Classification of Bursting Electrical Activity in Pancreatic Beta-cell

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Abstract—The mechanism of bursting electrical activity in clustered pancreatic β-cells is still unclear. In this study, we classify the bursting types using mathematical model of β-cell. We investigate the effects of ionic currents to the bursting patterns in the β-cell network, and classify β-cells' bursting activity using mathematical model. According to our classification, bursting behavior of β-cell has two types: (1) bursting activity driven by Ca^{2+} dependent potassium current; (2) bursting activity driven by ATP dependent potassium current. Therefore, differences of bursting patterns in β-cells can be explained by the differences of the ionic currents contributing to the bursting activity.

1. Introduction

Pancreatic β-cells exist in the islet of Langerhans. These cells maintain blood glucose homeostasis by secreting insulin, the hormone for glucose homeostasis. They exhibit bursting electrical activity, which is correlated with the insulin secretion. It is known that insulin secretion is controlled by oscillations of membrane potential, called bursting oscillations.

It has been reported that isolated single β-cells show continuous spikes or fast and irregular bursts [1, 2]. On the other hand, β-cells in a cluster or in an intact islet exhibit regular bursting [3]. It is known that the cells in an islet are coupled by gap junctions [1]. Moreover, it is known that there is a large variability in terms of β-cell size, gap junctional conductances, and ionic channel densities [1, 4]. In spite of such heterogeneous cells, because of coupling, cells within an islet exhibit a unified collective behavior.

Bursting behavior of β-cells in a cluster and single spiking behavior in isolated cells are explained by gap junctional coupling, and there are several experimental evidences which indicate β-cell bursting activity depends on gap junctional coupling [1]. There is also direct evidence that coupling enhances insulin secretion [5]. Although gap junctional couplings obviously contribute to β-cell bursting, it is unclear how regular bursting in clustered cells occur. In this study, we show the effects of ionic currents to the regular bursting in the β-cell network, and classify β-cells bursting activity using mathematical model. According to our classification, bursting behavior of β-cell has two types: (1) bursting driven by Ca^{2+} dependent potassium current, and (2) bursting driven by ATP dependent potassium current. Difference of bursting patterns in β-cells can be explained by the type of the ionic currents inducing bursting activity.

2. Mechanism of Bursting Activity in β-cells

A schematic of β-cell is briefly shown in Fig. 1.

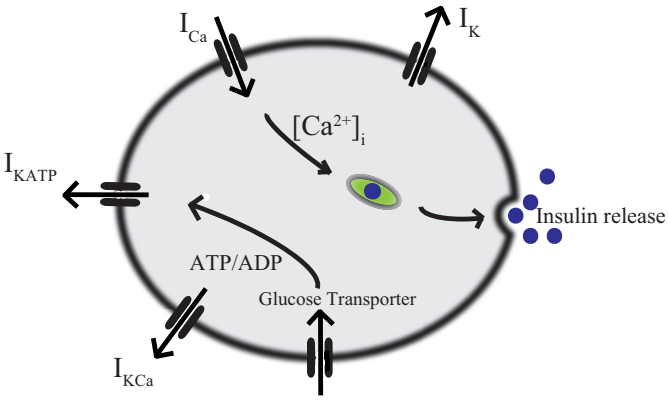


Figure 1: A schematic of β-cell. Glucose triggers depolarization and Ca^{2+} entry, which induces exocytosis of insulin granules.

The voltage-dependent Ca^{2+} channel conducts Ca^{2+} ions into the cell, which raises the transmembrane voltage V, whereas the K^+ channel gates efflux of K^+ and restores V to a low level. The temporal interaction of the two channels is sufficient to explain the repetitive spiking observed in β-cells. The Ca^{2+} influx also provides the primary chemical signal to trigger exocytosis of insulin-containing granules. Metabolism of glucose raises the ratio of ATP to ADP, which closes a third channel, the K(ATP) channel. Thus, in the absence of glucose, β-cells are electrically silent, but they generate Ca^{2+}-dependent action potentials when glucose is elevated.

In both mice [6] and humans [7], insulin secretion is controlled by oscillations of calcium, which are driven by bursts of action potentials. However, it is still unknown how bursting arises, and how it is modulated by glucose and other signals. Due to the difficulties of experimental

techniques, it is difficult to understand them without the aid of mathematical models.

3. Mathematical Description of β-cell

For numerical simulation of β-cells' electrical activity, the model of β-cells proposed by Keizer and Magnus [8], known as a modified model of Chay model [9] has been widely adopted. The dynamics of the membrane potential V of β-cell is given as follows:

$$C_m \frac{dV}{dt} = I_{C_a} + I_K + I_{KCa} + I_{KATP} + I_L + I_{ex}, \quad (1)$$

$$I_{C_a} = g_{C_a}(V_{C_a} - V), \quad (2)$$

$$I_K = g_K(V_K - V), \quad (3)$$

$$I_{KCa} = g_{KCa}\omega(V_K - V), \quad (4)$$

$$I_{KATP} = g_{KATP} f([ATP])(V_K - V), \quad (5)$$

$$I_L = g_L(V_L - V). \quad (6)$$

I_{C_a} is a voltage-dependent calcium current which is a fast depolarizing current responsible for generating the action potentials during the active phase of bursting. I_K is a fast depolarizing potassium current which is responsible for switching between the active and resting phases. I_{KCa} is a $C_a{}^{2+}$-dependent potassium current, and I_{KATP} is an ATP-sensitive potassium current. Activation variable ω is used to describe I_{KCa}, and is defined as a following equation:

$$\omega = \frac{c^2}{c^2 + K_D^2}, \quad (7)$$

$$\frac{dc}{dt} = f_{cyt} J_{mem}, \quad (8)$$

$$J_{mem} = -\alpha I_{Ca}(V) - kc \quad (9)$$

where c corresponds to a $[Ca^{2+}]$, J_{mem} is a net flux of Ca^{2+}, K_D, α, f_{cyt} and k are the parameters [8]. I_{KATP} is an ATP dependent potassium current, depending on ATP concentration $[ATP]$. $f([ATP])$ in the term of ATP dependent potassium current (Eq. (5)) is described by

$$f([ATP]) = \frac{1 + [ADP]/K_1}{1 + [ADP]/K_1 + [ATP]/K_2}, \quad (10)$$

where $[ADP]$ is a concentration of ADP, in the condition that $[ATP] + [ADP]$ is constant [8], K_1, K_2 are the parameters [8]. $[ADP]$ varies with time, and is described by the following equation:

$$\frac{d[ADP]}{dt} = k([ATP] - [ADP]\exp(r(1 - c/r))), \quad (11)$$

where r is a pump rate. Increase of $[Ca^{2+}]$ results in a slow rise in ADP and an increase in I_{KATP}. I_L is a leak current to reflect the occurrence of N_a leaks. Each current is expressed by Hodgkin-Huxley formalism, and the membrane current is the sum of all the contributions from the above ionic channels.

This model is based on the hypothesis of Atwater et al. that the slow dynamics of intracellular free Ca^{2+} are responsible for packaging impulses into bursts [10]. This means that the up state of each burst will slowly increase $[Ca^{2+}]$, which would gradually activate a Ca^{2+}-activated K^+ (K(Ca)) channel until a certain level that would terminate the bursting. In the absence of firing, c slowly recovers.

Chay and Keizer suggested that increased glucose would increase activity of the plasma membrane Ca^{2+}-ATPase (PMCA), slowing the rise of c and accelerating its fall [9]. By using the appropriate parameters as in [9], β-cell can exhibit bursting observed in the experiments. In this study, we change the balance of I_{KCa} and I_{KATP}. Using the ratio parameter γ, the amplitude of I_{KATP} is strengthened by γ, that is, multiplying the term of I_{KATP} by γ, $I_{KATP} \rightarrow \gamma I_{KATP}$. Other parameters are set the same as in [8].

4. Heterogeneous β-cell Network

It is well known that there is a large variability in terms of β-cell size, gap junctional conductances, and ionic channel densities [1, 4]. Benninger et al. numerically studied the effect of heterogeneity [11]. They introduced heterogeneity into their network by randomly distributing the electrical coupling strength between adjacent cells. They found that the model predicts traveling waves of calcium levels amongst the network. In this study, we introduce heterogeneity in the same way as in [11].

The membrane potential in the ith β-cell surrounded by j adjacent β-cells is

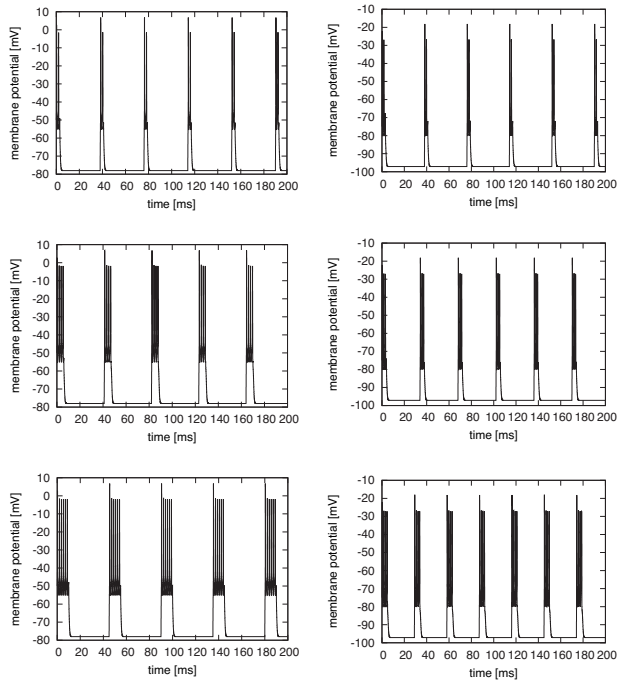
$$C_m \frac{dV_i}{dt} = I_i + \sum_j g_{ij}(V_i - V_j), \quad (12)$$

where g_{ij} is the gap junctional coupling conductance between cells i and j. The islet is modeled as a $10 \times 10 \times 10$ islet cube such that the index j represents coupling to six adjacent cells. In the presence of incomplete coupling, the index j has a probability of coupling to fewer than six cells. The total coupling conductance of a β-cell is the sum of over j, that is, the total coupling conductance from one β-cell to all surrounding β-cells. According to the study of Benninger et al. [11], for electrical heterogeneity, we randomly distributed the calcium-sensitive potassium channel conductance value for each cell.

5. Difference of Bursting Patterns

Figure 2 shows the bursting behavior of a single β-cell. Figure 2(a) shows the bursting behavior driven by Ca^{2+} dependent potassium current I_{KCa}. The number of spikes per bursts increases with the increase of the glucose level, that is, the increase of the external input I_{ex}. However, inter-burst intervals between each bursting period hardly

changes. On the other hand, Fig. 2(b) shows the bursting behavior driven by ATP dependent potassium current I_{KATP}. Inter-burst inrtervals decreases with the increase of the glucose level, however, the number of spikes per bursts hardly changes.



(a) (b)

Figure 2: (a) Bursting behavior driven by Ca^{2+} dependent potassium current ($\gamma = 0.2$). The figure in the top shows the case of $I_{\mathrm{ex}} = 6$, and the middle one shows the case of $I_{\mathrm{ex}} = 15$, and the bottom one shows the case of $I_{\mathrm{ex}} = 25$. The number of spikes per bursts increases with the increase of the glucose level. (b) Bursting behavior driven by ATP dependent potassium current when $I_{\mathrm{ex}} = 6$, $I_{\mathrm{ex}} = 15$, and $I_{\mathrm{ex}} = 25$, with $\gamma = 12.0$. Inter-burst inrtervals decreases with the increase of the glucose level. All the cell parameters are the same as in [8].

Figure 3 shows the inter-burst interval with increasing the input I_{ex}. We can observe that inter-burst interval of I_{KCa}-driven bursting does not change much. On the other hand, in I_{KATP}-driven bursting, inter-burst interval changes its value by the increase of the input.

Figure 4 shows the average number of spikes per burst with increasing the input I_{ex}. We can observe that the number of spikes per burst of I_{KCa}-driven bursting corresponds to the input. On the other hand, in I_{KATP}-driven bursting, the number of spikes per burst does not change much in spite of the increase of the input.

These results can be explained by the difference of the time scale of I_{KCa} and I_{KATP}. I_{KCa} depends on the calcium concentration inside the cell, which has relatively slow dynamics. Due to such slow dynamics, in the I_{KCa} superior condition, increase of the input prolongs the bursting period, *i.e.*, the number of spikes for each bursting period changes. On the other hand, I_{KATP} depends on the ATP concentration in the cell, which has a faster dynamics compared with Ca^{2+}. When the input increases, oscillations of the ATP concentrations get faster, result in the inter-burst interval change.

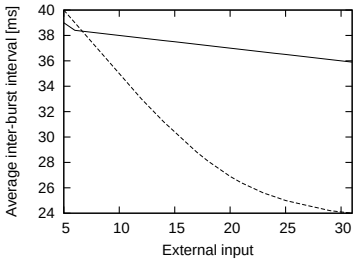


Figure 3: Inter-burst interval with increasing the input I_{ex}. Solid line shows the result of bursting driven by I_{KCa}, and the dashed line shows that of bursting driven by I_{KATP}.

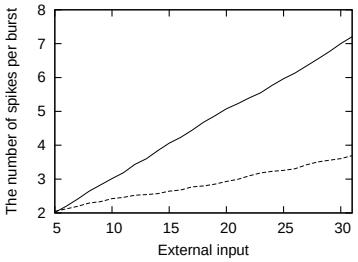


Figure 4: The average number of spikes per each burst with increasing the input I_{ex}. Solid line shows the result of bursting driven by I_{KCa}, and the dashed line shows that of bursting driven by I_{KATP}.

6. Discussion

In this study, we classified the bursting electrical activity in pancreatic β-cell. The first type is the I_{KCa}-driven bursting. I_{KCa} depends on the calcium concentration inside the cell, which has relatively slow dynamics. Due to such slow dynamics, in the I_{KCa} superior condition, the number of spikes for each bursting period changes with the input. The second type is the I_{KATP}-driven bursting. I_{KATP} depends on the ATP concentration in the cell, which has a faster dynamics compared with Ca^{2+}. In this bursting type, inter-burst interval changes with the input.

These findings may contribute to the understanding of the bursting electrical activity in pancreatic β-cells. The mechanisms of the arises of the bursting electrical activities are still physiologically unclear, however, our findings from mathematical modeling imply that the difference of bursting patterns in β-cells can be explained by the difference of ionic currents which produce bursting activity.

For example, there are several studies reporting β-cells whose spikes per each burst increase with the increase of the input [13]. On the other hand, there exist β-cells whose inter-burst interval changes with increase of the input [14]. Such differences in the physiological experiments may be explained by the difference of ionic currents contributing to the bursting properties. However, to our knowledge, there are no study reporting the differences of the ratio of the influence of the ionic currents (I_{Kca} and I_{KATP} in our study) among cells or species. In the physiological experiments, there is an technical difficulty for observing the concentration of ATP with high time resolution. Our study suggests that the balance of the calcium-dependent potassium current I_{Kca} and the ATP-dependent potassium current I_{KATP} may be different among cells, which has to be verified in the experimental study in near future.

Acknowledgments

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