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# Computational modeling of the effect of temperature variations on human pancreatic β-cell activity

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ABSTRACT

The effect of temperature variations on the pancreatic β-cell activity and the role of different model compartments in temperature sensing have been investigated using a computational modeling approach. The results of our study show that temperature variations by several degrees can change the dynamical states of the β-cell system. In addition, temperature variations can alter the characteristic features of the membrane voltage, which correlates with insulin secretion. Simulation results show that the ion channels such as the L-type calcium, the hERG potassium, sodium channels and the glycolysis pathway are the possible sites for sensing temperature variation. Results indicate that for a small temperature change, even though the frequency and amplitude of electrical activity are altered, the area under the membrane potential curve remains almost unchanged, which implies the existence of a thermoregulatory mechanism for preserving the amount of insulin secretion. Furthermore, the computational analysis shows that the β-cell electrical activity exhibits a bursting pattern in physiological temperature (37 °C) while in vitro studies reported almost the spiking activity at lower temperatures. Since hormone-secreting systems work more efficient in bursting mode, we propose that the pancreatic β-cell works better in the physiological temperature compared with the reference temperature (33 °C).

## 1. Introduction

Temperature has a substantial effect on cell functions. The composition of a cell membrane and the chemical reactions unfolding inside the cell may undergo transformation due to temperature variations (Quinn, 1988). The temperature variation can also directly affect several kinds of receptors and ion channels (Liman, 2006), glycolytic flux (Cruz et al., 2012; Postmus et al., 2008), enzymatic activity (Daniel et al., 2008), kinetics of ion channels (Collins and Rojas, 1982; Kimitsuki and Komune, 2013; Rosen, 2001; Sterratt, 2014b), the Nernst equilibrium potential of ion channels, half-maximal activation voltage along the channel (Yang and Zheng, 2014) and the membrane potential (Buzatu, 2009). The way that temperature affects cell functions and the underlying mechanisms have gained special attention in biology.

There are several studies regarding the effect of temperature on cellular compartments and functions. Rosen showed that the inactivation time constant of sodium channels were linearly temperature sensitive, while the activation time constant exhibited a nonlinear response to temperature, possibly due to the membrane structural changes in the thermotropic phase transition (Rosen, 2001). Milburn et al. reported the increase of sodium channel's conductance due to the temperature rise through the increasing of channel energy barrier at higher temperatures (Milburn et al., 1995). The conductance-temperature relationship in octopus cells of the mammalian ventral cochlear nucleus (VCN) showed that temperature changed the conductance of $K^+$ channels through affecting the kinetics and hyperpolarization-activated current (Cao and Oertel, 2005). Another study showed the temperature dependence of amylase secretion from the pancreas which might be possibly due to the alteration of the physical state of the membrane (Beaudoin and Mercier, 1980). Mair et al. used the sensitivity of phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase phases of glycolysis to temperature for controlling chemical reactions in the cellular systems (Mair et al., 2005). Chemin et al. showed that protein kinase in the specific temperature range (30–37 °C) increased the flux of low voltage-activated Cav3 T-type calcium channels in mammalian cell lines (Chemin et al., 2007).

The fundamental function of the pancreatic β-cell is insulin secretion. There are several studies which report the temperature sensitivity of insulin granule secretion. Ivarsson et al. showed that reducing the temperature could reduce the frequency and velocity of insulin granule

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diffusion (Ivarsson et al., 2004). Kinard et al. reported that rising temperature enhanced $Ca^{2+}$ current in mouse pancreatic β-cell (Kinard and Satin, 1996). Escolar et al. investigated the effect of hypothermia on glucose-stimulated insulin secretion and reported some levels of inhibition of insulin secretion by reducing temperature, possibly due to the inhibition of energetic substrates and consequently the deficiency of metabolic signals (Escolar et al., 1990). It was reported that cooling inhibited the secretion of insulin granules by affecting the peak current of $Ca^{2+}$ and also the mobilization of granules from the reserve pool of cytosol toward membrane area (Renström et al., 1996). The temperature dependence of secretion was not limited to glucose-stimulated condition and could be seen in basal secretion (Schumacher et al., 2015). Even though there are several studies about the effect of temperature on the pancreatic β-cells, the mechanism of such effect and the role of different compartments are not well understood. Also, most of the studies are limited to animal species. Furthermore, these studies were usually concentrated on one specific component of the system. In this regard, a more comprehensive study of the effect of temperature on the human pancreatic β-cells is demanded.

In the current study, a theoretical approach has been used to check out the effect of temperature on the β-cell electrical activity. Theoretical studies on biological systems can be used for testing the hypothesis about these systems. Recently we have used the theoretical framework for investigating the role of ion channels in the human β-cell hubs (Farashi et al., 2018c) and the way that low-frequency electric fields affect the pancreatic β-cells (Farashi et al., 2018a). Furthermore, these studies might be useful for justifying the experimental observations of biological systems. Since almost all components of cellular systems and also the interaction between them are temperature-sensitive, it is very difficult to interpret the results obtained by experimental studies. In this regard, mathematical modeling can be used as a powerful tool for studying the effect of temperature on the specific components of the system. In such framework, it is very straightforward to focus on the system's desired components. However, the theoretical outcome should be confirmed via the experimental studies.

The main purpose of this study is to use a computational modeling approach to investigate the response of the human pancreatic β-cell during temperature variation. Since these cells are the only insulin secretory machinery in the human body, the stability of these systems during a temperature change is of great importance for preserving the glucose homeostasis. For this reason, the existence of a thermoregulatory mechanism might be inevitable in the pancreatic β-cells. In addition, the temperature might be an important factor to justify the experimentally observed differences between electrical activity of the pancreatic β-cells in the reference temperature (32–33 °C) (in which the in vitro experiments of the human β-cells are usually performed) and the physiological temperature (37 °C). The obtained results can be used for evaluating the effect of fever and other interventions that perturb the temperature on the β-cell activity.

## 2. Material and methods

### 2.1. The pancreatic β-cell model

There are different types of ion channels, pumps and exchangers in the human pancreatic β-cell (Barnett et al., 1995; Braun et al., 2008; Nunemaker et al., 2006; Pedersen, 2009, 2010; Riz et al., 2014; Rosati et al., 2000a). The specific roles of these compartments have been summarized in Table 1.

The overall voltage-current relation of the pancreatic β-cell model can be described by Eq. (1).

$$C_m \frac{\partial V}{\partial t} = -(I_{hERG} + I_{BK} + I_{Kv} + I_{Na} + I_{CaL} + I_{CaPQ} + I_{CaT} + I_{KATP} + I_{SK} + I_{GABAR} + I_{leak} + I_{TRPM5}) \quad (1)$$

where $C_m$ is the membrane capacitance, $V$ denotes the membrane potential and $t$ is the time index. Since the currents are usually normalized to the membrane capacitance (Braun et al., 2008; Riz et al., 2014), the $C_m$ parameter has been adjusted to 1 in Eq. (1). The channels, pumps and exchangers which contribute to the generation of the membrane voltage and not considered in Eq. (1) can be considered via the leakage term. It should be noted that $I_{TRPM5}$ is a new term which has been added into the model by us to accommodate the presence of these types of channels in the pancreatic β-cells.

The mathematical model proposed by Riz et al. (Pedersen, 2010; Riz et al., 2014) has been used throughout this paper for evaluating the effect of temperature on the β-cell electrical activity. For the simulations performed in this study, the model parameters have been adjusted based on the default values in Table 1 in Ref. (Riz et al., 2014). Any change in the model parameter values for producing different patterns of signals has been stated.

### 2.2. Effect of temperature on ionic current and channel kinetics

The mathematical expression of channel activations (e.g. activation function ($m$)), is mostly expressed by a first order differential equation as

$$\frac{dm_X}{dt} = \frac{m_{X,\infty}(V) - m_X}{\tau_{mX}} \quad (2)$$

where $\tau_{mX}$ is the time constant of the channel activation and $m_{X,\infty}$ is the steady-state voltage-dependent activation, which can be described by a Boltzmann function as below (Pedersen, 2010)

$$m_{X,\infty}(V) = 1/1 + \exp((V - V_{mX})/n_{mX}) \quad (3)$$

In Eq. (3), $n_{mX}$ describes the slope parameter of the Boltzmann function and $V_{mX}$ is the half-maximal activation voltage. The inactivation function can be described by equations similar to (2) and (3), except that the slope parameter is positive in case of inactivation function, while it is negative for the activation function (Pedersen, 2010). Altogether, the activation and inactivation functions determine the steady-state condition of a voltage-dependent channel over a voltage range.

The effect of temperature on the channel kinetics can be described by Q10 temperature coefficient which defines the rate of the physiological process as a result of increasing the temperature by 10 °C (Sterratt, 2014a). This effect can be considered through inserting the Q10 parameter into Eq. (2) (Olivares et al., 2015).

$$\frac{dm_X}{dt} = \varnothing(T)\frac{m_{X,\infty}(V) - m_X}{\tau_{mX}} \quad (4)$$

where

$$\varnothing(T) = Q_{10}^{\frac{T-T_{EQ}}{10}} \quad (5)$$

In Eq. (5), $T$ represents the current temperature in degrees Kelvin and $T_{EQ}$ is the reference temperature, at which the physiological measurement is normally made ($T = 33$ °C). The value of Q10 for the channel kinetics can be considered to be about 3 (Hille, 2001), while the effect of temperature on an ionic current can be considered by a temperature coefficient of about 1.3 using Eqs. (6) and (7) (Olivares et al., 2015).

$$I_X(T) = \psi(T) I_X(T_{EQ}) \quad (6)$$

where

$$\psi(T) = 1.3^{\frac{T-T_{EQ}}{10}} \quad (7)$$

### 2.3. Effect of temperature on the TRPM5 channels

The TRPM5 is a $Ca^{2+}$-activated monovalent cation channel, permeable to $K^+$ and $Na^+$ ions but impermeable to $Ca^{2+}$ (Colsoul et al.,