Simulation of the Electrical Activity of the Pancreatic \( \beta \) Cells Induced by Ingesting of Glucose During an Oral Glucose Tolerance Test

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Introduction

The Type 2 Diabetes Mellitus constitutes a serious problem of public health. For a precise diagnosis of the diabetes, a denominated Oral Glucose Tolerance test is made. Diabetes Mellitus is diagnosed when the levels of the glucose concentration in the blood exceed a certain limit after ingesting a standard glucose load. This excess in the glucose concentration in the blood is caused fundamentally by an insufficient liberation of the insulin, released by the pancreatic \( \beta \)-cells. Electrophysiological studies of the \( \beta \)-cells have shown the mechanisms by which the insulin is secreted to the circulatory torrent. The \( \beta \)-cells store the insulin in packages, and when the glucose concentration in blood arises, the insulin is released by exocytosis. So that the exocytosis process goes off is required as well of a pulsating elevation of the concentration of the intracellular \( \text{Ca}^{++} \) \([\text{Ca}^{++}_i]\). The source of \( \text{Ca}^{++} \) comes from the extracellular medium, and enter to the \( \beta \)-cell via voltage dependent \( \text{Ca}^{++} \) channels \([1, 4]\). The pulsating elevation of the \([\text{Ca}^{++}_i]\) in the \( \beta \)-cell is product of the burst of electrical activity, that consists of action potentials over a depolarized plateau \([2, 4]\). The action potentials are generated by currents of \( \text{Ca}^{++} \) that increase the \([\text{Ca}^{++}_i]\) \([1, 5]\). When the glucose concentration is in its basal level, the \( \beta \)-cells shown a resting potential without electrical activity. The resting potential is mediated by \( \text{K}^+ \) channels, such as the \( \text{K}_{ATP} \) channels. \( \text{K}_{ATP} \) channels are open in absence of ATP\(_i\) and they close on depending by the concentration of intracellular ATP\(_i\) \([\text{ATP}_i]\) \([7]\). When [glucose] in blood is increased, and introduces into the \( \beta \)-cells causing an increase in the basal level of ATP\(_i\) \([1]\), which diminishes the fraction of opened \( \text{K}_{ATP} \) channels, depolarized the cell \([7]\). This depolarization reaches a level threshold that generates burst of action potentials with the consequent pulsating elevation of \( \text{Ca}^{++}_i \) and insulin liberation \([5]\). Electrophysiological techniques have contributed to a detailed description of the voltage dependence and the kinetic of the ionic channels in the \( \beta \)-cells, which has allowed to formulate equations that describe their behavior. Also, has been reported functions that describe the behavior of \( \text{K}_{ATP} \) channels with respect to \([\text{ATP}_i]\) \([5]\). Furthermore, experimental graphs offer information about the temporary course of the increase on ATP\(_i\) before an extracellular glucose load. In this work, we described the simulation of the electrical activity of the \( \beta \)-cells induced during an oral glucose tolerance test in normal subjects. The model describes the glucose level in blood, the increase of associated ATP\(_i\), the burst of action potentials and the pulsating elevation of \( \text{Ca}^{++}_i \) indispensable for the liberation of insulin. The model reproduces experimental data at systemic and cellular level. The model predicts a basal level of optimal ATP\(_i\) for a suitable electrical answer before an extracellular glucose load. This could indicate that the alteration in the basal level of ATP\(_i\) can be one of the mechanisms that generate Type 2 Diabetes Mellitus.
Methods

Simulations were developed in MatLab v.7 (The MathWorks, Inc.). For the quantitative description of [glucose] in blood during the oral glucose tolerance test, we used the model developed by Trujillo [6]. Mathematical model for the description of the electrical activity of the β-cells was taken from Godinez [4], that is a modified version of Chay [3] which describes the electrical properties of the β-cells and also consider the changes in [Ca\textsuperscript{2+}]. To this model, we incorporate the change in the membrane resistance generated by the action of the glucose, for which the mathematical description reported by Fridlyand [5] was used. The model completed when incorporating the increase of the ATP\textsubscript{i} according to the extracellular glucose levels, for which the data published by Ainscow [1] were used. To the experimental graph of the temporary course of the change in the basal level of ATP\textsubscript{i} that reports these authors, we fit an exponential function with time constant of 100 seconds.

Results

We simulate the electrical activity of a β-cells in absence of extracellular glucose (not shown); the membrane potential $V_M$ is greater than -50 mV and the concentration of Ca\textsuperscript{2+} was 150 nM.

![Graphs of membrane potential, Ca\textsuperscript{2+}, and glucose concentration over time.](image)

Figure 1: A. Reduction of resting potential (top), increase of Ca\textsuperscript{2+} (middle) due an increase in blood glucose (5 mM) in oral glucose tolerance test at t=0 min (bottom). B. Burst of action potential (top), oscillations in Ca\textsuperscript{2+} (middle) and maximum glycemia (15 mM) at t=60 min. after a glucose load (bottom).

Fig 1A, shows the results obtained at the beginning of the OGTT after a glucose load. At $t=0$ with normal glycemia, the β-cells are silent but show a reduction in the resting potential and increases the basal level of Ca\textsuperscript{2+}.
At $t=60$ min, when the maximum glucose is reached (Fig 1B), burst activity causes a depolarization. Associated to this type of electrical activity, an increase in the $\text{Ca}^{++}$ is induced. The level average of the $\text{Ca}^{++}$ was increased and it was accompanied by oscillations at the end of each burst of action potentials.

**Discussion**

Several models have seen used to describe the electrical activity of pancreatic $\beta$-cells. Each one of them makes emphasis in some topic related to some recent experimental finding. Nevertheless, there is not a model of the electrical activity and the changes in $[\text{Ca}^{++}]$ in terms of the values of $[\text{glucose}]$ in blood. The electrophysiological studies at cellular level report a depolarization and increase in the electrical activity of the $\beta$-cells when increasing extracellular glucose. Our model reproduces these results. Due the importance of the oscillation of $\text{Ca}^{++}$ in the pulsating insulin liberation, diverse mechanisms have seen proposed to explain the transitory of $\text{Ca}^{++}$. Our results indicate that the increase average of the $\text{ATP}_i$ induced by hyperglycemia, is the factor generates burst of action potentials and the oscillating increase of the $\text{Ca}^{++}$ is product of the activation and inactivation of ionic channels. In addition, basal $[\text{ATP}_i]$ is critical for a suitable induction of the insulin release in response to an increase of glucose.

**References**


