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ORIGINAL PAPER

Effect of cell size on insulin secretion in human β-cells: a simulation study

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Abstract

By using a computational model of a single human β-cell, in this work we analyze the effect of cell size on insulin secretion. The model includes an electric component capable of reproducing the electrical behavior of the human β-cell, a buffered diffusion component to determine the concentration of Ca^{2+} at any point of the intracellular space, and a secretion component that describes the distribution and mobilization of insulin granules throughout the simulated cell. The performed simulations suggest that smaller human β-cells could have faster secretory response with a greater amplitude than bigger cells. This phenomenon is due to the inverse proportionality relationship between the amplitude of the Ca^{2+} transients in the submembrane domain of the simulated cells and the cells' size.

Keywords Insulin · Human β-cell · Ca^{2+} diffusion · Mathematical model

1 Introduction

Insulin secretion, exclusively produced in the pancreatic β-cells, is a process that depends on the increase in intracellular Ca^{2+}. This is a well-established process that consists of an increase in the metabolic activity (i.e. ATP production) due to the entry of glucose into the β-cell, followed by the closure of the ATP-dependent K^+ channels. This promotes the depolarization of the cell and the beginning of the electrical activity pattern produced by the interaction of Ca^{2+}, K^+, and Na^+ channels. Such an electrical activity promotes the entry of Ca^{2+} into the cell through the Ca^{2+} channels, thus increasing the intracellular Ca^{2+} concentration, which is the signal ultimately driving the mobilization and secretion of insulin granules [6].

According to Braun et al. [2], assuming sphericity, the average radius of the human β-cell is 8.8 μm. Each of these β-cells contains approximately 10,000 insulin granules, each storing ~1.8 attomoles of insulin (1.8E-18 mol) [9]. In addition, the electrophysiological properties of the macroscopic Ca^{2+}, K^+ and Na^+ currents present in the human β-cells, were also characterized by Braun et al. [2]. Based on these experimental-derived data, mathematical models of the macroscopic Ca^{2+} currents [4], and the electrical activity of the human β-cells [5] were developed using a three-dimensional model that allowed us to describe the intracellular Ca^{2+} transients in different scenarios of interest.

This work proposes an extended version of previously proposed cell models. In addition to the aforementioned mechanisms, our model takes into account mobilization and secretion of insulin granules. The goal is to assess the effect of cell size on insulin secretion and the underlying Ca^{2+} transients produced in the submembrane space of a human β-cell.

2 Methodology

2.1 Conceptual model

The central idea behind our model is to generate the characteristic electrical activity pattern of the human β-cell; that is, the firing of action potentials in response to a glucose stimulus. This electrical component allows the entry of Ca^{2+} into the cell where the model of buffered diffusion of Ca^{2+} simulates the Ca^{2+} transients in the intracellular

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space. Finally, the secretion model responds to the changes in submembrane Ca^{2+} by promoting the release of the insulin granules located in the vicinity of the cell membrane, and the accompanying mobilization of granules from other pools to the membrane to replenish the pool of granules docked below the cell membrane.

2.2 Model of the electrical activity of the human β-cell and buffered diffusion of intracellular Ca^{2+}

Our model was developed following the Hodgkin and Huxley formalism [7], according to which changes in membrane potential are described as follows:

$$\frac{dV}{dt} = -\frac{1}{C_m}\sum I_{ion} \tag{1}$$

where C_m is the cell capacitance, and $\sum I_{ion}$ represents the sum of the currents shaping the electrical activity pattern.

In this case, our model includes three Ca^{2+} currents ($I_L + I_T + I_{PQ}$), one Na^+ current (I_{Na}), two voltage-dependent K^+ currents (I_{Kv}, I_{ERG}), a Ca^{2+} dependent K^+ current (I_{KCa}), an ATP-dependent K^+ current, and finally, a leak current (I_{Leak}), representing other minor currents not considered explicitly. A scheme of the model described above is shown in Fig. 1. As reported in the original article [5], the model reproduces the morphology, frequency, and amplitude of the action potential observed experimentally. For further details on the electrical activity model, readers can consult the subject matter of [5].

As previously mentioned, our model simulates the dynamics of intracelullar Ca^{2+} in a spherical cell by means of a model of the buffered diffusion of Ca^{2+} that considers the presence of endogenous Ca^{2+}-binding proteins [5]. Here, we used a simplified version of the model in which we have assumed that the flux of Ca^{2+} (both inward and outward) takes place uniformly throughout the entire cell membrane. By doing this, our model was thus reduced to a unidimensional version. In terms of the reaction-diffusion equations in spherical coordinates, this can be stated as follows:

$$\frac{\partial[Ca^{2+}]}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D_{Ca}\frac{\partial[Ca^{2+}]}{\partial r}\right) - \sum_i R_i, \tag{2}$$

$$\frac{\partial[B_i]}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D_{B_i}\frac{\partial[B_i]}{\partial r}\right) - \sum_i R_i, \tag{3}$$

$$\frac{\partial[CaB_i]}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D_{B_i}\frac{\partial[CaB_i]}{\partial r}\right) + \sum_i R_i, \tag{4}$$

where r is the radius of the cell, D_{Ca} and D_{B_i} are the diffusion coefficients for Ca^{2+} and Ca^{2+} buffers, respectively, CaB_i represents Ca^{2+} bound to the Ca^{2+} buffers, and R_i is the interaction term between Ca^{2+} and the Ca^{2+} binding proteins, given by a first order reaction as follows:

$$R_i = k_f[Ca^{2+}][B_i] - k_r[CaB_i], \tag{5}$$

where k_f and k_r are the rate constant associated to the binding and release of Ca^{2+} by the Ca^{2+} buffers.

2.3 Insulin secretion model

We added Pedersen and Sherman's [8] secretion component (developed to reproduce the secretion of insulin from rodent β-cells) into the models of electrical activity and buffered diffusion of Ca^{2+}. The secretion model assumes the existence of different pools along which insulin granules transit, depending on their level of maturity. As shown in Fig. 2, the model contemplates a reserve pool, an almost-docked pool (AD), a high-Ca^{2+} sensitive pool (HCSP), a docked pool (DP), a primed pool (PP), and an immediately releasable pool (IRP), located in the vicinity of the Ca^{2+} channels. We used the equations reported in the

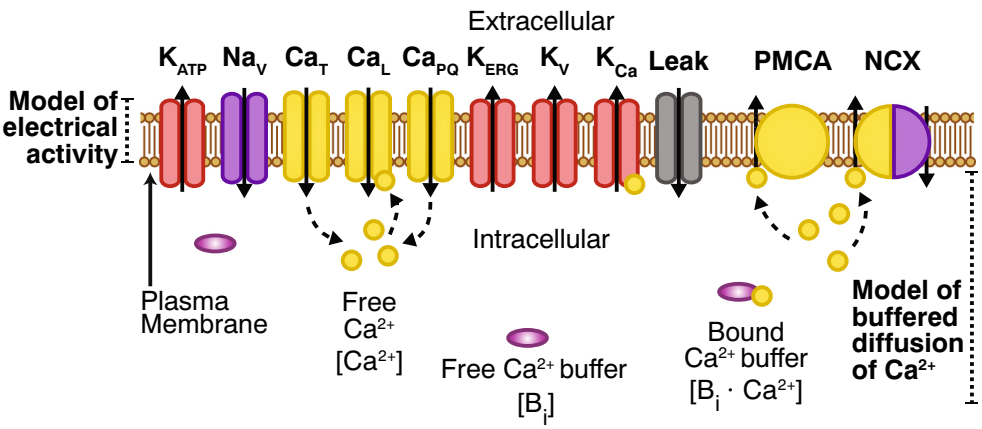

Fig. 1 Scheme of the electrical model and the model of buffered diffusion of intracellular Ca^{2+} in human β-cells. In addition to the Ca^{2+}, K^+ and Na^+ currents, the model includes both Ca^{2+} buffers and Ca^{2+} extrusion mechanisms, such as the plasma-membrane Ca^{2+} ATP-ase (PMCA) and the Na^+/Ca^{2+} exchanger (NCX)

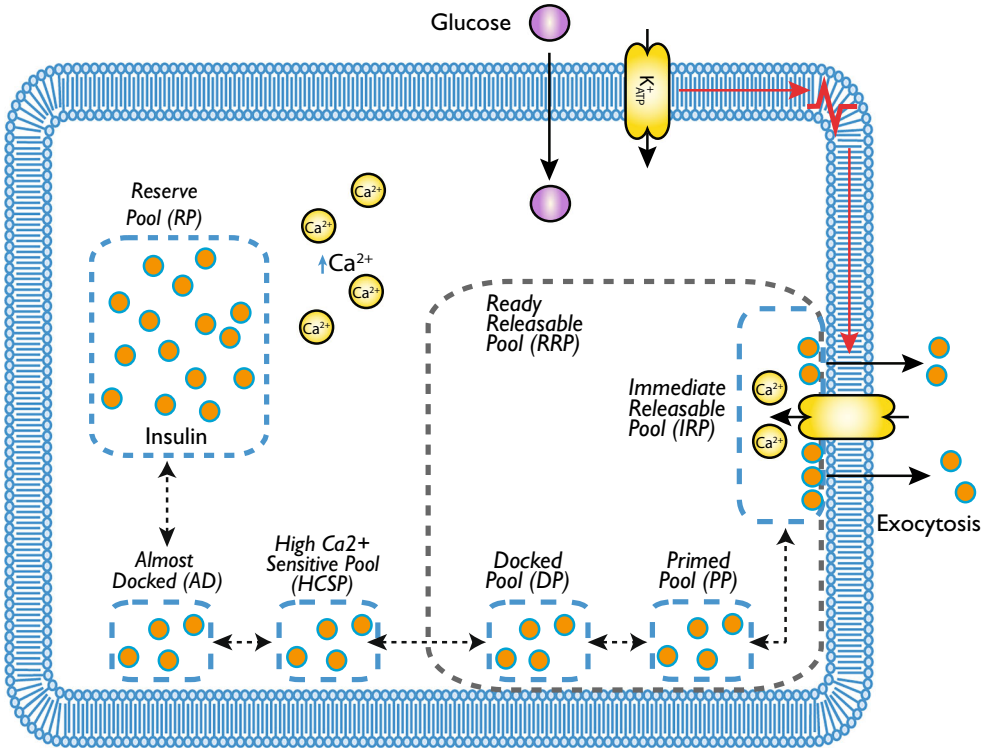

Fig. 2 Scheme of the secretion model adapted from [8]. Insulin granules are mobilized from one pool to another until they are released from the immediate releasable pool (IRP) in a process that depends on the concentration of Ca^{2+} in the vicinity of the cell membrane

model of Pedersen and Sherman [8] without making any modifications.

2.4 Computational aspects

Electric and secretion models are composed of ordinary differential equations, which were solved numerically using the fourth-order Runge-Kutta method. On the other hand, to solve the buffered diffusion model we used the Crank-Nicholson method. All the models were implemented in Python 2.7.

2.5 Simulations

The simulations performed in this work consisted in elevating glucose levels from a low level (close to 0 mM) to a high level of approximately 6 mM, as can be seen in Fig. 3a. The goal of this procedure was to drive the electrical activity pattern of the cell and the corresponding mobilization and secretion of insulin granules in spherical cells of different sizes (6, 8, 10 and 12 μm). As a result, we show simulations of the electrical activity of the human β-cell, the concentration of Ca^{2+} in the vicinity of the cell membrane, and the number of granules released for cells of the different sizes considered.

3 Results

Figure 3a illustrates the simulations of a glucose stimulus from $\sim$0 to 6 mM. This concentration (6 mM) is high enough to produce the electrical response shown in Fig. 3b. The simulated cells did not show relevant differences in terms of the electrical responses simulated as a function of the cell radius. In contrast, the Ca^{2+} transients produced in the submembrane space (Fig. 3c) by the entrance of Ca^{2+} as a result of the electrical activity pattern showed important differences, both in their amplitudes and the reached peak concentrations. For instance, a 6 μm-radius cell produced Ca^{2+} transients reaching a peak concentration close to 1.2 μM, while a 12 μm-radius cell presented Ca^{2+} transients of lower amplitude, reaching a maximal concentration of $\sim$ 1 μM. In summary, the performed simulations suggest that an increase in the cell radius is accompanied by a decrease in both the amplitude and peak concentration of the Ca^{2+} transients. In spite of this, it should be noted that at the end of the simulations shown in Fig. 3c the Ca^{2+} levels approached a similar average value in all the instances.

In terms of the secretory response of the cells, presented in Fig. 3d as the number of insulin granules released, there is a clear effect of the cell radius on both the secretion velocity

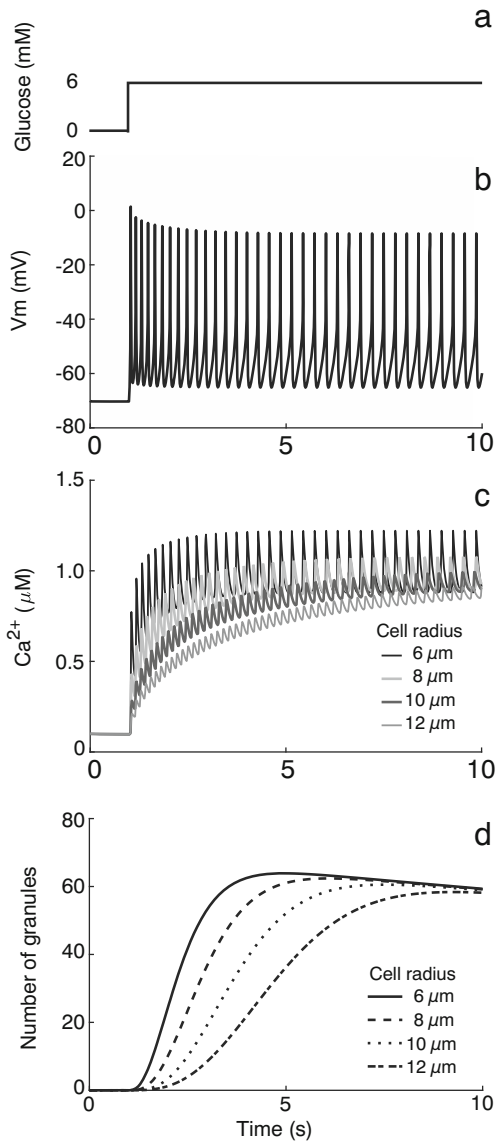

Fig. 3 An increase in glucose concentration **a** produces a similar electrical pattern **b** consisting in the firing of action potentials in cells of radius 6, 8, 10 and 12 μm. **c**. Ca^{2+} transients generated in the submembrane space. **d** Number of insulin granules secreted in response to the increase in the Ca^{2+} concentration

and the maximal value reached during the first seconds of secretion. Following the example described in the last paragraph, the 6 μm-radius cell shows a faster secretory response in comparison to the 12 μm-radius cell. Similarly, we found that the maximal number of secreted granules during the first seconds of secretory activity is greater for the smaller cells and decreases as cell radius increases. Such results are consistent with the simulated Ca^{2+} transients, since the release of insulin granules from the immediate releasable pool directly depends on Ca^{2+} concentration. As a consequence, as Ca^{2+} concentrations increase, insulin granule release is faster and steeper.

4 Discussion

This research relies on computational modelling to evaluate the effect of cell size on the secretory response of human β-cells. In human pancreatic islets, β-cells form an heterogeneous population in terms of both their size and their relative location within the islets [3]. Therefore, it is important to study, not only theoretically, but also experimentally, how these aspects could affect insulin secretion in response to a glucose stimulus. In this regard, the scenarios simulated in this research indicate that smaller cells could have a greater and faster secretory response, at least during the first seconds following a glucose stimulus. This result could be relevant given the fact that secretory response in human pancreatic islets is pulsatile, as shown by the experimental observations of Almaça et al [1].

Finally, as in any other computer-simulation-based research, our findings must be tested and validated through experimental work. Once this is done, our model of the electrical activity, intracellular Ca^{2+} dynamics, and insulin secretion will be able to predict human β-cell behavior from geometrical and morphological aspects that can be relevant for the study of the pathogenesis of important diseases, such as type 2 diabetes.

5 Conclusions

The secretory response of human β-cells depends on cell size. The simulations performed in this work suggest that, unlike larger cells (10 to 12 μm radius), smaller human β-cells (6 to 8 μm radius) could respond faster, releasing a greater number of insulin granules from the immediate releasable pool as a result of the greater amplitude of the Ca^{2+} transients produced in the submembrane domain.

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Compliance with Ethical Standards

Conflict of interests The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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