Analysis on the mechanism of enhancing insulin secretion by TRPM2 channel in a pancreatic β-cell

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Abstract: It has been reported that the activation of the Ca²⁺-permeable transient receptor potential melastatin2 (TRPM2) channel enhances a pancreatic β-cell’s insulin secretion. Further, it increases the resting potential, and prolongs the burst duration of the pancreatic β-cell. However, the mechanism by which the TRPM2 channel activation enhances insulin secretion is unknown. Therefore, in this paper, using a mathematical model that represents the dynamics of the membrane potential, we investigate the reproducibility of the results obtained from physiological experiments, and reveal the mechanism of enhancing insulin secretion. We demonstrate that the TRPM2 channel activation prolongs the burst duration when the TRPM2 reversal potential is close to the value observed in the physiological experiments. This could be a plausible theoretical explanation of the experimental value of the TRPM2 reversal potential. In addition, we reveal that the TRPM2 channel activates the voltage-dependent and Ca²⁺-sensitive channels with large conductance, thereby inducing insulin secretion.

Key Words: pancreatic β-cell, TRPM2 channel, insulin secretion
1. Introduction

Insulin is secreted by the pancreatic $\beta$-cells in the islet of Langerhans. Insulin is a critical regulator of metabolism so that pancreatic $\beta$-cell dysfunction leads to both type 1 and type 2 diabetes. In type 1 diabetes condition, the body no longer produces insulin, and in type 2 diabetes condition, the produced insulin is not enough or does not work effectively. It is widely known that the membrane excitability of the pancreatic $\beta$-cell leads to the insulin secretion [1]. Therefore, it is important to preserve the membrane excitability of the pancreatic $\beta$-cell to prevent from insulin secretory dysfunction. However, the detailed mechanism of how pancreatic $\beta$-cell dysfunction leads to the insulin secretory dysfunction is still unknown [2, 3].

It is generally difficult to investigate the properties of ion channels in pancreatic $\beta$-cells. Then, several mathematical models have been proposed to clarify these properties. Chay and Keizer proposed a pioneering model of the pancreatic $\beta$-cells incorporating a Hodgkin-Huxley type gating mechanism for Ca$^{2+}$ and K$^+$ channels [4]. Since then several models have been proposed including those of human $\beta$-cells [5]. Although these models are simple and are able to partly reproduce experimental results of the pancreatic $\beta$-cells, their ion channel constitutions are not sufficient. For example, the closure of the adenosine triphosphate (ATP)-sensitive K$^+$ (KATP) channels triggers the membrane depolarization of a pancreatic $\beta$-cell, and triggers insulin secretion. Riz et al. proposed a detail mathematical model of the pancreatic $\beta$-cells incorporating 12 types of ion channels including KATP channel [6]. This model describes a detailed ion channel mechanism of the pancreatic $\beta$-cells, which enables us to investigate the detailed membrane activation through ion channels. Therefore, we analyze the $\beta$-cell activity based on this model [6] in this paper.

Although the dynamics of the membrane potential is mainly determined by the activity of the KATP channels, these channels alone cannot evoke the membrane depolarization. The inward currents through the transient receptor potential melastatin2 (TRPM2) channels are crucial for inducing the membrane depolarization that follows the closure of the KATP channels [1]. The TRPM2 channel is a Ca$^{2+}$-permeable non-selective cation channel. It has been reported that the TRPM2 channel activation enhances insulin secretion, and prolongs the duration of the Ca$^{2+}$ concentration [7].

The dynamics of the membrane potential, including the TRPM2 current, has been expressed using mathematical models [8, 9]. However, the TRPM2 conductance is not a quantitative value, and the prolongment of the burst duration in the TRPM2 channel activation cannot be observed in these models. Therefore, in this paper, we incorporated the TRPM2 current into the mathematical model proposed by Riz et al. [6], and clarified effects of the TRPM2 channel on the membrane potential. Our mathematical analysis reveals the mechanism of enhancing insulin secretion by the TRPM2 channel in pancreatic $\beta$-cells. We investigated the reproducibility of the results obtained following the physiological experiments [7]. Furthermore, we revealed the mechanism through which the TRPM2 channel activation enhances the insulin secretion.

2. Methods

The TRPM2 current

The TRPM2 channel is Ca$^{2+}$-permeable. The relationship between the membrane potential and the TRPM2 current is linear. It is reported that in rat $\beta$-cells the TRPM2 channel activation enhances insulin secretion, increases resting potential, and prolongs the duration of Ca$^{2+}$ and inward currents [7]. In [7], if the TRPM2 channel is activated by its activator ex-4, the slope conductance and reversal potential are 0.0823[nS] and $-19.2$[mV], respectively; otherwise, they are 0.0252[nS] and $-4.4$[mV], respectively. Such tendency that the TRPM2 channel activation induces the increase of TRPM2 channel conductance and the decrease of the reversal potential of the TRPM2 channel is consistent with other study [10]. In this paper, we set several values for the conductance and the reversal potential of the TRPM2 channel to express several levels of TRPM2 activation.

We expressed the TRPM2 current $I_{TRPM2}$ as follows:

$$I_{TRPM2} = g_{TRPM2}(V(t) - V_{TRPM2}),$$

where $V(t)$ is the membrane potential, and $g_{TRPM2}$ and $V_{TRPM2}$ are the TRPM2 conductance and
reversal potential, respectively.

The dynamics of the membrane potential
We incorporated the TRPM2 current shown in Eq. (1) into the model that expresses the dynamics of the membrane potential of a pancreatic β-cell by Riz et al. [6]. The Riz model has a small conductance Ca$^{2+}$-sensitive K$^+$ (SK) channel, a large conductance Ca$^{2+}$-sensitive K$^+$ (BK) channel, a delayed rectifier K$^+$ (KV) channel, an ATP-sensitive K$^+$ (KATP) channel, a Na$^+$ channel, three voltage-dependent calcium channels, an L-type Ca$^{2+}$ (CaL) channel, a PQ-type Ca$^{2+}$ (CaPQ) channel, a T-type Ca$^{2+}$ (CaT) channel, and a leak channel.

The dynamics of the membrane potential $V(t)$ is expressed as follows:

$$C_m \frac{dV(t)}{dt} = -(I_{\text{KATP}} + I_{\text{SK}} + I_{\text{BK}} + I_{\text{KV}} + I_{\text{Na}} + I_{\text{CaL}} + I_{\text{CaPQ}} + I_{\text{CaT}} + I_{\text{leak}} + I_{\text{TRPM2}}),$$

where $C_m$ is the membrane capacitance, variables $I_{\text{KATP}}$, $I_{\text{SK}}$, $I_{\text{BK}}$, $I_{\text{KV}}$, $I_{\text{Na}}$, $I_{\text{CaL}}$, $I_{\text{CaPQ}}$, $I_{\text{CaT}}$, $I_{\text{leak}}$ and $I_{\text{TRPM2}}$ are the currents of the KATP, SK, BK, KV, Na, CaL, CaPQ, CaT, leak, and TRPM2 channels.

The KATP channel closes as a result of an increase in the intracellular ATP concentration induced by a glucose metabolism corresponding to the elevation of glucose concentration in the blood. The closure of the KATP channel depolarizes the membrane potential, and triggers the insulin secretion in a pancreatic β-cell. The KATP current $I_{\text{KATP}}$ is expressed as follows:

$$I_{\text{KATP}} = g_{\text{KATP}} \frac{1}{1 + [\text{ATP}]}(V(t) - V_K),$$

where $[\text{ATP}]$ is a variable that mimics ATP levels, $g_{\text{KATP}}$ is a KATP conductance, and $V_K$ is a reversal potential of the K$^+$ channel.

The SK channel is one of the Ca$^{2+}$-activated K$^+$ channel, and its conductance is small. The SK current $I_{\text{SK}}$ is expressed as follows:

$$I_{\text{SK}} = g_{\text{SK}} \frac{[\text{Ca}^{2+}]_m(t)^{5.2}}{K_{\text{SK}}^{5.2} + [\text{Ca}^{2+}]_m(t)^{5.2}}(V(t) - V_K),$$

where $g_{\text{SK}}$ is an SK channel conductance, a variable $[\text{Ca}^{2+}]_m(t)$ is a submembrane Ca$^{2+}$ concentration, and $K_{\text{SK}}$ is a dissociation constant.

The BK channel is one of the voltage-dependent K$^+$ channels, it is activated by the Ca$^{2+}$ concentration. Therefore, we incorporated the TRPM2 current $I_{\text{TRPM2}}$ into the BK current. The BK current $I_{\text{BK}}$ is expressed as follows:

$$I_{\text{BK}} = g_{\text{BK}}m_{\text{BK}}(-I_{\text{CaL}} - I_{\text{CaPQ}} - I_{\text{CaT}} - I_{\text{TRPM2}} + B_{\text{BK}})(V(t) - V_K),$$

where $g_{\text{BK}}$ is a BK conductance, $m_{\text{BK}}$ is an activation variable of the BK channel, and $B_{\text{BK}}$ is the basal Ca$^{2+}$-independent activation of the BK channel.

The KV channel is the voltage-dependent K$^+$ channel. The KV current $I_{\text{KV}}$ is expressed as follows:

$$I_{\text{KV}} = g_{\text{KV}}m_{\text{KV}}(V(t) - V_K),$$

where $g_{\text{KV}}$ is a KV conductance, and $m_{\text{KV}}$ is an activation variable of the KV channel.

The flux of Ca$^{2+}$ through the voltage-dependent Ca$^{2+}$ channels regulates the intracellular signal transduction, such as insulin secretion. The Riz model has three voltage-dependent Ca$^{2+}$ channels: CaL, CaPQ, and CaT. The CaL channel participates in the upstroke of action potential, and increases the excitability of the pancreatic β-cell. The CaL channel has high voltage-dependence and large conductance. The CaL current $I_{\text{CaL}}$ is expressed as follows:

$$I_{\text{CaL}} = g_{\text{CaL}}m_{\text{CaL}}h_{\text{CaL}}(V)h_{\text{CaL}}(V(t) - V_{\text{Ca}}),$$

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where \( g_{\text{CaL}} \) is a CaL conductance, \( m_{\text{CaL},\infty}(V) \) is an equilibrium activation variable, \( h_{\text{CaL}} \) is an inactivation variable, and \( V_{\text{Ca}} \) is a reversal potential of the Ca\(^{2+}\) channel.

The CaPQ channel is highly voltage-dependent, whose inhibition increases the spike frequency. The CaPQ current \( I_{\text{CaPQ}} \) is expressed as follows:

\[
I_{\text{CaPQ}} = g_{\text{CaPQ}} m_{\text{CaPQ},\infty}(V) (V(t) - V_{\text{Ca}}),
\]

where \( g_{\text{CaPQ}} \) is a CaPQ conductance, and \( m_{\text{CaPQ},\infty}(V) \) is an equilibrium activation variable.

The CaT channel has low voltage-dependence; it also has small conductance, compared to both the CaL and CaPQ channels. The CaT current, \( I_{\text{CaT}} \), is expressed as follows:

\[
I_{\text{CaT}} = g_{\text{CaT}} m_{\text{CaT},\infty}(V) h_{\text{CaT}} (V(t) - V_{\text{Ca}}),
\]

where \( g_{\text{CaT}} \) is a CaT conductance, \( m_{\text{CaT},\infty}(V) \) is an equilibrium activation variable and \( h_{\text{CaT}} \) is an inactivation variable.

Blocking the Na\(^+\) channel reduces and prolongs the action potential amplitude. The Na\(^+\) current, \( I_{\text{Na}} \), is expressed as follows:

\[
I_{\text{Na}} = g_{\text{Na}} m_{\text{Na},\infty}(V) h_{\text{Na}} (V(t) - V_{\text{Na}}),
\]

where \( g_{\text{Na}} \) is a Na conductance, \( m_{\text{Na},\infty}(V) \) is an equilibrium activation variable, \( h_{\text{Na}} \) is an inactivation variable, and \( V_{\text{Na}} \) is a reversal potential of the Na\(^+\) channel.

The leak channel is always open. The leak current, \( I_{\text{leak}} \), is expressed as follows:

\[
I_{\text{leak}} = g_{\text{leak}} (V(t) - V_{\text{leak}}),
\]

where \( g_{\text{leak}} \) and \( V_{\text{leak}} \) are the leak conductance and reversal potential, respectively.

The submembrane Ca\(^{2+}\) concentration is changed due to the influx of Ca\(^{2+}\) currents. Therefore, we incorporated the TRPM2 current into the dynamics of the submembrane Ca\(^{2+}\) concentration. The submembrane Ca\(^{2+}\) concentration variable, \( [Ca^{2+}]_m(t) \), and the cytosolic Ca\(^{2+}\) concentration variable, \( [Ca^{2+}]_c(t) \), are expressed as follows:

\[
\frac{d[Ca^{2+}]_m(t)}{dt} = f \alpha C_m (-I_{\text{CaL}} - I_{\text{CaPQ}} - I_{\text{CaT}} - I_{\text{TRPM2}})/Vol_m - f (Vol_c/Vol_m)[B([Ca^{2+}]_m(t) - [Ca^{2+}]_c(t))] + J_{\text{PMCA}} + J_{\text{NCX}}],
\]

and

\[
\frac{d[Ca^{2+}]_c(t)}{dt} = f [B([Ca^{2+}]_m(t) - [Ca^{2+}]_c(t))] - J_{\text{SERCA}} + J_{\text{leak}},
\]

where \( f \) is the free-to-total ratio of the Ca\(^{2+}\) concentration, \( \alpha \) converts the currents to flux, \( Vol_m \) and \( Vol_c \) are the volumes of the submembrane compartment and the bulk cytosol, \( B \) describes the Ca\(^{2+}\) flux from the submembrane compartment to the bulk cytosol, \( J_{\text{PMCA}} \) and \( J_{\text{NCX}} \) are the functions of the flux through the plasma membrane Ca\(^{2+}\)-ATPases (PMCA) and Na\(^+\)-Ca\(^{2+}\) exchangers (NCX), respectively. In Eq. (13), \( J_{\text{SERCA}} \) is a function of the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) pump-dependent sequestration of Ca\(^{2+}\) in the endoplasmic reticulum, and \( J_{\text{leak}} \) is a constant from the leak flux from the endoplasmic reticulum to the cytosol.

In the original Riz model, there exist two more currents expressing the ligand-gated Cl\(^-\) channel current carried by GABA\(_A\) receptor, and the human ether-a-go-go K\(^+\)-channel current. However, these channel currents are specific to human \( \beta \)-cells. In this paper, we excluded these human-specific currents because our study is based on the experimental results of rat \( \beta \)-cells [7]. Table I shows the parameter values used in the numerical experiments. The undescribed variables and parameter values are the same as that of the Riz model [6].

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Table I. Parameter values used in the numerical experiments.

| Parameter | Value |
|-----------|-------|
| $C_m$ | 1 [pF] |
| $V_K$ | $-75$ [mV] |
| $g_{KATP}$ | 0.13 [nS] |
| $g_{SK}$ | 0.1 [nS] |
| $g_{BK}$ | 0.02 [nS] |
| $g_{KV}$ | 1 [nS] |
| $g_{CaL}$ | 65 [mV] |
| $g_{TRPM2}$ | 0.283 [nS] |
| $g_{CaPQ}$ | 0.17 [nS] |
| $V_{leak}$ | $-30$ [mV] |
| $g_{leak}$ | 0.02 [nS] |
| $V_{Na}$ | 70 [mV] |
| $g_{Na}$ | 0.4 [nS] |
| $V_{leak}$ | $-30$ [mV] |
| $g_{leak}$ | 0.02 [nS] |
| $K_{SK}$ | 0.57 [$\mu$M] |
| $f$ | 0.01 |
| $V_{leak}$ | 0.1 [pL] |
| $V_{leak}$ | 1.15 [pL] |
| $B$ | 0.1 [$\text{ms}^{-1}$] |
| $J_{leak}$ | 0.00094 [$\mu$M/ms] |

Firing patterns and definition of bursts

The model reproduces various firing patterns of the membrane potential (Fig. 1). Figure 1(a) reveals that the parameters in Table I, except for $g_{CaL} = 0$ [nS] and $g_{TRPM2} = 0$ [nS], are consistent with the resting membrane potential. Figure 1(b) shows a firing followed by the resting state of the membrane potential at the parameters in Table I, except $g_{CaL} = 0.07$ [nS] and $g_{TRPM2} = 0$ [nS]. Figure 1(c) shows continuous burst firings at the parameter $g_{TRPM2} = 0$ [nS]. Figure 1(d) shows that persistent firings by the membrane potential always correspond to the parameters in Table I, excluding $g_{KATP} = 0.01$ [nS], $g_{CaL} = 0.07$ [nS], and $g_{TRPM2} = 0$ [nS]. Normal insulin is secreted when there are action potential burst firings [11].

![A resting state of the membrane potential](image1.png)

![Firings followed by a resting state of the membrane potential](image2.png)

![Bursts](image3.png)

![Persistent firings](image4.png)

Fig. 1. Various firing patterns of the membrane potential.

We numerically integrated the differential equations using the Euler method with the step size of $h = 0.01$ [ms]. When $t_0$ and $t_1$ were two consecutive times, $t_1 = t_0 + h$. If $V(t_1) - V(t_0) < 0.05$ was maintained for 5 [s] or more, and the difference between the maximum and minimum membrane potential was less than 20 [mV], we determined that the membrane potential was in a resting state. When the membrane potential was not in a resting state, we determined that it was in an active state. When the active state was maintained for 5 [s] or more, we determined it as a burst and its duration is defined as burst duration. Thus, we determined that bursts fired continuously in active states of the membrane potential, and did not fire at all in the resting states.

Using the above-mentioned condition, we investigated the burst duration, because it corresponds to the duration of insulin secretion. A burst duration was defined as the first spike to the last spike in a burst. When the membrane potential was kept in the resting state of the membrane potential (Fig. 1(a)) or a firing followed the resting state of the membrane potential (Fig. 1(b)), the burst duration was 0. In addition, when the membrane potential fired persistently (Fig. 1(d)), the burst duration was equivalent to the observation time.
3. Results

Reproducibility of the physiological experiments

The values of the TRPM2 conductance and reversal potential vary for every trial in the physiological experiments [7]. Therefore, we investigated these effects on bursts by varying the TRPM2 conductance and the reversal potential. The TRPM2 activation is represented by the increase in the TRPM2 conductance. In addition, longer bursts correspond to increased insulin secretion. Figure 2 shows the resting membrane potential and burst duration per observation time when the TRPM2 conductance $g_{\text{TRPM2}}$ is increased from $0\,[\text{nS}]$ to $0.1\,[\text{nS}]$. These conductance values are quantitatively close to the physiological experiment [7]. In Fig. 2, the lines with filled circles show that $V_{\text{TRPM2}} = -10\,[\text{mV}]$, lines with open circles show that $V_{\text{TRPM2}} = -20\,[\text{mV}]$, lines with crosses show that $V_{\text{TRPM2}} = -30\,[\text{mV}]$, lines with triangles show that $V_{\text{TRPM2}} = -40\,[\text{mV}]$, and the lines with squares show that $V_{\text{TRPM2}} = -50\,[\text{mV}]$. When the membrane potential shows no bursts or persistent firings, their durations per observation time are 0 and 1, respectively.

Fig. 2. Variations in the resting membrane potential and the burst duration when the TRPM2 conductance is increased.
In Fig. 2(a), the resting potential increases at any reversal potential when the TRPM2 conductance \( g_{\text{TRPM2}} \) is increased. This result is consistent with the physiological experiments [7]. When \( V_{\text{TRPM2}} = -10[\text{mV}] \) (the line with filled circles), the membrane potential fires persistently, corresponding to excessive insulin secretion at \( g_{\text{TRPM2}} > 0.077[\text{nS}] \). For the same reason, the line with filled circles peaks at 1 in Fig. 2(b). On the other hand, the line with squares (\( V_{\text{TRPM2}} = -50[\text{mV}] \)) reaches 0 at \( g_{\text{TRPM2}} > 0.051[\text{nS}] \). This corresponds to a lack of insulin secretion.

The physiological experiments [7] show that the TRPM2 activation prolongs the burst duration; the TRPM2 conductance is 0.0823[\text{nS}] in the TRPM2 activated state. However, when \( V_{\text{TRPM2}} = -40[\text{mV}] \) (the line with triangles), the burst duration is not directly proportional to \( g_{\text{TRPM2}} \) at \( g_{\text{TRPM2}} = 0.0823 \). Further, when \( V_{\text{TRPM2}} = -30[\text{mV}] \) (the line with crosses), the burst duration does not increase at \( g_{\text{TRPM2}} < 0.08[\text{nS}] \). Therefore, it is assumed that the TRPM2 reversal potential is approximately \(-20[\text{mV}]\). This value is close to the value obtained in the physiological experiments \(-19.2[\text{mV}]\) under the control condition wherein the TRPM2 channel is not activated [7].

As shown above, we confirmed that the TRPM2 reversal potential affects bursts. Here, we investigated the effects of increased TRPM2 conductance \( g_{\text{TRPM2}} \) on the TRPM2 currents in Figs. 3(a)–(c).

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Fig. 3. The TRPM2 currents \( I_{\text{TRPM2}} \) when the TRPM2 conductance \( g_{\text{TRPM2}} \) is increased. Orange lines show that \( g_{\text{TRPM2}} = 0.02[\text{nS}] \), blue lines show that \( g_{\text{TRPM2}} = 0.035[\text{nS}] \), and black lines show that \( g_{\text{TRPM2}} = 0.08[\text{nS}] \).
In Fig. 3(a), the burst duration is prolonged, and the influx of the TRPM2 current is directly proportional to the TRPM2 conductance. Increasing the influx of the TRPM2 current increases the membrane potential, and shortens the quiescent duration.

As shown in Fig. 3(b), although the burst duration is long when $V_{\text{TRPM2}} = -20\,[\text{mV}]$, the TRPM2 currents persistently burst. A comparison of Fig. 3(a) and 3(b) reveals that the influx of the TRPM2 current decreases when the TRPM2 reversal potential is low. This contributes to lengthen the burst duration.

The TRPM2 reversal potential is directly proportional to the influx of the TRPM2 current, and inversely proportional to the efflux. The efflux of the TRPM2 current corresponds to a low membrane potential and firing difficulties. In Fig. 3(c), the relationship between the conductance and bursting duration is reversed compared to Fig. 3(a) and (b), because the low reversal potential $V_{\text{TRPM2}} = -50\,[\text{mV}]$ induces the efflux of the TRPM2 current increase as the TRPM2 conductance increases.

**Effects of TRPM2 channel on $\text{Ca}^{2+}$ concentration and channel currents**

The results of the TRPM2 reversal potential in our model were consistent with the physiological experiment [7] as shown in the previous section. In this section, we investigated the mechanism underlying enhancing insulin secretion by activating the TRPM2 channel.

The cytosolic $\text{Ca}^{2+}$ concentration increases while the membrane potential exhibits bursts [12]; the amount of insulin secretion may be inferred from the amplitude and duration of its concentration. Therefore, the amount of insulin secretion corresponds to its area of concentration.

Figures 4 and 5 show time series of the membrane potential $V$ and the cytosolic $\text{Ca}^{2+}$ concentration when the TRPM2 channel is blocked and under the control condition. Figures 4(a) and 5(a) represent time series when the closure of the TRPM2 channel, $g_{\text{TRPM2}} = 0\,[\text{nS}]$, and the control condition, where $g_{\text{TRPM2}} = 0.0252\,[\text{nS}]$ [7] in Figs. 4(b) and 5(b). The TRPM2 reversal potential $V_{\text{TRPM2}}$ is set to $-20\,[\text{mV}]$, because the value is optimal for replicating the physiological experiments as shown in the previous section.

Figures 4 and 5 show that the timing of the burst is consistent with the increase in the cytosolic $\text{Ca}^{2+}$ concentration, which is consistent with the physiological paper [12]. In Fig. 5, the line under the TRPM2 control condition (Fig. 5(b)) rises faster, and returns more slowly to the resting state.

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**Fig. 4.** Time series of the membrane potential under the TRPM2 channel block and control condition. (a) The line denotes that the TRPM2 channel is blocked, i.e., $g_{\text{TRPM2}} = 0\,[\text{nS}]$. (b) The line denotes the control condition, where the TRPM2 is represented as $g_{\text{TRPM2}} = 0.0252\,[\text{nS}]$.

**Fig. 5.** Time series of the cytosolic $\text{Ca}^{2+}$ concentration under the TRPM2 channel block and control condition. (a) The line denotes that the TRPM2 channel is blocked, i.e., $g_{\text{TRPM2}} = 0\,[\text{nS}]$. (b) The line denotes the control condition, where the TRPM2 is represented as $g_{\text{TRPM2}} = 0.0252\,[\text{nS}]$. 507
than the voltage in Fig. 4. In addition, the resting Ca\(^{2+}\) concentration rises, and the amplitude increases. These results indicate that insulin secretion can be increased by activating the TRPM2 channel. To compare these results quantitatively, we calculated the area \(S_1\) of the cytosolic Ca\(^{2+}\) concentration that represents the amount of insulin secretion in Fig. 6. The area, \(S_1\), is calculated using \(\int_{t_1}^{t_2} ([\text{Ca}^{2+}]_c(t) - [\text{Ca}^{2+}]_{\text{Res}}) \, dt\), where \(t_1\) and \(t_2\) are the start and end time of the active state and \([\text{Ca}^{2+}]_{\text{Res}}\) is the average resting Ca\(^{2+}\) concentration. The resting state of the cytosolic Ca\(^{2+}\) concentration is described as when the value of 0.999 < \([\text{Ca}^{2+}]_c(t+1)/[\text{Ca}^{2+}]_c(t)\) < 1.001 is maintained for 5[s] or more. In addition, the active state is defined as when the cytosolic concentration is not in the resting state. Figure 6 shows that the active state is the same as that of the membrane potential. In Fig. 7, the black boxes represent the condition under which the TRPM2 channel is blocked, and white boxes represent the control condition. The calculation conditions are the same as in Fig. 4. The outward and inward currents are represented by the rise and fall of the lines, respectively. Figure 7(a) shows the area \(S_2\) of the currents of all the channels, \(I(t) = I_{\text{KATP}} + I_{\text{SK}} + I_{\text{BK}} + I_{\text{KV}} + I_{\text{Na}} + I_{\text{CaL}} + I_{\text{CaPQ}} + I_{\text{CaT}} + I_{\text{leak}} + I_{\text{TRPM2}}\). In Fig. 7(b)–7(k), the results obtained from calculating the areas \(S_2\) of the individual channel current. In Fig. 7(b), \(I(t) = I_{\text{TRPM2}}\), in Fig. 7(c), \(I(t) = I_{\text{CaL}}\), in Fig. 7(d), \(I(t) = I_{\text{CaPQ}}\), in Fig. 7(e), \(I(t) = I_{\text{CaT}}\), in Fig. 7(f), \(I(t) = I_{\text{SK}}\), in Fig. 7(g), \(I(t) = I_{\text{BK}}\), in Fig. 7(h), \(I(t) = I_{\text{KATP}}\), in Fig. 7(i), \(I(t) = I_{\text{KV}}\), in Fig. 7(j), \(I(t) = I_{\text{Na}}\) and in Fig. 7(k), \(I(t) = I_{\text{leak}}\).

In Fig. 7(a), the inward currents are increased by activating the TRPM2 channel. Increasing the inward currents induces the membrane depolarization to initiate the insulin secretion. In addition, \(S_2\) of each channel current is shown in Fig. 7(b)–7(k).

Figure 7(b)–(e) show results obtained from calculating \(S_2\) of Ca\(^{2+}\) currents. These currents are negative because of the inward currents. All the inward Ca\(^{2+}\) currents increase when the TRPM2 channel is under the control condition. Specifically, activating the TRPM2 channel increases the inward CaL and CaPQ currents (Fig. 7(c) and (d)). This is because the CaL and CaPQ channels are voltage-dependent; thus, these channels are activated when the membrane potential is increased by the activation of the TRPM2 channel. The increases in these inward currents exceed that in the TRPM2 current. This indicates that the TRPM2 channel contributes to enhancing the insulin secretion by increasing the CaL and CaPQ currents.

Figure 7(f)–(i) show the calculation results obtained for \(S_2\) of K\(^{+}\) currents. These currents are positive, because of the outward currents. All the outward K\(^{+}\) currents increased when the TRPM2
Fig. 7. The areas $S_2$ of channel currents during the active states. In (a), $I(t) = I_{\text{KATP}} + I_{\text{SK}} + I_{\text{KV}} + I_{\text{Na}} + I_{\text{CaL}} + I_{\text{CaPQ}} + I_{\text{CaT}} + I_{\text{leak}} + I_{\text{TRPM2}}$, in (b), $I(t) = I_{\text{TRPM2}}$, in (c), $I(t) = I_{\text{CaL}}$, in (d), $I(t) = I_{\text{CaPQ}}$, in (e), $I(t) = I_{\text{CaT}}$, in (f), $I(t) = I_{\text{leak}}$, in (g), $I(t) = I_{\text{SK}}$, in (h), $I(t) = I_{\text{BK}}$, in (i), $I(t) = I_{\text{KV}}$, in (j), $I(t) = I_{\text{Na}}$, and in (k), $I(t) = I_{\text{leak}}$.

channel was under the control condition. The outward KV current, in particular, increased as a result of the TRPM2 channel activation (Fig. 7(i)). This is because the increase in the membrane potential due to the TRPM2 activation activates the voltage-dependent KV channel. Furthermore, the BK channel is activated by the $\text{Ca}^{2+}$ currents that are increased by the TRPM2 channel activation. Thus, the outward BK current is increased by the TRPM2 channel activation (Fig. 7(g)).

Figure 7(j) and (k) show the calculation results of $S_2$ of $\text{Na}^+$ current and leak current. Both inward currents are increased slightly by the TRPM2 channel activation. These results reveal that the TRPM2 channel increases the inward currents. Specifically, the TRPM2 channel activates the
voltage-dependent and Ca\textsuperscript{2+}-sensitive channels with large conductance, and these activation increases the cytosolic Ca\textsuperscript{2+} concentration. This increase in the cytosolic Ca\textsuperscript{2+} concentration leads to the increase of inward currents, then contributes to the membrane activation and prolongment of the burst duration. Consequently, insulin secretion is induced by the TRPM2 channel activation.

4. Conclusion
The activation of the TRPM2 channel has been reported to enhance insulin secretion, and prolong the burst duration in the pancreatic \(\beta\)-cell [7]. In this paper, we incorporated the TRPM2 current into the mathematical model proposed by Riz et al. [6], and investigated the reproducibility of the experimental result [7] and effects of the TRPM2 channel on the membrane potential.

The results of the numerical experiments showed that the activation of the TRPM2 channel prolongs the burst duration when the TRPM2 reversal potential is close to the value observed in the physiological experiments. These results support the relevance of the physiological experiments, and confirm the effects of the TRPM2 channel on insulin secretion. This also indicates that the value of the TRPM2 reversal potential is optimal in terms of efficient insulin secretion.

Furthermore, we investigated the effects of the TRPM2 channel on the other channel’s currents. It was revealed that the TRPM2 channel increases the inward currents by activating the voltage-dependent Ca\textsuperscript{2+}-sensitive channels with large conductance; this activation increases the cytosolic Ca\textsuperscript{2+} concentration. These results imply that this is the mechanism through which insulin secretion is increased by the TRPM2 channel activation.

We have constructed a mathematical model including the TRPM2 channel. The effects and relationship between multiple ion channels in the pancreatic \(\beta\)-cells are still physiologically unknown in detail. It is an important future issue to investigate the dynamics of our model by detailed analyses such as a bifurcation analysis.

Pancreas consists of hundred millions of \(\beta\) cells and they are connected via gap-junctional connections. It may be beneficial to construct a network of our proposed model for understanding overall network dynamics of the pancreas. In addition, our theoretical investigation contributes to a new treatment for diabetes by activating TRPM2 channel. There exist several drugs such as calmodulin and ex-4, which are known as a TRPM2 channel activator [13]. Using our model, we can design and control the timing and the duration of drug perturbation for diabetes.

Finally, our model of TRPM2 channel is a simple conductance model, so that it can also be incorporated into neural models. Recently it has been reported that the TRPM2 channel could be a therapeutic target for treating a wide variety of brain diseases, including Alzheimer’s disease, neuropathic pain, bipolar disorder, and Parkinson’s disease [14]. It would be a future problem to investigate the effects of TRPM2 channel to treatments for such diseases.

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