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ORIGINAL PAPER

Effects of both glucose and IP_3 concentrations on action potentials in pancreatic β-cells

Xuan Zhan · Dan Wu · Lijian Yang · Quan Liu · Ya Jia

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Abstarct Considering the ATP-driven (SERCA) pump flux as function of glucose concentration and the calcium flux from the endoplasmic reticulum (ER) through the IP_3R channel, the calcium-based phantom bursting model (PBM) of β-cells (Bertram and Sherman in Bull Math Biol 66:1313, 2004) is theoretically extended to discuss the effects of glucose and inositol 1,4,5-trisphosphate (IP_3) concentration on the membrane potential activities. When IP_3 concentration is fixed, it is found that there is a critical glucose concentration at which electrical bursting oscillations transfer into spiking, and the critical concentration of glucose is increased with the increasing of IP_3 concentration. To get the bursting oscillations in β-cells, our theoretical results show that the stimulatory glucose concentration should be more than 10 mM, which is consistent with the normal physiological IP_3 level. When the stochastic opening and closing of IP_3R channels are considered, it is shown that the membrane potential oscillation transfers from spiking to bursting with the channel number decreasing, and the average cytosolic free Ca^{2+} concentration is increased with the increase of glucose concentration.

Keywords β-cell · Glucose · IP_3 · Channel number

X. Zhan · D. Wu · L. Yang · Q. Liu · Y. Jia (✉)
Department of Physics, Central China Normal University, Wuhan 430079, China
e-mail: jiay@phy.ccnu.edu.cn

X. Zhan
e-mail: zhanx@phy.ccnu.edu.cn

D. Wu
e-mail: wud@phy.ccnu.edu.cn

Introduction

Located in pancreatic islets of langerhans, β-cells are responsible for the secretion of insulin following an elevation in the blood glucose level. The proper functioning of β-cells is crucial for glucose homeostasis with insulin being necessary for the uptake of glucose by other cells in the body and malfunctioning β-cells can lead to type II diabetes (Bertram and Sherman 2004; Lang et al. 1981).

It has been experimentally reported that β-cells actually show continuous spikes or bursting action potentials (Falke et al. 1989; Kinard et al. 1999; Smith et al. 1990; Dean and Matthews 1968; Sánchez-Andrés et al. 1995), and Ca^{2+} brought in by action potentials evokes the secretion of insulin (Atwater et al. 1989). Electrical bursting, which consists of active phase of spiking followed by a silent phase of hyperpolarization, was first detected in vitro in mouse islets by Dean and Mathews (1970), and has been confirmed in vivo (Sánchez-Andrés et al. 1995; Valdeolmillos et al. 1996). It has been shown that the bursts appear more effective in maintaining glucose homeostasis than continuous spikes (Halban et al. 1982; Pipeleers et al. 1982), which means burst being more helpful for insulin secretion (Henquin and Meissner 1984). One of the striking features of bursting in islets and isolated β-cells is the heterogeneity of periods, which range from a few seconds to a few minutes (Kinard et al. 1999; Valdeolmillos et al. 1996; Zhang et al. 2003; Cook et al. 1981; Bertram et al. 1995; Ashcroft et al. 1984). In vitro these oscillations have been shown to be in-phase with oscillations in the free cytosolic Ca^{2+} concentration (Bergsten 1995; Bergsten et al. 1994).

On the other hand, some mathematical models of β-cells have been constructed to describe the action potentials of β-cells. Based on a hypothesis of slow negative feedback by cytosolic Ca^{2+} acting on Ca^{2+}-activated K^+ channels drives bursting proposed by Atwater and Rojas (Atwater et al. 1980), Chay and Keizer (1983) developed the first Hodgkin–Huxley type model for β-cells. But it was found that the subsequent Ca^{2+} imaging data change too rapidly to account for bursting (Santos et al. 1991). Thus, the following β-cell models differed largely in the slow process postulated to drive bursting. For example, voltage-dependent inactivation of Ca^{2+} current (Keizer and Smolen 1991), oscillations in nucleotide concentrations (Keizer and Magnus 1989), and the two slow conductances induced the phantom burster model(PBM) (Bertram et al. 2000).

Recently, a calcium-based phantom bursting model has been proposed by Bertram and Sherman (2004). In their model (1) the role of endoplasmic reticulum (ER) had been added to the Chay–Keizer model (1983). The key role of the ER is to slow the rise and fall of the cytosolic Ca^{2+} concentration. So the model can describe many experimental phenomena, such as the bursting periods varying from a few seconds to several minutes, dumping the ER increasing bursting frequency, etc. (2) In order to account for the observations that slow bursting is insensitive to store depletion, the conductance $g_{K(ATP)}$ of the nucleotide-sensitive K^+ current $I_{K(ATP)}$ as a second negative feedback target for Ca^{2+} is added. (3) It was firstly found that the key elements of the triphasic response to a step in glucose from basal to stimulatory level. Although the calcium-based PBM model proposed by Bertram and Sherman has a great success in disclosing the effects of intracellular calcium oscillations on the potential of β-cells, the effects of glucose on the membrane potential was only referred to two constants k_{SERCA} and r, and the two constants as function of glucose have not been markedly given. In addition, how to explain the experimental results, such as the isolated β-cells show fast and irregular bursts (Falke et al. 1989; Kinard et al. 1999; Smith et al. 1990) while β-cells in a cluster or in an intact islet produce regular bursting action potentials, has not been discussed.

Based on the calcium-based PBM model, we present here a model of ATP-driven (SERCA) pump which as function of both glucose and cytosolic free Ca^{2+} concentrations, and we also modified the calcium flux from ER through the IP_3R channel by the Li-Rinzel model (Li and Rinzel 1994). We indeed explore theoretically the possible role of both glucose and IP_3 concentration in the regulation of potential oscillations on the membrane of β-cells. This process plays a vital role in the regulation of oscillation pattern, and it is shown that β-cells display a bursting pattern of action potential when the glucose concentration is up to stimulatory concentration, which is in accordance with the experimental results (Dean and Mathews 1970; Bergsten et al. 1994), and the stimulatory concentration is affected by the concentration of inositol 1,4,5-trisphosphate (IP_3). On the other hand, the effects of intrinsic noise due to the random opening and closing of ionic channels are considered in present paper. Our theoretical results indicate that high IP_3 concentration will exhibit membrane potential of β-cells from bursting activities and there exits irregular bursting only if IP_3R channel number is small.

The paper is organized as follows. A modified mathematical model for β-cells is presented in the second section. The third section describes the effects of both of glucose and IP_3 concentrations on membrane potentials. The effects of random opening and closing of IP_3R channels on membrane potentials have been discussed in the fourth section. We end with some conclusions and discussions.

The model

The calcium-based PBM model proposed by Bertram and Sherman (2004) consists of a Ca^{2+} current I_{Ca}, a delayed rectifier K^+ current I_K, a Ca^{2+}-dependent K^+ current $I_{K(Ca)}$, and a nucleotide-sensitive K^+ current $I_{K(ATP)}$. The membrane potential V, delayed rectifier activation n, cytosolic free Ca^{2+} concentration c, and the ER Ca^{2+} concentration c_{er}, are governed by the following ordinary differential equations:

$$\frac{dV}{dt} = -[I_{Ca} + I_K + I_{K(Ca)} + I_{K(ATP)}]/C_m, \quad (1)$$

$$\frac{dn}{dt} = [n_\infty(V) - n]/\tau_n, \quad (2)$$

$$\frac{dc}{dt} = f_{cyt}(J_{mem} + J_{er}), \quad (3)$$

$$\frac{dc_{er}}{dt} = -f_{er}(V_{cyt}/V_{er})J_{er}, \quad (4)$$

with

$$I_{Ca} = g_{Ca}m_\infty(V)(V - V_{Ca}), \quad (5)$$

$$I_K = g_K n(V - V_K), \quad (6)$$

$$I_{K(Ca)} = g_{K(Ca)}\omega(V - V_K), \quad (7)$$

$$I_{K(ATP)} = \bar{g}_{K(ATP)} a (V - V_K), \tag{8}$$

$$J_{mem} = -(\alpha I_{Ca} + k_{PMCA} c), \tag{9}$$

$$J_{er} = J_{leak} + J_{IP_3} - J_{SERCA}, \tag{10}$$

where C_m is the membrane capacitance, τ_n is the activation time constant for the delayed rectifier channel, $n_\infty(V)$ is the steady state function for the activation variable n. The total cytoplasmic free Ca^{2+} concentration (c) considered here is involved in the Ca^{2+} flux through the plasma membrane (J_{mem}) and the net Ca^{2+} efflux from the ER (J_{er}), and multiplied by the fraction (f_{cyt}). c_{er} and J_{er} have been scaled by the ratio of the volumes of the cytoplasmic compartment (V_{cyt}) and the ER compartment (V_{er}). f_{er} is the fraction of free Ca^{2+} in the ER. The steady state activation functions have an increasing dependence on voltage and saturate at positive voltages: $m_\infty(V) = [1 + e^{(v_m - V)/s_m}]^{-1}, n_\infty(V) = [1 + e^{(v_n - V)/s_n}]^{-1}$. The variable $\omega = c^5/(c^5 + k_D^5)$ in Eq. (7) is the fraction of K(Ca) channels activated by cytosolic Ca^{2+}, k_D is the dissociation constant for Ca^{2+} binding to the channel, the value of the exponent in the expression of ω is not critical and the other values could be used (Bertram and Sherman 2004). The nucleotide ratio a = ADP/ ATP in Eq. (8) satisfies the first-order kinetic equation: $da/dt = (a_\infty(c) - a)/\tau_a$, and $a_\infty(c)$ has an increasing sigmoidal dependence on cytosolic Ca^{2+} concentration as $a_\infty(V) = [1 + e^{(r-c)/s_a}]^{-1}$. The parameter α in Eq. (9) converts units of current to units of flux, and k_{PMCA} is the flux through the plasma membrane Ca^{2+} ATPase pumps. It was assumed that the Ca^{2+} influx into the ER via SERCA pumps in Eq. (10) depends linearly on the cytosolic Ca^{2+} concentration in the calcium-based PBM model (Bertram and Sherman 2004)

$$J_{SERCA} = k_{SERCA} c. \tag{11}$$

The efflux out of the ER has two components, one is Ca^{2+} leakage flux $J_{leak} = p_{leak}$ (c_{er} –c) which is taken to be proportional to the gradient between Ca^{2+} concentrations in the cytosol and the ER (c_{er}). The other is Ca^{2+} flux from the ER through the IP_3R channel

$$J_{IP_3} = o_\infty (c_{er} - c), \tag{12}$$

where O_∞ is the fraction of open channels. There are three and independent subunits involved in conduction in an IP_3R. Each subunit has one IP_3 activation site, one Ca^{2+} activation site and one Ca^{2+} inactivation site. For the convenience of analysis, the steady-state function for O_∞ in Ref. (Bertram and Sherman 2004) is taken the form

$$o_\infty = \left(\frac{c}{d_{act} + c}\right)^3 \left(\frac{IP_3}{d_{IP_3} + IP_3}\right)^3 \left(\frac{d_{inact}}{d_{inact} + c}\right)^3, \tag{13}$$

which is a simplified form of the Li-Rinzel model (Li and Rinzel 1994). The more detailed meanings of other parameters in the calcium-based PBM model can be found in Ref. (Bertram and Sherman 2004).

Experimental results have indicated that the bursting activities of β-cells need stimulatory glucose concentration (Berridge and Irvine 1989). In the calcium-based PBM model (Bertram and Sherman 2004), the parameter k_{SERCA} is referred to the variation of glucose concentration (Bertram and Sherman 2004; Andreu et al. 1997; Gilon and Henquin 1999). In order to discuss the effects of glucose on the action potential of β-cells, here, a explicit expression for the parameter k_{SERCA} as function of glucose concentration (glu) is given by

$$k_{SERCA} = k_1 (glu - glu_k), \tag{14}$$

where k_1 is the fraction of glucose, and glu_k is considered as the basal glucose level. Meanwhile, there exits another possible mechanism for negative feedback of Ca^{2+} on ATP production in islets which has been experimentally found by Ainscow and Rutter (2002) and theoretically investigated by Larsen et al. (2004). Combining Eq. (14) with the negative feedback of Ca^{2+} on ATP production in islets, the SERCA pumps flux (J_{SERCA}) in Eq. (10) is expressed as

$$k_{SERCA} = \frac{k_1 c^2}{k_2^2 + c^2} (glu - glu_k). \tag{15}$$

Therefore, the SERCA pumps flux used in Ref. (Bertram and Sherman 2004) [as shown by Eq. (11)] has been replaced by Eq. (15) in present paper.

On the other hand, the intracellular Ca^{2+} controls the action potential of β-cell through both direct and indirect negative feedback pathways in the calcium-based PBM model (Bertram and Sherman 2004). While intracellular Ca^{2+} signals are due to release of Ca^{2+} from intracellular stores. It is well known that the opening and closing of Ca^{2+} channels are stochastic in the cellular level, which can lead to the irregular period and amplitude of cytosolic Ca^{2+} oscillations. Therefore, such a deterministic description of Ca^{2+} channels in the calcium-based PBM model (Bertram and Sherman 2004) is no longer valid for the cellular or sub-cellular level, a mesoscopic stochastic model for the Ca^{2+} channels should be considered. To study the effects of both IP_3 and stochastic Ca^{2+} release of IP_3R channels on the action

potential of β-cell, we will employ the Li-Reinzel model (Li and Rinzel 1994) to describe the efflux out of ER through the IP_3R channels here:

$$J_{IP_3} = c_1 v_1 m_{er}^3 n_{er}^3 h_{er}^3 (c_{er} - c), \quad (16)$$

where h_{er}, m_{er} and n_{er} represent the three equivalent and independent subunits involved in an IP_3R channel. $m_{er} = IP_3/(IP_3 + d_1), n_{er} = c/(c + d_4)$, and

$$\frac{dh_{er}}{dt} = \alpha_h(1 - h_{er}) - \beta_h h_{er}, \quad (17)$$

where $\alpha_h = a_1 d_2(IP_3 + d_1)/(IP_3 + d_3)$, and $\beta_{er} = a_1\ c$. More detail meanings of the parameters in the Li-Reinzel model can be found in Ref. (Li and Rinzel 1994). Thus, the Ca^{2+} flux from the ER through the IP_3R channel, J_{IP3}, used in Bertram and Sherman (2004) (as shown by Eqs. (12, 13)) has been replaced by Eq. (16) with Eq. (17) in this paper.

In order to discuss the effects of glucose and IP_3 on membrane potentials, numerical simulations are needed. Equations (1)–(4) with (5)–(10) and (15)–(17), are simulated by using a simple forward Eular algorithm with a time step of 0.1 ms. In each calculation the time evolution of the system lasted 1,000 s after transient behavior was discarded. The parameter values are given in Table 1.

Effects of glucose and IP_3 on membrane potentials

Experimental data showed that β-cells show continuous spikes or bursting action potentials (Falke et al. 1989; Kinard et al. 1999; Smith et al. 1990; Dean and Matthews 1968; Sánchez-Andrés et al. 1995), Ca^{2+} brought in by action potentials evokes the secretion of insulin (Atwater et al. 1989), and the intracellular Ca^{2+} release is controlled by IP_3 receptors or ryanodine receptors (Li and Rinzel 1994; Shuai and Jung 2002a). It was also shown that the bursting periods of β-cells are longer than 2 s (Valdeolmillos et al. 1996; Zhang et al. 2003; Cook et al. 1981; Bertram et al. 1995; Ashcroft et al. 1984), which can be considered as a critical condition to distinguish the spiking from the bursting. It was also found that the key elements of the triphasic response to a step in glucose from basal to stimulatory level (Bertram and Sherman 2004). In this section, the effects of glucose and IP_3 concentration on action potential of β-cells will be theoretically investigated. When the IP_3 concentration is fixed (e.g. IP_3 = 0.15 μM), the time courses of membrane potential are shown in Fig. 1 for different glucose concentrations glu. It can be seen that the membrane potential exhibits spike when the stimulating of glucose is lower (e.g. glu = 4 mM). In fact, this spiking is not a regular spike oscillations (Bertram and Sherman 2004). However, with the increasing of glucose concentration, the spiking oscillation of membrane potential will change into bursting (e.g. glu = 12, 16, 20 mM), and the higher the glucose concentration is, the longer the bursting period will be.

When the concentration of glucose is fixed (e.g. glu = 12 mM), the time courses of membrane potential are shown in Fig. 2 for different IP_3 concentrations IP_3. It is shown that the membrane potential exhibits bursting when the concentration of IP_3 is lower (e.g. IP_3 = 0.05 μM). With the increasing of IP_3 concentration, the period of bursting will be shorter (e.g. IP_3 = 0.15 and 0.25 μM). At a certain IP_3 concentration the bursting oscillation of membrane potential will change into spiking (e.g. IP_3 = 0.4 μM). Experimental results have revealed that the bursting oscillations of membrane potential show more effective in maintaining insulin secreting (Pipeleers et al. 1982; Henquin and Meissner 1984), that is, bursting seems more helpful in glucose homeostasis than spiking. From above results, there is a transition between the spiking phase and the bursting one with the variation of glucose and IP_3, respectively. Thus, it is important to distinguish the two oscillation phases of β-cells. Two methods are used here. One is the oscillation frequency which corresponds to the peak of power spectrum since bursting periods are larger than 2 s (Valdeolmillos et al. 1996; Zhang et al. 2003; Cook et al. 1981; Bertram et al. 1995; Ashcroft et al. 1984). The other is the average cytosolic free Ca^{2+} concentration (<c>),

Table 1 Parameter values

Parameter	Value	Parameter	Value
g_{Ca}	1,200 ps	g_K	3,000 ps
$g_{K(Ca)}$	700 ps	V_{Ca}	25 mV
$\bar{g}_{K(ATP)}$	500 ps	V_K	–75 mV
C_m	5,300 fF	α	4.5×10^{-6} $fA^{-1}\mu$ Mms^{-1}
τ_n	16 ms	f_{cyt}	0.01
k_{PMCA}	0.2 ms^{-1}	k_D	0.3 μM
v_n	–16 mV	s_n	5 mV
v_m	–20 mV	s_m	12 mV
r	0.14 μM	τ_a	3×10^5 ms
s_a	0.1 mM	d_{act}	0.35 μM
d_{IP3}	0.5 μM	d_{inact}	0.4 μM
f_{er}	0.01	k_{SERCA}	0.4 ms^{-1}
p_{leak}	0.0005 ms^{-1}	V_{cyt}/V_{er}	5
k_1	$5.0 \times 10^{-5} ms^{-1}$	glu_k	2.0×10^3 μM = 2.0 mM
k_2	0.16 μM	c_1	18.5
v_1	$6.0 \times 10^{-3} s^{-1}$	d_1	0.13 μM
d_2	1.049 μM	d_3	0.9434 μM
d_4	0.08234 μM	a_1	2.0×10^{-4} μM^{-1} s^{-1}

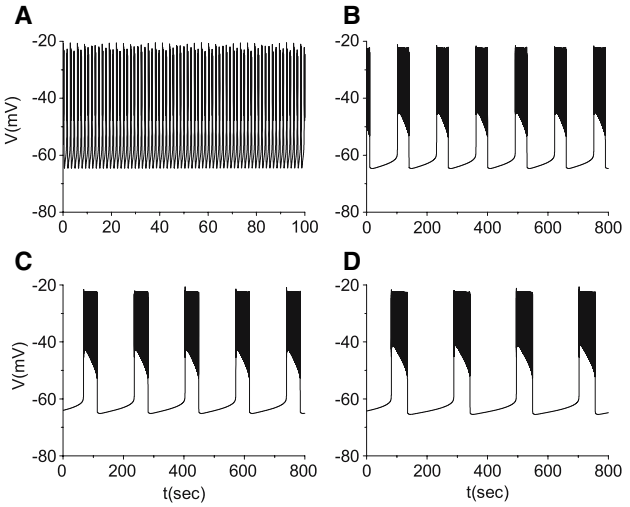

Fig. 1 Temporal evolution of membrane potential at a fixed level IP_3 = 0.15 μM for different concentration of glucose. A glu = 4 mM; B glu = 12 mM; C glu = 16 mM; and D glu = 20 mM

since it was experimentally shown insulin secretion is oscillatory with period of several minutes (Chou and Ipp 1990; Longo et al. 1991; O'Meara et al. 1993), and this oscillations have shown to be in-phase with the oscillatory of cytosolic free Ca^{2+} concentration (Bergsten 1995; Bergsten et al. 1994). While these Ca^{2+} oscillations come with the bursting action potential on the membrane of β-cells (Zhang et al. 2003; Santos et al. 1991). The experimental results have shown that secretion of insulin from pancreatic β-cells is proportional to the average intracellular Ca^{2+} concentration

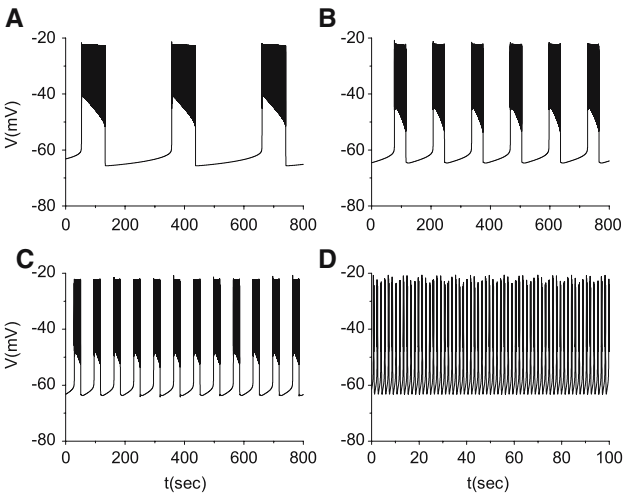

Fig. 2 Temporal evolution of membrane potential at a fixed glucose stimulation level glu = 12 mM for different concentration of IP_3. A IP_3 = 0.05 μM; B IP_3 = 0.15 μM; C IP_3 = 0.25 μM; D IP_3 = 0.4 μM

(Bergsten et al. 1994), i.e. high Ca^{2+} concentration indicates bursting (de Vries and Sherman 2000). When the stimulation of glucose is fixed, the average Ca^{2+} concentration $<c>$ and the oscillation frequency f_{max} with the increasing of IP_3 concentration are plotted in Fig. 3a, b, respectively. It can be found that (1) the average Ca^{2+} concentration is decreased, while the bursting frequency is increased with the increasing of IP_3. (2) There is mutation for the oscillation frequency at a certain IP_3 concentration ($IP_3 \approx 0.34$ μM). (3) The oscillation of membrane potential is bursting when $IP_3 < 0.34$ μM, and is spiking when $IP_3 > 0.34$ μM. Therefore, for a given value of glucose stimulating, there is a critical IP_3 concentration which can delimit the two oscillation phases (bursting and spiking) of β-cells. Figure 4a, b) show $<c>$ and f_{max} are changed with different glucose concentration, when IP_3 concentration is fixed. It is found that (1) the mutation of f_{max} exists at a certain glucose concentration (glu≈6.8 mM). (2) The oscillation is spiking when glu < 6.8 mM and is bursting when glu > 6.8 mM. (3) $<c>$ is increased with the increase of glucose concentration, and this is corresponding to the experimental results (Bergsten et al. 1994; Longo et al. 1991). Figure 5 shows the the two oscillation phases (bursting and spiking) of β-cells in the parameters IP_3–glu plane. There are two regions, one is spiking, and the other is bursting. It can be also found that, at the fixed IP_3 concentration, the oscillation of membrane potential will be transformed from spiking to bursting with the increasing of glucose stimulating. When them IP_3 concentration is high, the stimulatory glucose concentration inducing burst oscillations must be higher. In vitro, β-cells display a bursting pattern of electrical

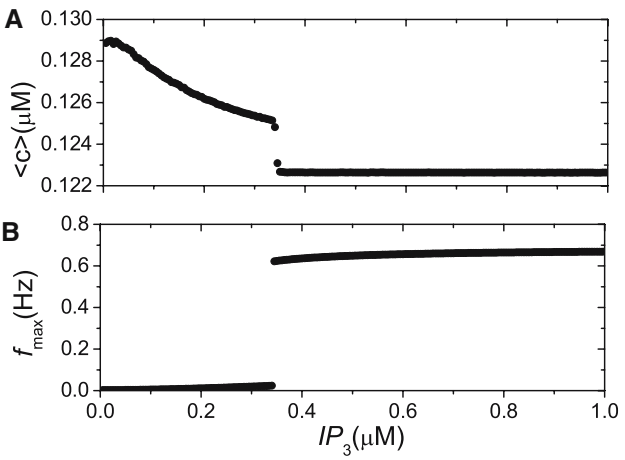

Fig. 3 The average Ca^{2+} concentration (**a**) and the oscillation frequency (**b**) as a function of the IP_3 concentration. glu = 12 mM

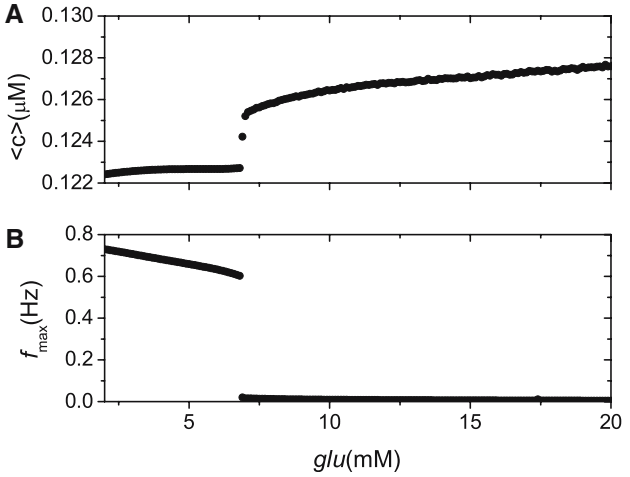

Fig. 4 The average Ca^{2+} concentration (**a**) and the oscillation frequency (**b**) as a function of the glucose concentration. IP_3 = 0.15 μM

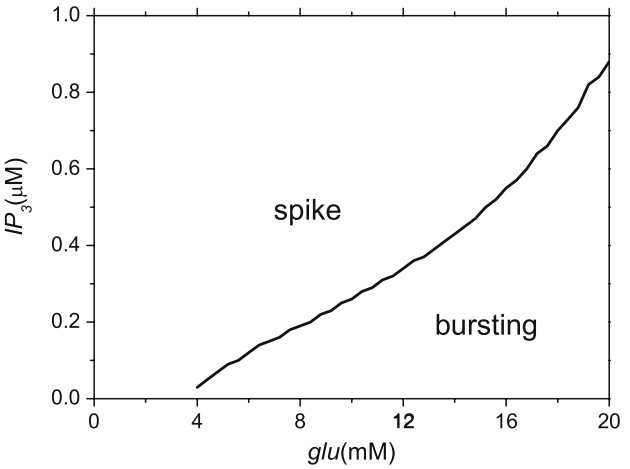

Fig. 5 Phase diagram in the parameters IP_3–glu plane

impulses when glucose concentration is above 10 mM (Dean and Mathews 1970). Figure 5 can indicate this result with IP_3 concentration changing between 0.25 and 0.6 μM (Shuai and Jung 2002a; Wu et al. 2004; and Jung 2002b), which is the normal physiological range.

Effects of IP_3R channels on membrane potentials

It is well known that the release of Ca^{2+} from intracellular poolscan be mediated by two types of receptor channel proteins, the IP_3receptor and the ryanodine receptor, which have quite different gating properties and single channel conductances. One major source of intrinsic noise of intracellular Ca^{2+} oscillations comes from the ion channels embedded in the membrane. These channels are macromolecules that are subjected to random changes of conformational state due to thermal agitation, and when these changes occur between a conducting and nonconducting state, the channel acts as a microscopic source of noise current that is injected into the cell. In this section, two methods will be used to simulate the intrinsic noise (i.e. the stochastic opening and closing of IP_3R channels) in the membrane of ER.

The first is the Langevin method (Fox and Lu 1994). For a large IP_3R channel number N (i.e. the total ion channel number), the differential equation of h_{er} (Eq. 17) can be approximated by a Fokker–Planck equation, which is a linear partial differential equation for the probability of fraction of h-open gates $h_{er} = n/N$ (Van Kampen 1976), where n is the opening ion channel number. For Fokker–Planck equation there is a statistically equivalent Langevin equation, i.e., stochastic differential equation (Fox and Lu 1994). The Langevin equation for the fraction of h-open gate $h_{er} = n/N$ is then expressed as

$$\frac{dh_{er}}{dt} = \alpha_h(1 - h_{er}) - \beta_h h_{er} + G_h(t), \tag{18}$$

where $G_h(t)$ is a Gaussian white noise with zero mean and its autocorrelation is

$$\langle G_h(t)G_h(t')\rangle = \frac{\alpha_h(1 - h_{er}) + \beta_h h_{er}}{N}\delta(t - t'). \tag{19}$$

The second is the two-state Markov method (Shuai and Jung 2002b). In this method, the binding and unbinding of three sites of gate h are described by two-state Markov process with opening and closing rate α_h and β_h, respectively. Thus, the stochastic scheme for all three gates is postulated

$$C \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} O. \tag{20}$$

Only if all three h gates in an IP_3R channel are open at time t, the channel is h-open. The expression for the calcium flux through the IP_3R channels replacing Eq. (16) is given by

$$J_{IP_3} = c_1 v_1 m_{er}^3 n_{er}^3 \frac{N_{h-open}}{N}(c_{er} - c), \tag{21}$$

where N and $N_{h\text{-open}}$ are the total number of IP_3R channels and the number of h-open channels, respectively. $N_{h\text{-open}}/N$ is the h-open fraction, replacing h^3 in Eq. (16), which is the deterministic model. It is well known that the intrinsic noise strength is inversely

proportional to N. The smaller N is, the larger the strength of internal noise will be. The stochastic kinetic of ion channels will recover to the deterministic one when $N \rightarrow \infty$. At a given glucose stimulating level (e.g. glu =12 mM), Figs. 6 and 7 show the time courses of membrane potential and the corresponding power spectrums for different N by using of the Langevin method and the two-state Markov method, respectively. Although there is a little difference in the case of much more smaller N, the statistical results obtained by two methods are consistent with each other for a wide range of N. In the case of large IP_3 concentration (e.g. IP_3 = 0.4 μM), it is shown that the membrane potential exhibits stochastic bursting when the IP_3R channel number is small (see Fig. 6). With the increasing of IP_3R channel number, the average period of stochastic bursting will be shorter. At certain IP_3R channel number, the bursting oscillation of membrane

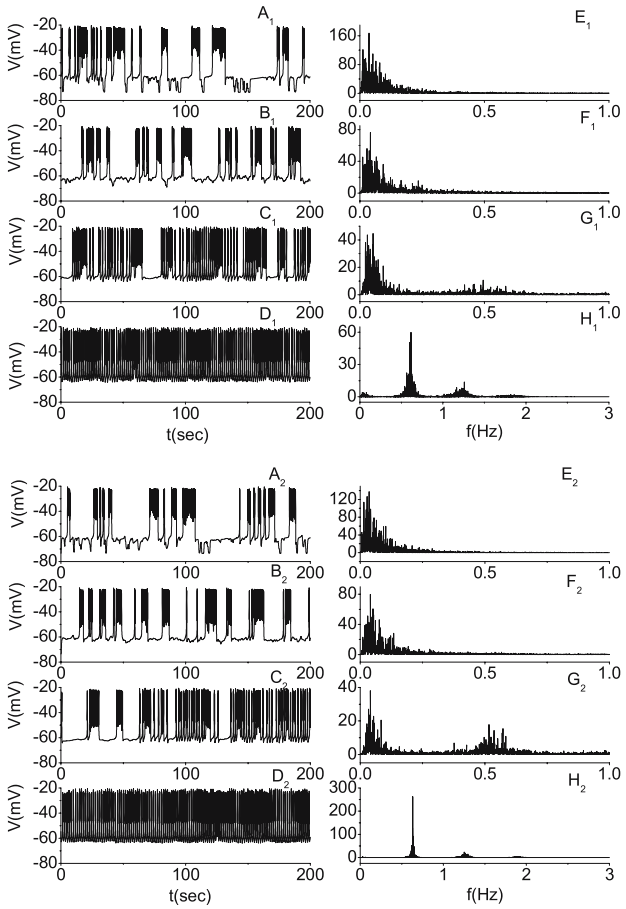

Fig. 6 Temporal evolution of membrane potential and its power spectrum at a fixed glucose stimulation level glu = 12 mM for different IP_3R channel number N. IP_3 = 0.4 μM. (A_1, A_2), N = 20; (B_1, B_2), N = 200; (C_1, C_2), N = 2,000; (D_1, D_2), N = 20,000. Fig. A_1–H_1 with Langevin method, and Fig. A_2–H_2 with Markov method

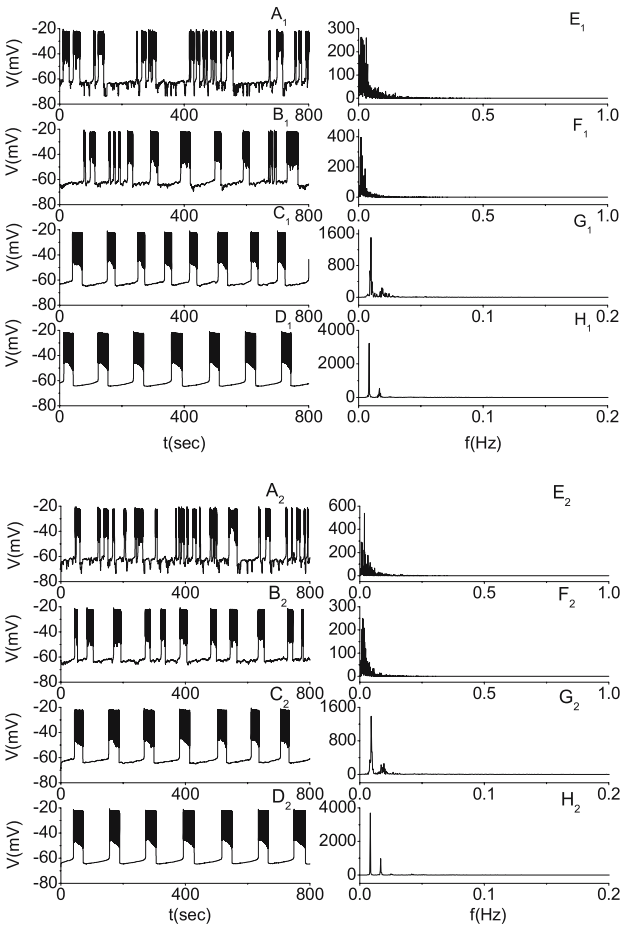

Fig. 7 Temporal evolution of membrane potential and its power spectrum at a fixed glucose stimulation level glu = 12 mM for different IP_3R channel number N. IP_3 = 0.15 μM. (A_1, A_2), N = 20; (B_1, B_2), N = 200; (C_1, C_2), N = 2,000; (D_1, D_2), N = 20,000. Fig. A_1–H_1 with Langevin method, and Fig. A_2–H_2 with Markov method

potential will change into spiking. However, in the case of small IP_3 concentration (e.g. IP_3 = 0.15 μM), it is shown that the membrane potential exhibits irregular bursting when the IP_3R channel number is small (see Fig. 7). With the increasing of IP_3R channel number, the average period of irregular bursting will be longer, and the stochastic bursting phase recovers to the deterministic one when the number of IP_3R channels $N \rightarrow \infty$. There is no transition from bursting phase to spiking phase in this case. Therefore, the phase transition between the bursting and the spiking is not only dependent on the IP_3R channels number, but also on the IP_3 concentration. At a given glucose stimulating level (e.g. glu = 12 mM), the dependent of transition on the IP_3R channels number and the IP_3 concentration is shown in Figs. 8 and 9, respectively. Figure 8 shows that, with the increasing of IP_3 concentration, the transition critical point of the frequency

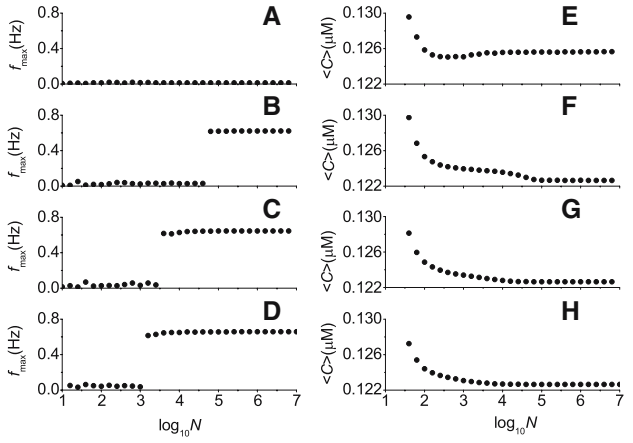

Fig. 8 The frequency of membrane potential oscillations and the average Ca^{2+} concentration as a function of the IP_3R channel number N for different IP_3 concentration. glu = 12 mM. A, E IP_3 = 0.2 μM; B, F IP_3 = 0.35 μM; C, G IP_3 = 0.5 μM;D, H IP_3 = 0.7 μM

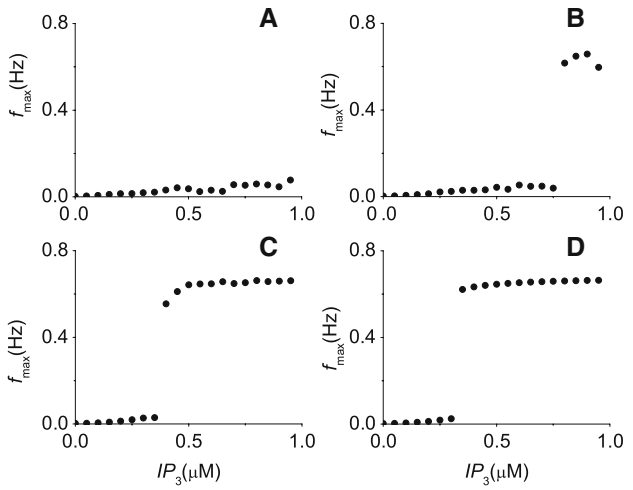

Fig. 9 The frequency of membrane potential oscillations as a function of the IP_3 concentration for different IP_3R channel number N. glu = 12 mM. A $N = 10^2$; B $N = 10^3$; C $N = 10^4$; D $N = 10^7$

corresponding to the peak of the membrane potential power spectrum is shifted from large IP_3R channel number to small IP_3R channel number. It can be found that the average intercellular Ca^{2+} concentration is kept in high level when the membrane potential is in the bursting phase, which is consistent with the experimental results of the secretion of insulin from pancreatic β-cells (Sato et al. 1999), i.e. high Ca^{2+} concentration induces the membrane potential bursting. Figure 9 shows that there also exits a transition from bursting to spiking. With the increasing of IP_3R channel number, the transition critical point of the frequency is shifted from high IP_3R concentration to low IP_3 concentration. When fixed IP_3 concentration and IP_3R channel number, the transition from spiking to bursting of β-cells can be induced by the increase of glucose concentration, which are shown in Fig. 10. The results indicate that (1) high glucose concentration can lead β-cells to bursting action potential. (2) Average cytosolic free Ca^{2+} concentration are increased with the increase of glucose concentration, and this is the same to the experimental data (Bergsten et al. 1994; Longo et al. 1991). Figure 11 shows the two oscillation phase (bursting and spiking) of β-cells in the parameter $\log_{10}N$–IP_3 plane. At a given value of glucose stimulating, each curve represents a critical line that the membrane potential is transformed between the bursting and the spiking. The region under the critical curve is the bursting phase and that above the critical

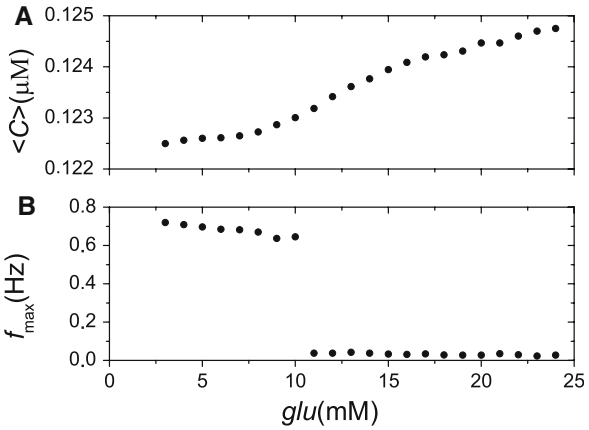

Fig. 10 **a** The average Ca^{2+} concentration and **b** the frequency of membrane potential oscillations as a function of glucose concentration. IP_3 = 0.5 μM and N = 1,000

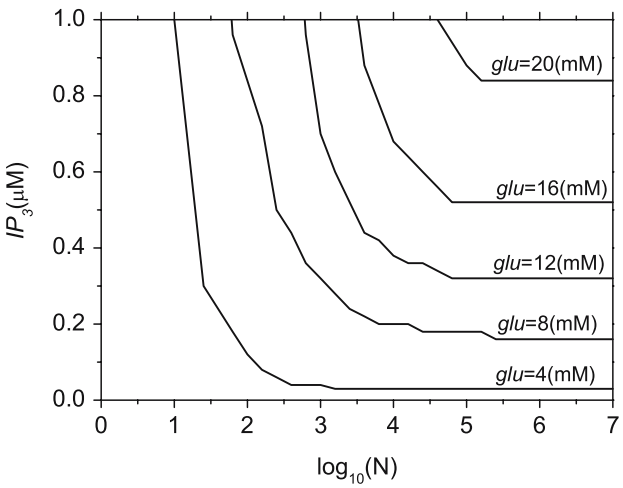

Fig. 11 Phase diagram in the parameters $\log_{10}N$-IP_3 plane

curve is the spiking phase. When the glucose concentration is fixed, there is no transition with the increasing of IP_3 concentration for the case of small channel number N, however, for the case of large channel number, the membrane potential oscillation will be transformed from bursting phase to spiking one with the increasing of IP_3. With the increasing of channel number, similar kinetics of the membrane potential can be found for the case of small and large IP_3 concentrations.

Conclusions

It has been experimentally reported that β-cells actually show continuous spikes or bursting action potentials, and it is shown that the bursts appear more helpful for insulin secretion than continuous spikes. Considering the ATP-driven pumps flux as function of glucose concentration and the calcium flux from the endoplasmic reticulum through the IP_3R channel, we have extended the calcium-based phantom bursting model (PBM) of β-cells (Bertram and Sherman 2004), and the effects of glucose and inositol 1,4,5-trisphosphate (IP_3) concentration on the membrane potentials activities have been discussed in this paper.

To distinguish bursting from spiking, two methods are used. One is the oscillation frequency f_{max}, which corresponds to the peak of power spectrum since bursting periods are larger than 2 s, and the other is the average cytosolic free Ca^{2+} concentration $<c>$, with the secretion of insulin is proportional to $<c>$. It is shown that (1) the stimulatory glucose concentration is higher than 10 mM with the physiological IP_3 concentration between 0.25 and 0.6 μM (Shuai and Jung 2002a; Wu et al. 2004; Shuai and Jung 2002b), when the bursting oscillations occur, and higher average cytosolic free Ca^{2+} concentration are induced by higher glucose concentration (Bergsten et al. 1994; Longo et al. 1991); (2) in different IP_3 concentrations, the critical glucose concentration, at which spiking transit into bursting, are different, and the low IP_3 concentration will decrease the critical glucose concentration; (3) low IP_3 concentration and high glucose concentration induce longer periods of bursts, while high IP_3 concentration and low glucose concentration lead to more robust spiking activities.

Considering the intrinsic noise of β-cells which is originated from the random opening and closing of IP_3R channels, it is found that (1) there exists a phase transition between the bursting and the spiking, and the phase transition is not only dependent on the IP_3R channel number, but also on both the IP_3 and the glucose concentration. When the channel number of IP_3R is small, the spiking oscillations will be changed into irregular bursting, while the bursting will not be changed by introducing channel noise, which is similar to the experimental results that the isolated β-cells actually show fast and irregular bursts (Falke et al. 1989; Kinard et al. 1999; Smith et al. 1990). When the channel number of IP_3R is large, however, the oscillations of potential are regular with longer period, which is same as the experimental observations in Dean and Matthews (1968), Sánchez-Andrés et al. (1995), Valdeolmillos et al. (1996), Andreu et al. (1997). (2) The average cytosolic free Ca^{2+} concentration is kept in high level when the membrane potential is in the bursting phase, which is consistent with the experimental results of the secretion of insulin from pancreatic β-cells (Sato et al. 1999), i.e. high Ca^{2+} concentration induces the membrane potential bursting, and the average Ca^{2+} concentration are increased with the increase of glucose concentration (Bergsten et al. 1994; Longo et al. 1991). (3) The phase diagram (bursting and spiking) has been presented in the parameter $\log_{10}N$–IP_3 plane.

Two methods have been used to simulate the random kinetics of IP_3R channels, one is the Langevin approach which is simple and efficient especially for a large number of channels, and the other is the Markov method which is more accurate and according to psychological realism. The simulation results are in accordance with some experimental results (Dean and Matthews 1968; Sánchez-Andrés et al. 1995; Valdeolmillos et al. 1996; Bergsten et al. 1994; Andreu et al. 1997; Shuai and Jung 2002a, 2002b; Longo et al. 1991; Wu et al. 2004; Sato et al. 1999). At the same time the results also give new phenomena which need experimental confirmation and are useful for physiological study: (1) High IP_3 concentration arises spiking membrane potentials in β-cells even the glucose concentration is above the stimulatory level (Fig. 5), and this might be one of the reasons that β-cells can not secrete insulin normally. (2) A few number of IP_3R channels will lead spiking activities into bursting pattern in high IP_3 concentration and low glucose concentration. It has been pointed that realistic IP_3R channel number in a cluster might be $N \approx 20$ (Shuai and Jung 2002b). Figures 8 and 9 show that when the IP_3R channel number is of only one or a few clusters, the system always bursts. Therefore, to stimulate the spiking β-cells into bursting, blocking most of the IP_3R channel clusters maybe feasible.

In conclusion, we extend the calcium-based PBM model by SERCA pump flux and the flux through IP_3R channel. Both deterministic and stochastic results from

the model are same to the experimental phenomena and give some feasible way to induce spiking β-cells into bursting pattern, which are important in glucose homeostasis (Matthews et al. 1983). There is much that the model still cannot do. Such as the oscillatory apex of free Ca^{2+} concentration increases with the increase of stimulatory glucose concentration (Chou and Ipp 1990; Longo et al. 1991). Maybe, this is because we didn't consider mitochondria, which is another Ca^{2+} store in β-cells and play an important role in Ca^{2+} oscillations (Wiederkehr and Wollheim 2006; Maechler and Wollheim 2000), in present model, and this requires future effort.

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