a consensus that IP_3-mediated Ca^{2+} release is the key event underlying pacemaker activity in the ICCs (Liu et al., 2005; Lowie et al., 2011; Suzuki and Hirst, 1999; Ward et al., 2000; Yoneda et al., 2002). Oscillatory release of Ca^{2+} from ER triggers activation of Ca^{2+}-associated pacemaker currents, which subsequently depolarize cell membrane. Thus, building a proper model

Table 1
Glossary.

Parameter	Unit	Description
V	mV	Membrane potential
t	ms	Time
I_{total}	pA	Total current of ion channels, exchanger, and pumps
I_{ext}	pA	Current applied through the electrode
$I_{net}X$	pA	Whole cell current carried by ion X
I_{K1}	pA	Inward rectifier K^+ current
I_{CaL}	pA	L-type Ca^{2+} current
$I_{CaL}X$	pA	Ion X component of I_{CaL}
I_{VDDR}	pA	Voltage-dependent and DHP-resistant current
I_{AI}	pA	Autonomous inward current
$I_{AI}X$	pA	Ion X component of I_{AI}
$p_{o(AI)}$		Probability of I_{AI} channel in open state
I_{NaLCN}	pA	Na^+-leak current
$I_{NaLCN}X$	pA	Ion X component of I_{NaLCN}
I_{NaCa}	pA	Na^+/Ca^{2+} exchange current
I_{NaK}	pA	Na^+/K^+ pump current
$I_{NaK}X$	pA	X component of I_{NaK}
I_{PMCA}	pA	Plasmalemmal Ca^{2+} pump current
α_x	ms^{-1}	Forward rate constant for gating variable x
β_x	ms^{-1}	Backward rate constant for gating variable x
x_∞		Steady-state value of gating variable x
τ_x	ms	Time constant of gating variable x
E_X	mV	Equilibrium potential for ion X
I_{pCa}	pA	ER Ca^{2+} pump current
I_{IP_3R}	pA	IP_3-mediated Ca^{2+} release current from the ER
$p_{o(IP_3R)}$		Probability of IP_3 receptor channel in conducting state
I_{leak}	pA	Ca^{2+} leak from ER uptake pool
I_{tr}	pA	Ca^{2+} transfer between ER uptake and release pool
CF_X	mM	Constant field for ion X