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ORIGINAL PAPER

RyR channels and glucose-regulated pancreatic β-cells

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Abstract Ryanodine receptor channel model is introduced to a dynamical model of pancreatic β-cells to discuss the effects of RyR channels and glucose concentration on membrane potential. The results show Ca^{2+} concentration changes responding to enhance of glucose concentration is more quickly than that of activating RyR channels, and both methods can induce bursting action potential and increase free cytosolic Ca^{2+} concentration. An interesting finding is that moderate stimulation to RyR channels will result in a kind of "complex bursting", which is more effective in enhancing average Ca^{2+} concentration and insulin section.

Keywords β-cell · Glucose · RyR · PBM

Introduction

Located in pancreatic islets of Langerhans, β-cells are a kind of electrical-excitable endocrine cells and are responsible for the secretion of insulin following an elevation in the blood glucose level. The absolute or relative deficiency of insulin secretion can lead to type II diabetes (Lang et al. 1981).

It has been reported that bursting action potential of β-cells evokes the secretion of insulin (Falke et al. 1989; Dean and Matthews 1968; Sánchez-Andrés et al. 1995; Smith et al. 1990; Atwater et al. 1989). In experiments bursting oscillations have been shown to be in-phase with oscillations of the free cytosolic Ca^{2+} concentration (Bergsten 1995; Bergsten et al. 1994). Measurements of β-cell electrical activity exhibit three interesting features. The first is β-cell displaying a bursting pattern of electrical impulses mostly in the presence of stimulatory glucose concentration (Dean and Mathews 1970; Berridge and Irvine 1989). The second 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). The last is "complex bursting" phenomenon, which was thought to be induced by high glucose concentration (Henquin et al. 1982; Wierschem and Bertram 2004; Bertram et al. 2004).

Many mathematical models of β-cell were constructed to explain the mechanism of action potentials (Bertram and Sherman 2004; Atwater et al. 1980; Chay an Keizer 1983; Santos et al. 1991; Keizer and Smolen 1991; Keizer and Magnus 1989; Bertram et al. 2000; Zhan et al. 2007). The role of ionic channels were concerned, such as the voltage-gated Ca^{2+} channel, Ca^{2+}-dependent K^+ channel and nucleotide-sensitive K^+ channel in the membrane of β-cell, and the ATP-driven (SERCA) pump Ca^{2+} channel and inositol 1,4,5-trisphosphate (IP_3R) channel in the endoplasmic reticulum (ER). While, there isn't a model, which has concerned the ryanodine receptors (RyR) channels. A substantial body of evidence confirms that RyR channels are located on membrane of ER in β-cells, and are activated by cytosolic Ca^{2+} (Islam et al. 1992; Islam 2002). In principle, this kind of Ca^{2+}-induced Ca^{2+} release (CICR) mechanism are the same as that of voltage-gated Ca^{2+} channels and IP_3R channels. Experiments show that RyR

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channels are emerging as distinct player in: RyR channels are involved in the control of insulin secretion (Johnson et al. 2004).

In this paper, we modify the β-cell model (Bertram and Sherman 2004; Zhan et al. 2007) with a RyR channel model (Keizer and Levine 1996), and discuss the effects of RyR channels on membrane potential and Ca^{2+} concentration of β-cells. The RyR channel model was originally constructed for that in cardiac cell, and experimental results indicate that RyR channel in β-cells are mainly type II, which are the same as that in cardiac cells (Islam et al. 1998; Takasawa et al. 1998; Holz et al. 1999). Although we simply represents an additional influence on the total Ca^{2+} flux across the endoplasmic reticulum (ER) membrane, some new results are found. The results show that bursting action potential will be induced by activating RyR channels even though glucose concentration being a little lower than the stimulatory level. A very interesting result is that RyR channels cause a kind of "complex bursting", and this form of potential activity seems more effective in insulin secretion. We also discuss the effects of glucose concentration on membrane potential and analyze the bifurcation diagrams to explain how glucose concentration affects the membrane potential in dynamics.

The paper is organized as follows. A modified mathematical model for β-cells is presented in the second section. Numerical results have been described in the third section. We end with some conclusions and discussions.

The model

The β-cell model is based on our last paper, which is a modified calcium-based phantom bursting model (PBM) (Bertram and Sherman 2004; Zhan et al. 2007). The model 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

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

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

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

$$J_{mem} = -(\alpha I_{Ca} + k_{PMCA}c), \quad (8)$$

$$I_{K(ATP)} = \bar{g}_{K(ATP)}a(V - V_K), \quad (9)$$

$$J_{er} = J_{leak} + J_{IP_3} - J_{SERCA}, \quad (10)$$

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 other values could be used (Bertram and Sherman 2004). The parameter α in Eq. 8 converts units of current to units of flux, and k_{PMCA} is the flux through the plasma membrane Ca^{2+} ATPase pumps. The nucleotide ratio $a = ADP/ATP$ in Eq. 9 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 $a_\infty(c) = [1 + e^{(r-c)/s_a}]^{-1}$. Considering that r is regulated by glucose concentration (Bertram and Sherman 2004), a explicit expression for r as function of glucose concentration (glu) is given by

$$r = r_1(\text{glu} - \text{glu}_k). \quad (11)$$

glu_k is considered as the basal glucose level. It was assumed that the Ca^{2+} influx into the ER via SERCA pumps in Eq. 10 depends on the cytosolic Ca^{2+} concentration and glucose concentration (Zhan et al. 2007):

$$J_{SERCA} = \frac{k_1 c^2}{k_2^2 + c^2}(\text{glu} - \text{glu}_k). \quad (12)$$

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. The first theoretical model for IP_3R channel was proposed by De Young and Keizer (1992). The model assumes that three equivalent and

independent subunits are involved in conduction in an IP_3R channel. Each subunit has one IP_3 binding site and two Ca^{2+} binding sites, one for activation, the other for inhibition. Only the state with one IP_3 and one activating Ca^{2+} bound contributes to the subunit's open probability. All three subunits must be in this state for channel to be open. A simplified version of the model was proposed by Li and Rinzel (1994). It is shown that the De Young–Keizer model is symmetric in some of the binding process and that the IP_3 binding is at lease 200 times faster than the Ca^{2+} activation binding, and the Ca^{2+} activation binding is at least ten times faster than the Ca^{2+} inactivation binding and the change rate of Ca^{2+} concentration during oscillations (Li and Rinzel 1994;Shuai and Jung 2002). Considering these factors the De Young-Keizer model can be reduced as follows, which is called as Li-Rinzel model(Shuai and Jung 2002):

$$J_{IP_3} = c_1 v_1 m_{er}^3 n_{er}^3 h_{er}^3 (c_{er} - c), \tag{13}$$

where h_{er}, m_{er} and n_{er} represent the three equivalent and independent subunits, Ca^{2+} inactivation binding, IP_3 binding and Ca^{2+} activation binding, involved in an IP_3R channel. $m_{er} = IP_3/(IP_3 + d_1)$, $n_{er} = c/(c + d_4)$, and

$$\frac{dh_{er}}{dt} = \alpha_h(1 - h_{er}) - \beta_h h_{er}, \tag{14}$$

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 can be found in Li and Rinzel (1994).

Experimental results have indicated that RyR channels are present in β-cells (Islam et al. 1992). A critical property of RyR channels is that cytosolic Ca^{2+} can activate these channels, which is called CICR mechanism. In principle, such CICR can provide amplification of Ca^{2+} signal, and this is the same to the voltage-gated Ca^{2+} channels and the IP_3R channels (Islam 2002). There is no mathematical β-cell model considering the effects of RyR channels on the membrane potential and cytosolic Ca^{2+} concentration, though many experiments have reported physiological function of RyR channels in β-cells (Islam et al. 1992; Islam 2002; Johnson et al. 2004; Islam et al. 1998; Takasawa et al. 1998; Holz et al. 1999; Zeng et al. 2000; Hernandez-Cruz et al. 1997). We introduce the RyR channel model constructed by Keizer and Levine (1996) into the above β-cell model. Thus, the net Ca^{2+} efflux from the ER is

$$J_{er} = J_{leak} + J_{IP_3} - J_{SERCA} + J_{RyR}, \tag{15}$$

and

$$J_{RyR} = v_2 P_{RyR}(c_{er} - c), \tag{16}$$

with v_2 being the rate constant for RyR. P_{RyR} is the open probability of RyR channels, which can be approximated by

$$P_{RyR} = \frac{w_R(1 + k_b c^3)}{1 + k_a/c^4 + k_b c^3}, \tag{17}$$

where w_R is governed by the differential equation: $dw_R/dt = -(w_R - w_{R\infty})/\tau_r$. $w_{R\infty}$ and τ_r are defined by $w_{R\infty} = (1.\ 0 + k_a/c^4 + k_b c^3)/(k_c + k_a/c^4 + k_b c^3)$ and $\tau_r = k_e w_{R\infty}$ respectively. More detail meanings of the parameters in RyR channel model can be found in Keizer and Levine (1996). Though this model originally constructed for RyR channels in cardiac cells (Keizer and Levine 1996), we are able to use it here with both the RyR channel in β-cell and those in cardiac cells belonging to type II calcium release RyR channels (Islam et al. 1998; Takasawa et al. 1998; Holz et al. 1999).

In order to discuss the effects of RyR channels and glucose concentration on membrane potentials, numerical simulations are needed. Equations above are simulated by using a simple forward Euler algorithm with a time step of 0.1 ms. In each calculation the time evolution of the system lasted 1000 s after transient behavior was discarded. All the figures for temporal evolution and phase analysis were got with C program. The periods of bursting were calculated with a program of fast Fourier transform(FFT) written by Press et al. (Press et al. 1992). The parameter values are given in Table 1.

Numerical results

Variation of membrane potential by RyR channels

Experimental data showed that β-cells display a bursting pattern of action potential usually in the present of stimulatory glucose concentration (Berridge and Irvine 1989; Wierschem and Bertram 2004), while Johnson et al. (2004) and Zeng et al. (2000) found that stimulating RyR channels will induce a increase of cytosolic Ca^{2+} concentration and the insulin release. We simulate this stimulation by simply change the rate constant for RyR, v_2. With the papermeter value listed above, the stimulatory glucose concentration is 6.5 mM (Zhan et al. 2007). Figure 1 exhibits that in low glucose concentration β-cells have no action potential. Ca^{2+} concentration is increasing in response to the activation of RyR channels, and at the same time bursting activity is induced, which means insulin release is enhanced (Bergsten 1995; Bergsten et al. 1994). This is according to the experimental results (Islam 2002; Johnson et al. 2004; Zeng et al. 2000; Hernandez-Cruz et al. 1997). In Fig. 1b, the increase of Ca^{2+} concentration is two-step process: a rapid increase just after the stimulation and the stable periodic oscillation beginning after about 30s. This two-step process was reporter by Hernandez-Cruz et al. (1997), and Zeng et al. (2000) found the Ca^{2+} increase

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
$\overline{g}_{K(ATP)}$	500 ps	V_K	−75 mV
C_m	5,300 fF	α	4.5×10^{-6} $fA^{-1}\mu$ Mm s^{-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_1	2.0×10^{-5}	τ_a	3×10^5 ms
s_a	0.1 μM	f_{er}	0.01
p_{leak}	0.0005 ms^{-1}	V_{cyt}/V_{er}	5
k_1	5.0×10^{-5} ms^{-1}	glu_k	2.0×10^3 μM = 2.0 mM
k_2	0.16 μM	c_1	18.5
v_1	6.0×10^{-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} $\mu M^{-1}s^{-1}$
k_a	0.0192 μM^4	k_b	3.887 μM^{-3}
k_c	18.5	k_e	1.0×10^4 ms
IP_3	0.15 μM		

induced by stimulation of RyR channels has a latency of 25–60 s.

When glucose concentration is above stimulatory value (in Fig. 2), bursting action potential is induced. Stimulating the RyR channel decreases bursting period and increases the amplitude of Ca^{2+} oscillation.

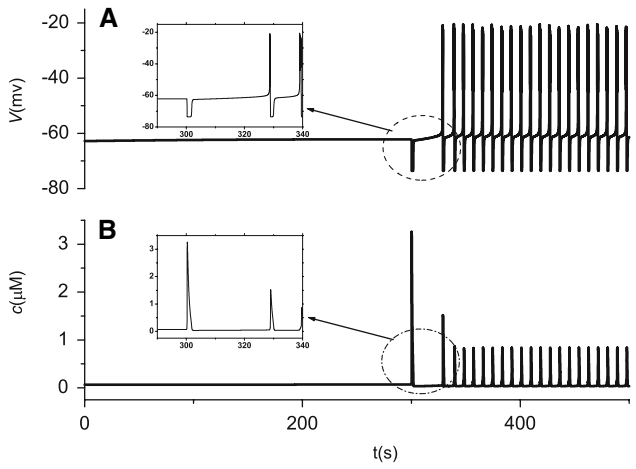

Fig. 1 Temporal evolution of membrane potential and cytosolic Ca^{2+} concentration at a fixed glucose stimulation level glu = 6 mM (below the stimulatory value). For $t < 300$ s, $v_2 = 0.0$ ms^{-1}, and $t \geq 300$ s, $v_2 = 0.5$ ms^{-1}, to simulate the enhance of stimulation to RyR channels

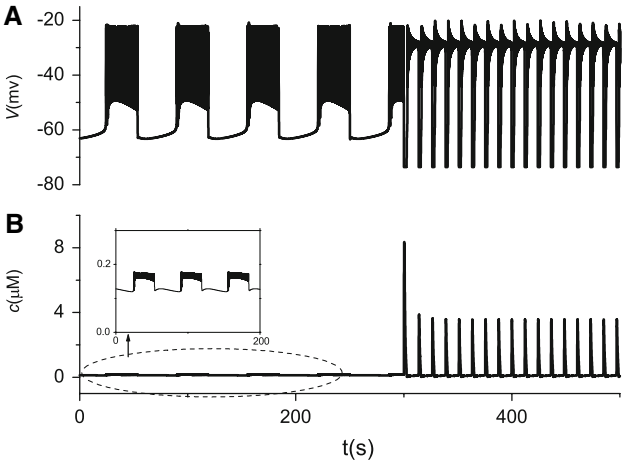

Fig. 2 Temporal evolution of membrane potential and cytosolic Ca^{2+} concentration at a fixed glucose stimulation level $glu = 10$ mM (above the stimulatory value), with $t < 300$ s, $v_2 = 0.0$ ms^{-1}, and $t \geq 300$ s, $v_2 = 0.1$ ms^{-1}

Variation of membrane potential by glucose

In in vitro recordings, β-cells display a bursting pattern of electrical impulses in the presence of stimulatory glucose concentration (Berridge and Irvine 1989; Wierschem and Bertram 2004), and this is repeated with our model. Figure 3 exhibits the effects of glucose concentration on membrane potential and Ca^{2+} concentration. Membrane potential is activated by glucose. The RyR channel stimulated level is higher, bursting period is shorter. After about 10s, steady cytosolic Ca^{2+} concentration turns into stable oscillation in phase with action membrane potential in response to the enhance of glucose concentration, and experimental results show the latency is 0–50 s. Figure 3b indicates that changing of Ca^{2+} concentration has a triphasic process: first, a small decrease (phase 1); then, a big and rapid elevation (phase 2); finally, sustained oscillations (phase 3), and this phenomenon has been found in experiments (Zeng et al. 2000; Grodsky 1989; Meissner and Atwater 1976; Roe et al. 1993) and been repeated in mathematical model constructed by Bertram and Sherman (2004). In Fig. 3d, RyR channels is stimulated to a moderate active level ($v_2 = 0.1$ ms^{-1}), and varying of Ca^{2+} concentration represents a two-step process: first, a small increase; second, stable oscillations. Bursting action potentials can be induced by very high activated level of RyR channel even in low glucose concentration (Johnson et al. 2004), under this condition enhancing glucose concentration induces the decrease of bursting periods with active phases prolonged and hyperpolarization phases shortened (see in Fig. 4a). Amplify of Ca^{2+} concentration is increased after more glucose is added (in Fig. 4b). Figure 4 indicates the application of more glucose can enhance average Ca^{2+} concentration and insulin release,

which has been reported in considerable experiments (Lang et al. 1981; Bergsten et al. 1994; Berridge and Irvine 1989; Islam 2002; Johnson et al. 2004; Zeng et al. 2000; Longo et al. 1991; Liu et al. 1998).

To understand why glucose concentration affects the membrane potential, fast/slow analysis is a convenient dynamic method (Rinzel and Lee 1986; Rinzel 1985). Figure 5 is the bifurcation diagram of β-cell model with c as the bifurcation parameter at glu = 6.0 mM and 7.0 mM (below and above the stimulatory value, respectively). The Z-shape curve is the fixed points, the stable oscillation around the upper steady state is denoted by the maximum and minimum of V over one cycle. For a range of values of c membrane potential V is bistable, with a stable fixed point and upper stable period orbit, and this is crucial to bursting activities. The curve defined by $dc/dt = 0$ is the c nullcline. When V is above the c nullcline, $dc/dt > 0$,and so c increases. When V is below the c nullcline, c decreases (more details about bifurcation diagrams and fast/slow analysis for bursting electrical activity were described in Keener and Sneyd (1998) and Bertram and Sherman (2004)). Figure 5 shows that bifurcation curve and z-curve move rightward with the increase of glu, while the c nullclines almost are the same (with $v_2 = 0$ ms^{-1}). When glu = 6 mM, the nullcline intersects the z-curve on lower stable stationary branch. V and c have fixed value, and the system is at rest. When glu = 7 mM, the intersection point is above the saddle-node (SN) and in the middle branch of z-curve, resulting in bursting action potentials.

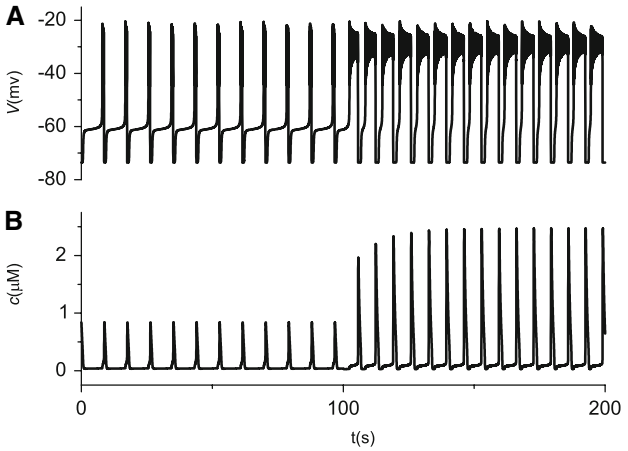

Fig. 4 Temporal evolution of membrane potential and cytosolic Ca^{2+} concentration at a fixed stimulated RyR channels level $v_2 = 0.5$ ms^{-1}. glu = 6 mM in the first 100 s, then glu = 10 mM

Effects of RyR channels and glucose concentration on bursting periods and average cytosolic Ca^{2+} concentration

Figures 2 and 4 indicate that bursting periods are regulated by glucose concentration and the activation level of RyR channels. The detail numerical results are shown in Figs. 6 and 7. Figure 6 shows the periods and average cytosolic Ca^{2+} concentration, $\langle c \rangle$, are varied with the increase of glucose concentration. The results indicate that with glucose concentration increasing the periods of bursting on the whole decreases, and $\langle c \rangle$ increases. Experimental results

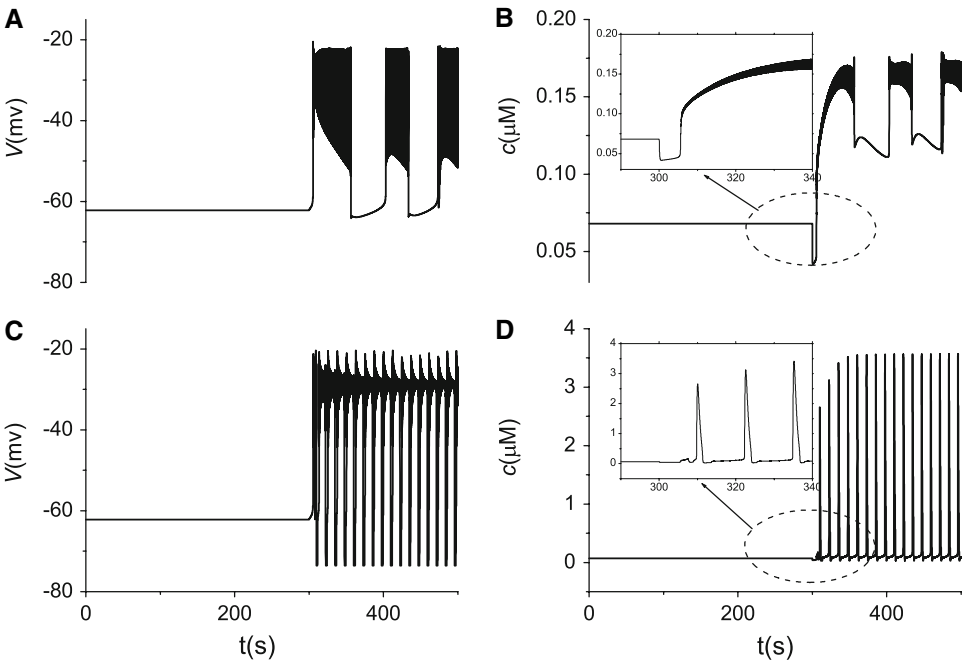

Fig. 3 Temporal evolution of membrane potential and cytosolic Ca^{2+} concentration at a fixed stimulated RyR channels level $v_2 = 0.001$ ms^{-1} for (**a**) and (**b**), and $v_2 = 0.1$ ms^{-1} for (**c**) and (**d**). In all these pictures glu = 6 mM in the first 300 s, then glu = 10 mM

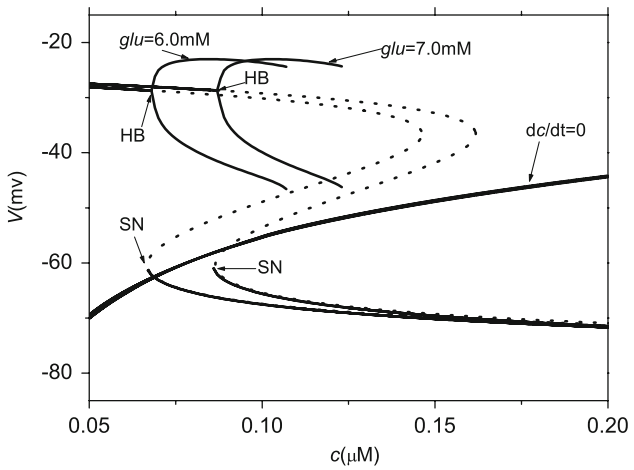

Fig. 5 Bifurcation diagram for β-cell model, with glu = 6.0 and 7.0 mM. HB denotes Hopf bifurcation, and SN denotes the saddle-node bifurcation. Two c nullclines are plotted here with glu = 6.0 and 7.0 mM, respectively, and $v_2 = 0$ ms^{-1}

have confirmed that increasing glucose concentration can enhance the Ca^{2+} concentration, which is in accordance with Fig. 6, and insulin from pancreatic β-cells is proportional to the average intracellular Ca^{2+} concentration (Bergsten et al. 1994; de Vries and Sherman 2000; Sato et al. 1999; Longo et al. 1991). Figure 6 also indicates when glucose concentration is much below the stimulatory value, bursting cannot induced by stimulating RyR channels. Compare Fig. 6a with Fig. 6c, it can be found that intensity stimulating RyR channels will induce the cell into bursting activities and the increasing of $\langle c \rangle$, when glucose concentration is a little lower than stimulatory level, which is in accordance with experimental results (Islam 2002; Johnson et al. 2004; Hernandez-Cruz et al. 1997) (in Fig. 6a bursting begins at glu = 5.7 mM and in Fig. 6c and e bursting begins at glu = 5.4 mM). Fig. 7 shows the effects of RyR channels on bursting periods and $\langle c \rangle$. It is found that very little stimulating to RyR channels will slightly change the periods of bursting, and moderate stimulation to RyR channels will highly enhance $\langle c \rangle$. Different glucose concentration has different optimal v_2 responding to maximal $\langle c \rangle$, and the higher of glucose concentration, the smaller the optimal v_2 is. It is interesting to see the change of bursting periods regulated by v_2, and Fig. 8 exhibits the heterogeneity of bursting periods and forms. Bursting periods range from about 5s to 200s, and this is in accordance with experimental results (Kinard et al. 1999; Valdeolmillos et al. 1996; Zhang et al. 2003; Cook et al. 1981; Bertram et al. 1995; Ashcroft et al. 1984). It is interesting in Fig. 8b and c that a kind of "complex bursting" is shown. The "complex bursting", first reported by Henquin et al. (1982), was stimulated β-cells with 15 mM glucose, and the periods is about 2 min. Figures 7 and 8 indicate that "complex bursting" could be induced by activating RyR channels and does not need very high glucose concentration. The periods of "complex bursting" range from about 10 s to more than 2 min. Figs. 7 and 8 also show that with the same glucose concentration stimulated "complex bursting" appears more effective to get higher $\langle c \rangle$. Considering that $\langle c \rangle$ is proportional to insulin secretion (Bergsten et al. 1994; de Vries and Sherman 2000; Sato et al. 1999; Longo et al. 1991), numerical results here indicate that moderately

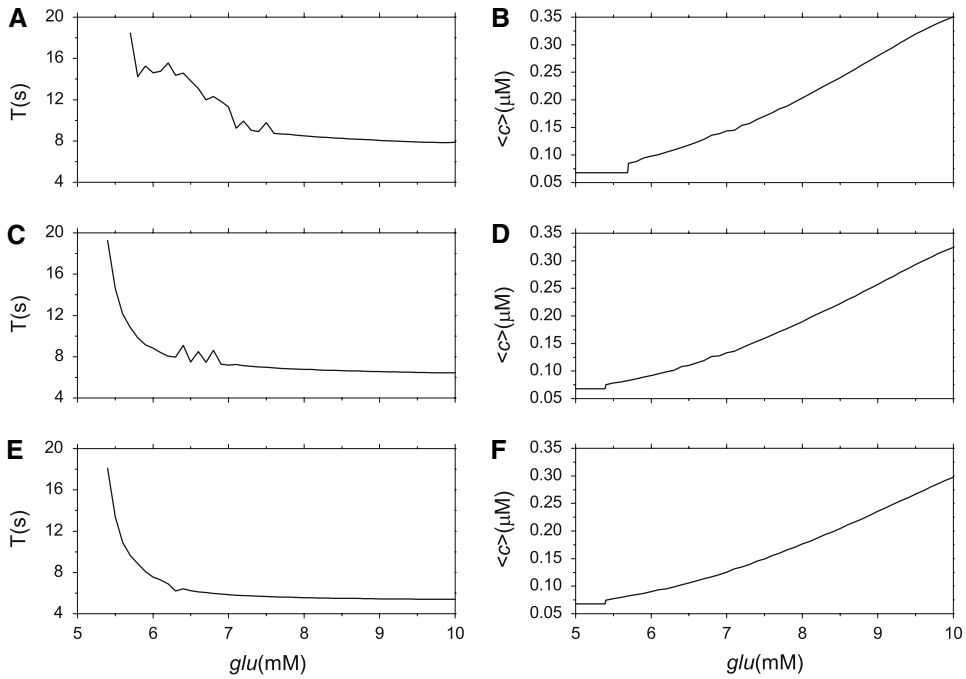

Fig. 6 Bursting periods (**a**, **c**, **e**) and average cytosolic Ca^{2+} concentration (**b**, **d**, **f**) are changed with glucose concentration increased. **a** and **b** are $v_2 = 0.3$ ms^{-1}; **c** and **d** are $v_2 = 0.5$ ms^{-1}; **e** and **f** is $v_2 = 0.8$ ms^{-1}

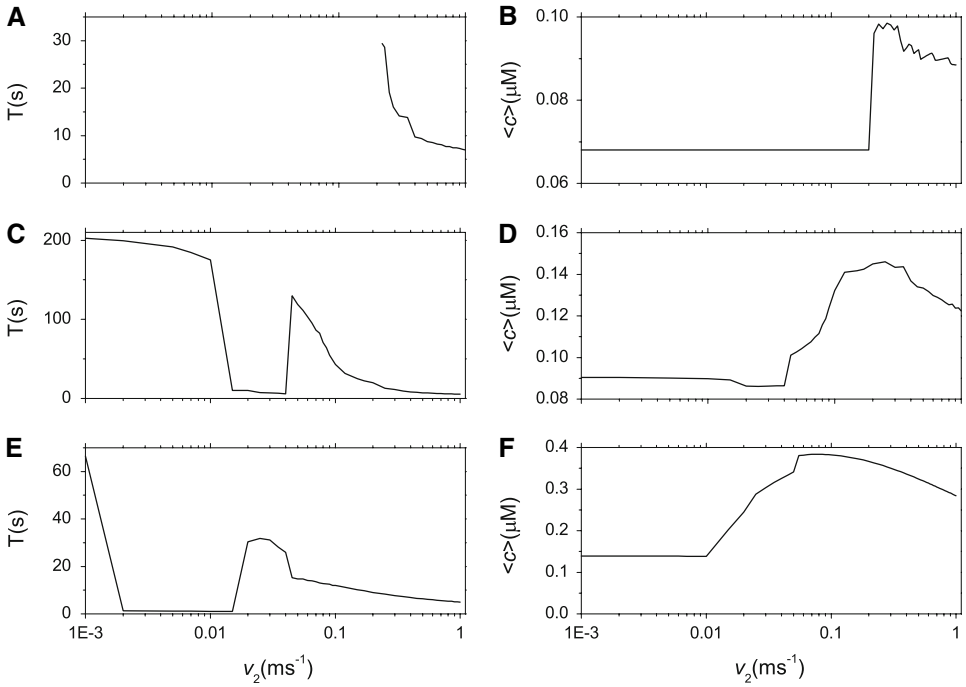

Fig. 7 Bursting periods (**a**, **c**, **e**) and average cytosolic Ca^{2+} concentration (**b**, **d**, **f**) are changed with v_2 increased. **a** and **b** are glu = 6 mM; **c** and **d** are glu = 7 mM; **e** and **f** are glu = 10 mM

stimulating RyR channels is a good way to increase insulin release.

Conclusions

Experimental measurements on β-cell electrical activities exhibit three interesting features: (1) β-cell displaying a bursting pattern of electrical impulses mostly in the presence of stimulatory glucose concentration (Dean and Mathews 1970; Berridge and Irvine 1989); (2) the 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); (3) "complex bursting" (Wierschem and Bertram 2004), which was thought to be induced by high glucose concentration (Wierschem and Bertram 2004; Bertram et al. 2004; Henquin et al. 1982). Many mathematical models for β-cells were constructed to explain these phenomena (Bertram and Sherman 2004; Atwater et al. 1980; Chay an Keizer 1983; Santos et al. 1991; Keizer and Smolen 1991; Keizer and Magnus 1989; Bertram et al. 2000; Zhan et al. 2007), and none of them considered the effects of RyR channels, which locate on ER and have similar CICR mechanism with IP_3R channels (Islam et al. 1992; Islam 2002). At the same time, experimental results showed that stimulated RyR channels can induced bursting activity of membrane potential and increase insulin section even though glucose concentration is lower than stimulatory level (Johnson et al. 2004; Zeng et al. 2000).

To discuss the effects of RyR channels and glucose concentration on membrane potential of pancreatic β-cells, we introduce the RyR channel model constructed by Keizer and Levine (1996) to the mathematical β-cell model (Bertram and Sherman 2004; Zhan et al. 2007). The numerical results repeat some experimental findings: (1) when glucose concentration is lower than stimulatory level, stimulating RyR channels will induce bursting action potential; and Ca^{2+} concentration exhibits a two-step process enhancement responding to this stimulation and the stable oscillation occurs after 30s; (2) membrane potential can be led from rest phase to bursting activity by increasing glucose concentration, and Ca^{2+} concentration show a triphasic process change after enhance glucose concentration and the stable increase of Ca^{2+} concentration begins after 10s; (3) enhancing glucose concentration always increasing the average Ca^{2+} concentration, which is proportional to insulin section.

Bifurcation diagram analysis explain the effects of glucose concentration on membrane potential: the bifurcation diagram moves rightward with the glucose concentration increased, but the c nullcline does not change. When glucose concentration is lower than stimulatory level, the intersection of c nullcline and bifurcation curves is on the stable branch with system being at rest phase. When glucose concentration is increased above the stimulatory value, the intersection point is on the unstable branch and the membrane potential oscillates.

Numerical results also give new phenomena which need experimental confirmation and are useful for physiological study: (1) experimental results show that bursting pattern

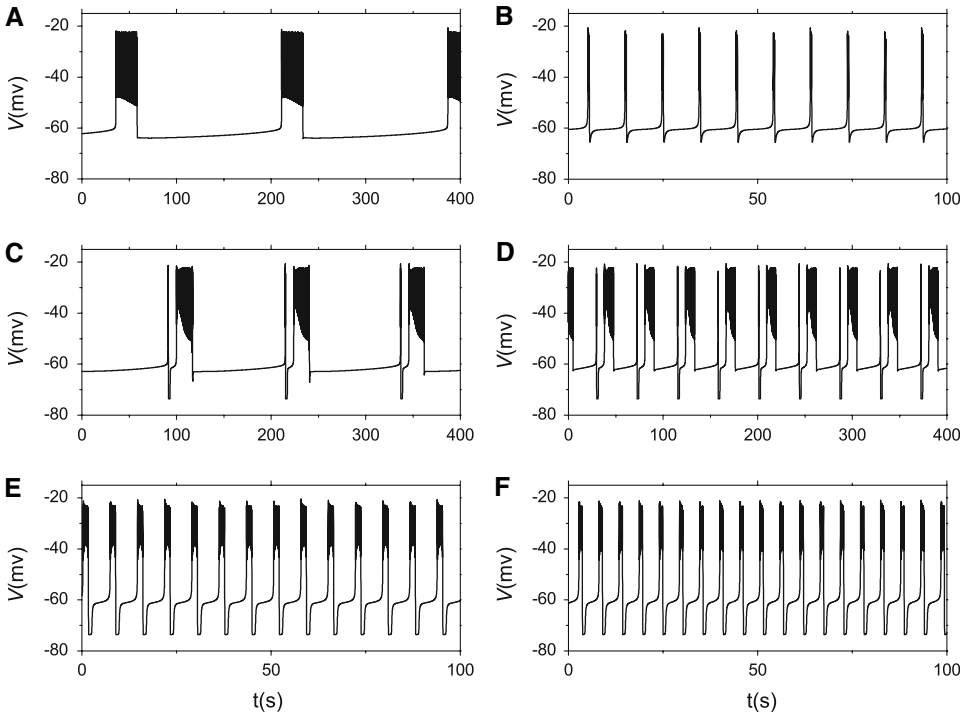

Fig. 8 Temporal evolution of membrane potential at a fixed glucose stimulation level glu = 7 mM.
a $v_2 = 0.01\ \mathrm{ms}^{-1}$;
b $v_2 = 0.02\ \mathrm{ms}^{-1}$;
c $v_2 = 0.05\ \mathrm{ms}^{-1}$;
d $v_2 = 0.1\ \mathrm{ms}^{-1}$;
e $v_2 = 0.5\ \mathrm{ms}^{-1}$;
f $v_2 = 1.0\ \mathrm{ms}^{-1}$

of action potential is effective in maintaining glucose homeostasis (Halban 1982; Pipeleers 1982; Henquin and Meissner 1984), and this is shown in Fig. 6, while periods of bursting have no direct connection with insulin section; (2) modulate activated RyR channels will induce "complex bursting" with the periods range from about 10s to more than 2 min, and this kind of bursting has been found in high glucose concentration stimulated β-cells with the period being of 2 min; (3) stimulating RyR channels can get higher average Ca^{2+} concentration in the same glucose concentration; (4) "complex bursting" is more effective to enhance mean intracellular Ca^{2+} concentration, which is proportional to insulin section. The above conclusions indicate that to stimulation insulin release from β-cells, two methods are effective: one is enhance glucose concentration and the other is stimulate RyR channels. It is known that diabetes patients cannot endure the stimulation of high glucose concentration, so activating RyR channels to enhance insulin section is more feasible to help them.

It has been pointed out that IP_3R channels and RyR channels are two families of intracellular Ca^{2+} channels, share some structural and functional similarities (Islam 2002). The effects of IP_3R channels on membrane potential has been discussed in our former paper (Zhan et al. 2007), it was found that the period of bursting is affected by the IP_3 concentration there. When both RyR channel and IP_3R channel are considered, although the IP_3R channels and the RyR channels are similar, our simulation results (the data is not shown) indicate that IP_3 can only affect periods of bursting and not induce "complex busting". While Fig. 8 shows that not only the bursting periods are regulated by RyR channels but also the change from "bursting" to "complex bursting" can be induced by RyR channels.

IP_3R channels and RyR channels are located on ER which is an important Ca^{2+} store in β-cell, and there is another important Ca^{2+} store, mitochondria, which play an important role in Ca^{2+} oscillations (Wiederkehr and Wollheim 2006; Maechler and Wollheim 2000). We do not discuss mitochondria here, but we believe more interesting phenomena will be found after we consider it into β-cell model.

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