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ON THE MECHANISM OF SPIKING AND BURSTING IN EXCITABLE CELLS

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A mathematical model previously developed to explain β-cell membrane potential oscillations has been modified to accommodate the external variation of K^+, Na^+ and Ca^{2+} concentrations. Our model, which is applicable to excitable cells, incorporates the barrier kinetics, Hodgkin-Huxley-type gating mechanism, and an electrogenic Na^+-K^+ pump. Numerical solutions of our model are in agreement with many of the experimental results reported in the literature on excitable cells.

1. Introduction

A wide variety of nerve cells, secretory cells and muscle fibers display oscillations in the membrane potential, which is known as bursting. This consists of an active phase during which membrane action potentials or spikes are generated and a silent phase during which the membrane is hyperpolarized. Bursting is interesting because it reflect the regulation of ion permeation at the molecular level.

Experimental evidence indicates that bursting is due to an interaction of ionic channels in the cell membrane, which open up at different rates; both 'slow' and 'fast' outward currents are carried by K^+ through the calcium-sensitive K^+ channel [1,2] and a voltage-gated K^+ channel [3], respectively. In nerve cells, a substantial fraction of the fast inward current is carried by Na^+, while that of the slow inward current is carried by Ca^{2+} [2–4]. In secretory cells [4–6] and muscle fibers [7], on the other hand, both the fast and slow inward currents are carried primarily by Ca^{2+} through a voltage-gated calcium channel.

Based on the experimental work of Atwater et al. [5], Chay and Keizer [8] have formulated a mathematical model for pancreatic β-cell bursting using the 'equivalent circuit' model of Hodgkin and Huxley [9]. In particular, their model incorporates a calcium current, a calcium-dependent K^+ current, a voltage-dependent K^+ current, and a leak current. Although this model illustrates quantitatively the contribution of several variables to the experimental results, additional transport mechanisms such as an Na^+-K^+ pump should be added to the model to account for other observed effects, such as external variation of K^+, Na^+ and Ca^{2+}. Since the Na^+-K^+ pump was not included, their model is not capable of describing the effect of changing external concentrations of Na^+ and K^+ on the bursting activity. Furthermore, since large changes in ionic species are involved as the external salt concentration varies, large changes in the resting potential of ion occur. This means that a linearization around a fixed resting potential, as generally used in the Hodgkin-Huxley model, is not appropriate. To account for the external variation of salt and to include the moderating effect of external Ca^{2+}, we include the electrogenic Na^+-K^+ pump in the model and replace the equivalent circuit model with a kinetic model.

In the following, we formulate a mathematical

model for bursting of the excitable membranes using the barrier kinetic model [10] and incorporating the gating mechanism of Hodgkin and Huxley [9]. We then apply it to study the bursting behavior of β-cells.

2. Membrane current

The voltage equation which governs the change in the charge density, q, on the surface of membrane can be written as

$$I_{ext} = C_m dV/dt + I_{ionic}, \tag{1}$$

where I_{ext} is the external current applied, V the membrane potential (i.e., the difference in electrostatic potential between the interior surface and the exterior surface), C_m the membrane capacitance per unit area, and I_{ionic} the total ionic current. Total ionic current is the sum of the contributions of the following currents:

$$\begin{aligned} I_{ionic} &= I_K(Ca) + I_K(V) + (1 - r_{Na\text{-}K}) I_{Na\text{-}K} + 2I_{Ca}(V) + I_{Na}(V) \\ &\quad + 2I_{Cap} + 2I_{CaL} + I_{NaL} + I_{Cl} + (r_{Na\text{-}Ca} - 2) I_{Na\text{-}Ca}, \end{aligned} \tag{2}$$

where $I_K(Ca)$ and $I_K(V)$ are, respectively, the currents carried by K^+ through the calcium-sensitive and voltage-dependent K^+ channels; $I_{Ca}(V)$, I_{Cap} and I_{CaL} are those carried by Ca^{2+} through the voltage-dependent Ca^{2+} channel, Ca^{2+}-ATPase and calcium leak, respectively; $I_{Na}(V)$ and I_{NaL} those carried by Na^+ through the voltage-dependent channel and Na^+ leak, respectively; I_{Cl} that carried by Cl^-; and $I_{Na\text{-}Ca}$ that carried by Ca^{2+} through the Na^+-Ca^{2+} exchange system. In the same equation, $r_{Na\text{-}Ca}$ is the coupling ratio of Na^+ to Ca^{2+}, $r_{Na\text{-}K}$ that of Na^+ to K^+, and $I_{Na\text{-}K}$ the current carried by K^+ through the Na^+-K^+ pump and takes the followed form [11]:

$$I_{Na\text{-}K} = \frac{V_{Na\text{-}K}}{(1 + K_{Kp}/[K]_{out})^2 (1 + K_{Nap}/[Na]_{in})^3 (1 + [Ou]/K_{Ou})}. \tag{3}$$

where $[K]_{out}$ is the K^+ concentration outside, $[Na]_{in}$ the intracellular Na^+ concentration, [Ou] the inhibitor (i.e., ouabain) concentration, and K_{Kp}, K_{Nap} and K_{Ou} the effective dissociation constants of K^+, Na^+ and inhibitor at the binding sites of the pump, respectively.

For the binding of the jth ion to a site on the inner surface of the membrane, we expect the dissociation constant K_j (i.e., K_{Nap}) to show voltage dependence of the form [12,13]:

$$K_j = K_j^* \exp(-A_j V Z_j F/RT - w/RT). \tag{4}$$

where A_j is a parameter whose value is between zero and unity, and K_j^* the dissociation constant of ion from a neutral binding site, w the chemical work necessary to remove 1 mol of adsorbed ions from the surface to the solution phase, Z_j the valency of the jth-type ion, F the Faraday constant, and RT has its usual meaning. For the adsorption of jth-type ions on the outer surface of the membrane, the dissociation constant in eq. 3 (i.e., K_K) takes the form [13]

$$K_j = K_j^* \exp(Z_j F V(1 - A_j)/RT - w/RT). \tag{5}$$

It is reasonable to assume w to be independent of the ionic concentrations, and thus we redefine K_j^* by combining it with $\exp(-w/RT)$.

In eq. 2, I_j is the current carried by the jth ion through the jth channel and takes the following form:

$$I_j = \rho_j f_j(V), \tag{6}$$

where ρ_j is the probability of opening the jth channel, and f_j a voltage-dependent flux term.

3. Exoression for f_j

According to the barrier kinetic model [10], the expression for f_j is given by

$$f_j = F k_j \{[j]_{os} \exp(-FZV/2RT) - [j]_{is} \exp(FZV/2RT)\}, \tag{7}$$

where k_j is the 'jumping' constant of the jth ion, and $[j]_{os}$ and $[j]_{is}$ the concentrations of jth ion on the outer and inner surfaces of the membrane, respectively.

Now, we assume that the concentration of the jth ion at the inner surface of the membrane is proportional to that of the internal medium. We

also assume that the concentration of the jth ion at the outer surface is proportional to that of the outer medium with the same proportionality constant. That is, by defining ψ to be the potential of the membrane surface taking the reference in the solution phase, we have

$$[j]_{is} = e^{z_j F\psi/RT}[j]_{in} = \beta_j[j]_{in}; \quad (8)$$

and

$$[j]_{os} = \beta_j[j]_{out}, \quad (9)$$

where we have introduced β_j, the partition coefficient of the jth type ions, and $[j]_{in}$ and $[j]_{out}$, the intracellular and extracellular concentrations of the jth ion, respectively.

Using eqs. 8 and 9, we find from eq. 7 that

$$f_j = P_j\{[j]_{out}\exp(-FZV/2RT) - [j]_{in}\exp(FZV/2RT)\}. \quad (10)$$

where P_j is the permeability coefficient of the jth ion times the Faraday constant and is defined as Fk_j times β_j.

4. The probability of the opened state for the channels

Lux et al. [14] have shown the existence of the calcium-sensitive K^+ channel in excitable cells, and Hodgkin and Huxley [9] have shown that the spiking activity is due to the voltage-gated inward and outward currents. Thus, there are three channels which are of importance in the excitable cells: a Ca-sensitive K^+ channel, a voltage-gated K^+ channel, and voltage-dependent Na^+ and/or Ca^{2+} channels.

An expression for the probability of opening a Ca-sensitive K^+ channel may be obtained as follows [12]: If we assume a cooperative scheme in which n_H Ca^{2+} must bind simultaneously to sites on a receptor (in order to open a calcium-sensitive channel), we may write

$$\rho_k(Ca) = \frac{1}{\{1+(K_{KCa}/[Ca]_{in})^{n_H}\}\{1+[Qu]/K_{Qu}\}}, \quad (11)$$

where K_{KCa} and K_{Qu} are, respectively, the effective dissociation constants of Ca^{2+} and inhibitor from the receptor enzyme; [Qu], the concentration of the inhibitor such as guanine; and n_H, the Hill coefficient whose value was found to be 3 in the anterior pituary clone membrane [12].

According to Hodgkin and Huxley [9], there are three variables which determine the probability of opening of the voltage-gated channels: The probability of opening for the inward current is determined by m (the activation) and h (the inactivation):

$$\rho_1 = m^3h. \quad (12)$$

The probability of opening of the channel responsible for the outward current is determined by n

$$\rho_K(V) = n^4. \quad (13)$$

Each of these variables, m, h and n, obeys a differential equation of the following form:

$$dx/dt = [x(\infty) - x]/\tau_x. \quad (14)$$

where x stands for m, h or n, and $x(\infty)$ and τ_x are, respectively, given by

$$x(\infty) = \alpha_x(V_x^*)/[\alpha_x(V_x^*) + \beta_x(V_x^*)]. \quad (15)$$

and

$$\tau_x^{-1} = \lambda_x[\alpha_x(V_x^*) + \beta_x(V_x^*)]. \quad (16)$$

Here, α_x and β_x are defined as usual for $x = m$, h and n in the Hodgkin-Huxley model, V_x^* is related to V by [1,8]

$$V_x^* = V + V_x, \quad (17)$$

and λ_x depends on the activation and inhibitor concentrations [15] and also on the temperature, such that it is proportional to the Hodgkin-Huxley's $\phi = 3^{(T-6.3)/10}$, where T is the temperature in Celsius.

There is evidence that ions such as Ca^{2+} are adsorbed at the sites of the outer surface of membrane and that the number of adsorbing sites are finite [16]. If we assume that the ion responsible for the inward current exhibits a saturation effect, we have

$$\rho_I = m^3h/(1+[I]_{out}/K_I), \quad (18)$$

where [I] is the concentration of the ion such as

Na^+ or Ca^{2+}, and K_I the apparent dissociation constant of that ion from the receptor site.

5. The intracellular ionic concentrations

The change in intracellular K^+ concentration with time depends on the inward current carried by K^+ through the Na^+-K^+ pump and the outward K^+ current through the voltage-gated and calcium-sensitive K^+ channels. Thus, we have

$$d[K]_{in}/dt = (I_K(V) + I_K(Ca) + I_{Na\text{-}K})/R, \quad (19)$$

where R is the ratio of the volume to the surface of the cell times the Faraday constant.

Similarly, the change in intracellular Na^+ with time is due to the Na^+ currents through the Na^+ channel, Na^+-K^+ pump, and Na^+-Ca^{2+} exchange system:

$$d[Na]_{in}/dt = (I_{Na}(V) + I_{NaL} + r_{Na\text{-}Ca} I_{Na\text{-}Ca} - r_{Na\text{-}K} I_{Na\text{-}K})/R, \quad (20)$$

The rate of change of the intracellular calcium, on the other hand, depends on the calcium currents through the voltage-gated Ca^{2+} channel, leak, Ca^{2+} pump (i.e., Ca^{2+}-ATPase), Na^+-Ca^{2+} exchange system, and uptake and release of ionized calcium by the mitochondria and/or endoplasmic reticulum. Thus, we can write

$$d[Ca]_{in}/dt = f[I_{Ca}(V) + I_{DNP} - P_{gl}[Ca]_{in} + I_{Cap} + I_{CaL} - I_{Na\text{-}Ca}]/R. \quad (21)$$

where f is the fraction of ionized Ca^{2+} inside the cell [17]; P_{gl}, the permeability of intracellular Ca^{2+} through the mitrochondrial membrane; I_{DNP}, the current that accounts for releasing Ca^{2+} from mitochondria by the action of 2,4-dinitrophenol (DNP). Note that k_{gl} is sensitive to variation of glucose.

6. Application to β-cells

The work of Atwater et al. [5] on β-cells and of Morris and Lecar [7] on barnacle muscle fibers shows that the inward current is due to the movement of Ca^{2+} through the voltage-gated Ca^{2+} channel. Thus, we find from eq. 18 that

$$\rho_{Ca} = \rho_I = m^3 h/(1 + [Ca]_{out}/K_{Ca}). \quad (22)$$

In order to facilitate our computation, we make the following simplifications: The exponential factor in eqs. 4 and 5 is taken to be unity; i.e., we assume all the dissociation constants to be constant. We also assume $I_{Ca\text{-}Na}$ to be very small because there is no strong evidence that the Na^+-Ca^{2+} exchange system plays any important role in these cells. Since there is no experimental evidence [6,18,19] that Na^+ affects the membrane potential, we assume $I_{Na}(V)$ to be very small. There should, however, be a significant inward Na^+ current to maintain a constant Na^+ flux. We assume that this inward Na^+ current is due to a leak, i.e., we let $\rho_{NaL} = 1$. It has been shown experimentally that there is a significant amount of calcium leak in excitable cells [20]; thus, we also let $\rho_{CaL} = 1$.

There are some ionic currents which are insensitive to an external variation of ions and chemical agents. The current due to Cl^- should be very insensitive, since the earlier studies by Dean and Mathews [21] demonstrate that a reduction of external Cl^- to 12 mM does not affect β-cell membrane potential. The current carried by Ca^{2+} through the Ca^{2+}-ATPase and the leak currents due to Na^+ and Ca^{2+} should also be insensitive. Thus, we combine I_{Na}, I_{Cap}, I_{Cl} and I_{CaL} in eq. 2 and write

$$I_L = I_{NaL} + I_{Cap} + I_{CaL} + I_{Cl} = I_L^*\{\exp[-F(V - V_L)/2RT] - \exp[F(V - V_L)/2RT]\}, \quad (23)$$

where I_L^* and V_L are the effective leak current and potential, respectively.

In order to simplify our computation further we combine I_{Cap} and $P_{gl}[Ca]_{in}$ in eq. 21 and define

$$k_{Ca}[Ca]_{in} = P_{gl}[Ca]_{in} - I_{Cap}. \quad (24)$$

With these simplifications we apply our model to the study of the β-cell bursting activity

7. Results

The differential equations developed in the previous sections were integrated by using the

Table 1

Values of parameters in the model

The initial conditions were $V = -55$ mV, $[Na]_{in} = 20$ mM, $[K^+]_{in} = 130$ mM, and $[Ca]_{in} = 1$ μM. The external salt concentrations were kept at $[K^+]_0 = 5$ mM, $[Ca^{2+}]_0 = 2$ mM, and $[Na^+]_0 = 145$ mM. The Na^+-K^+ ratio $r_{Na\text{-}K}$ taken to be 1.5.

Parameter	Numerical value
C_m (μF cm^{-2})	1
P_{KCa} (A cm mol^{-1})	2.4×10^{-3}
P_{KV} (A cm mol^{-1})	2.0
P_{Ca} (A cm mol^{-1})	2.6×10^{3}
P_{Na} (A cm mol^{-1})	4.0×10^{-4}
P_{CaL} (A cm mol^{-1})	2.0×10^{-3}
I_L^* (μA cm^{-2})	7.0×10^{-2}
$V_m = V_h$ (mV)	50
V_n (mV)	30
V_L (mV)	−40
K_{CA} (mM)	0.01
K_{KCa} (μM)	1
K_{Kp} (mM)	1
K_{Nap} (mM)	30
R (cm C mol^{-1})	25
f	0.1
k_{Ca} (A cm mol^{-1})	80
$V_{Na\text{-}K}$ (μA cm^{-2})	0.8
λ_m^{-1}	3
λ_h^{-1}	2.8
λ_n^{-1}	3
n_H	3

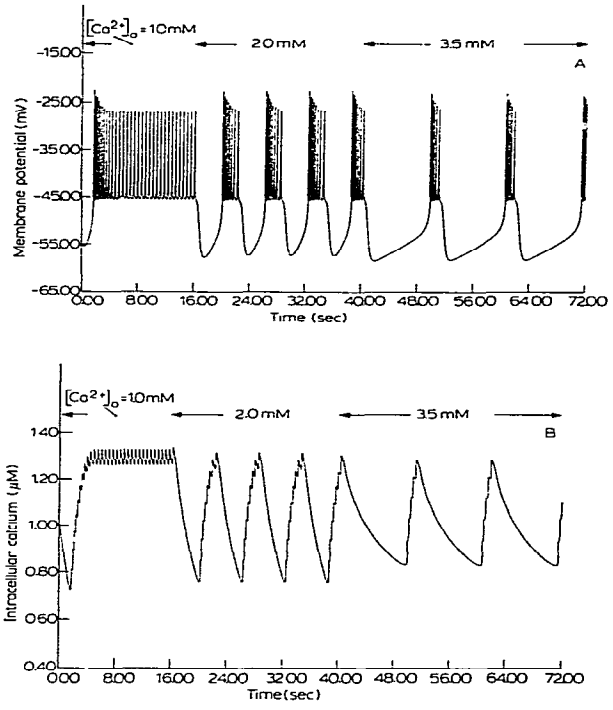

Fig. 1. The effect of varying external Ca^{2+} level. The external calcium was increased at 16 and 40 s. Panel A shows a bursting behavior of the membrane potential, and panel B shows the associated changes in concentration of intracellular Ca^{2+}.

Runge-Kutta-Fehlberg method with automatic estimation of local error and step size adjustment. This method is applicable to the solution of stiff differential equations, such as those of the Hodgkin-Huxley model. The size of absolute and relative errors required in the integration code was taken to be 10^{-7}. The upper bound on the step size was taken to be 0.5. The values of parameters used in most of our computations are given in table 1. Whenever values other than those in table 1 were used, we list them in the figure captions.

Fig. 1A shows effects of varying external Ca^{2+} concentration on the membrane potential (which is elicited by the addition of glucose), and fig. 1B shows the effect on the internal calcium concentration. Note that the amplitude of bursts diminishes at very low calcium concentrations. Also, note that increasing external Ca^{2+} lengthens the duration of the hyperpolarizing phase and causes a decrease in spike duration. This is consistent with the experimental observations on β-cells (see fig. 1 of ref. 19; fig. 4 of ref. 6; and fig. 4 of ref. 22). In agreement with the experimental findings (fig. 4 of ref. 6 and fig. 9 of ref 19), the frequency of the spikes during a burst is reduced when the external calcium concentration decreases. Unlike the experiment of Meissner and Preissler [6] but in agreement with that of Ribalet and Beigelman [19], the amplitude of spikes remain constant at high external calcium level. It is interesting to note from fig. 1B that the burst pattern of intracellular Ca^{2+} resembles that of pH in a synthetic membrane carrying immobilized acetylcholinesterase [23].

Fig. 2 shows membrane potential oscillations induced by the addition of glucose in the presence of various K^+ concentrations. At the physiological

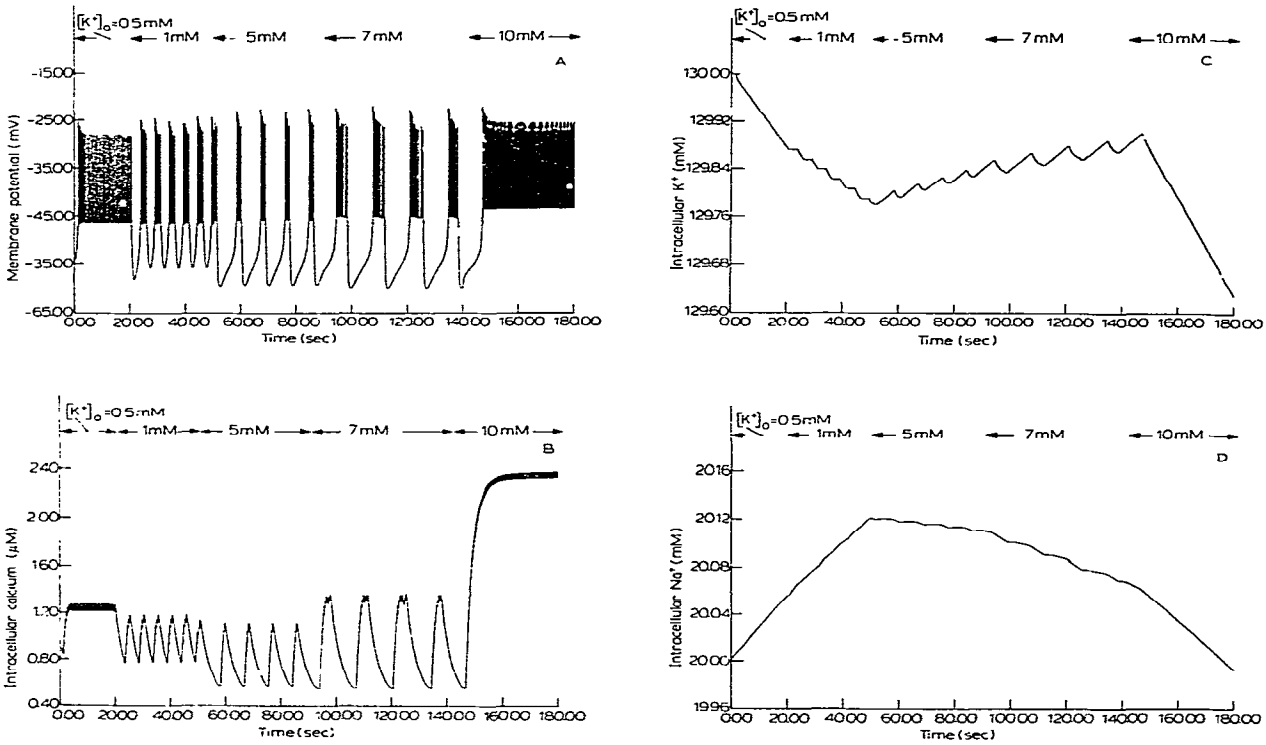

Fig. 2. The effect of varying external K^+ level on the bursting pattern. The external K^+ level was increased at 20, 50, 90 and 140 s. Panels A–D show a bursting pattern of membrane potential, intracellular calcium, sodium and potassium, respectively. Here, we used the value $P_{KCa} = 0.002$ A cm mol^{-1} and $V_{Na\text{-}K} = 1.6\ \mu A/cm^2$ for this computation.

$[K^+]_0$, the membrane potential oscillates in a burst pattern. At lower $[K^+]_0$, the burst frequency is increased considerably and the potential of silent phases is depolarized significantly while the potential at plateau of bursts remains unchanged. This agrees well with the experimental observations on β-cells [5,24]. Note that at very low and high $[K^+]_0$, the silent phases are suppressed and the membrane potential oscillates continuously with a spiking mode. As explained previously [24,25], the disappearance of burst is due to the following reasons: At very low $[K^+]_0$ the Na^+-K^+ pump becomes inactive and thus the polarization phase is inhibited. At high external K^+, the Ca-sensitive K^+ channel becomes ineffective due to a low flux in K^+.

In fig. 2C and D we show how little intracellular K^+ and Na^+ change in response to an external variation of K^+. These figures suggest that the intracellular levels of these ions do not play any significant role in controlling membrane oscillations in β-cells. In fact, we have found that intracellular K^+ and Na^+ change very little with all the external variations we have investigated in this work.

The work of Meissner and Preissler [6] shows that external Na^+ is necessary for the occurrence of normal burst activity. They have observed that when Na^+ was removed from the external medium, the membrane remained depolarized almost at the plateau potential level, the periodic repolarization phases were suppressed, and a continuous spike

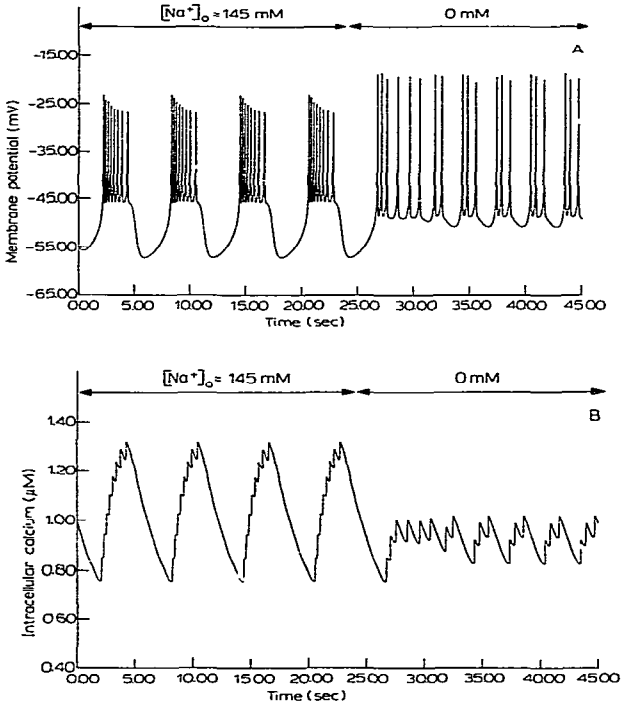

Fig. 3. The effects of varying external Na^+ level. The external Na^+ was removed at 24 s. Panels A and B illustrate a bursting of the membrane potential and intracellular calcium, respectively. The value of λ_m was increased to 1 when the Na^+ was removed from the system.

activity was established. By increasing the value of λ_m, we were able to simulate this experimental observation in fig. 3. The increase of λ_m is justified considering the fact that Ribalet and Beigelman [19] have found a competitive inhibitor such as Mn^{2+} inhibits the opening of the voltage-dependent calcium channel by affecting the rate of depolarization. Interestingly, the bursting pattern in the absence of Na^+ resembles that seen in the pacemaker neuron [2,26,27].

A portion of fig. 4A and B illustrates the effect of glucose on bursting activity. These figures also show the effect of TEA * at various glucose concentrations. Notice that an elevation of glucose results in elongation of the active phase and shortening of the silent phase. Beyond a certain glucose concentration, the bursting activity ceases completely and continuous spike activity persists (see the activity between 80 to 100 s). Although it is not shown here, the depolarization phase is inhibited completely for the value of k_{Ca} less than 40 A cm s^{-1}, i.e., for very low glucose concentration. The effect of glucose stimulated in this figure agrees very well with the experimental findings (see fig. 1 of ref. 6 and also fig. 4 of ref. 28). It may be seen from this figure that TEA suppresses the burst pattern that is elicited by glucose, and also induces isolated action potentials of large ampli-

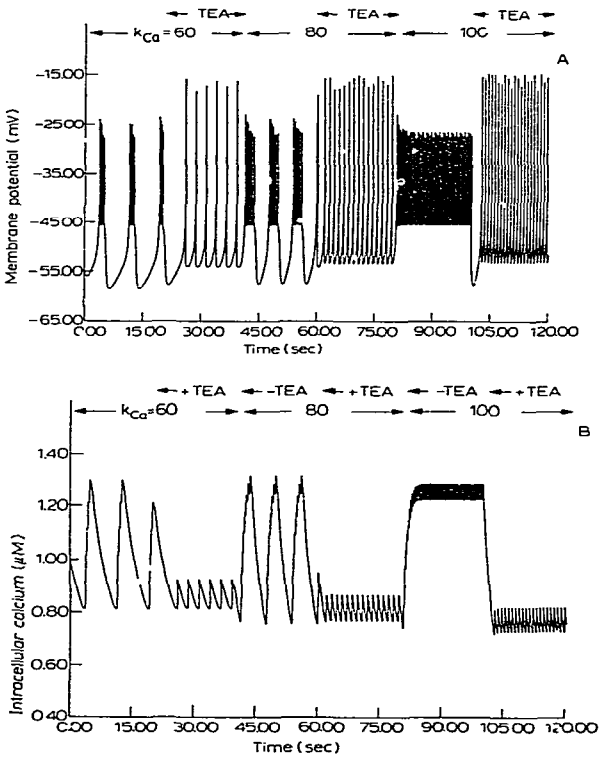

Fig. 4. The effect of glucose and TEA on the bursting activity. The glucose concentration was increased at 40 and 80 s. TEA was added at 20, 60 and 100 s, and removed at 40 and 80 s. The values of k_{Ca} used for this computation are listed in the figure, and the value of λ_n was taken to be 1/6 when TEA was added to the system.

* TEA, tetraethylammonium ions.

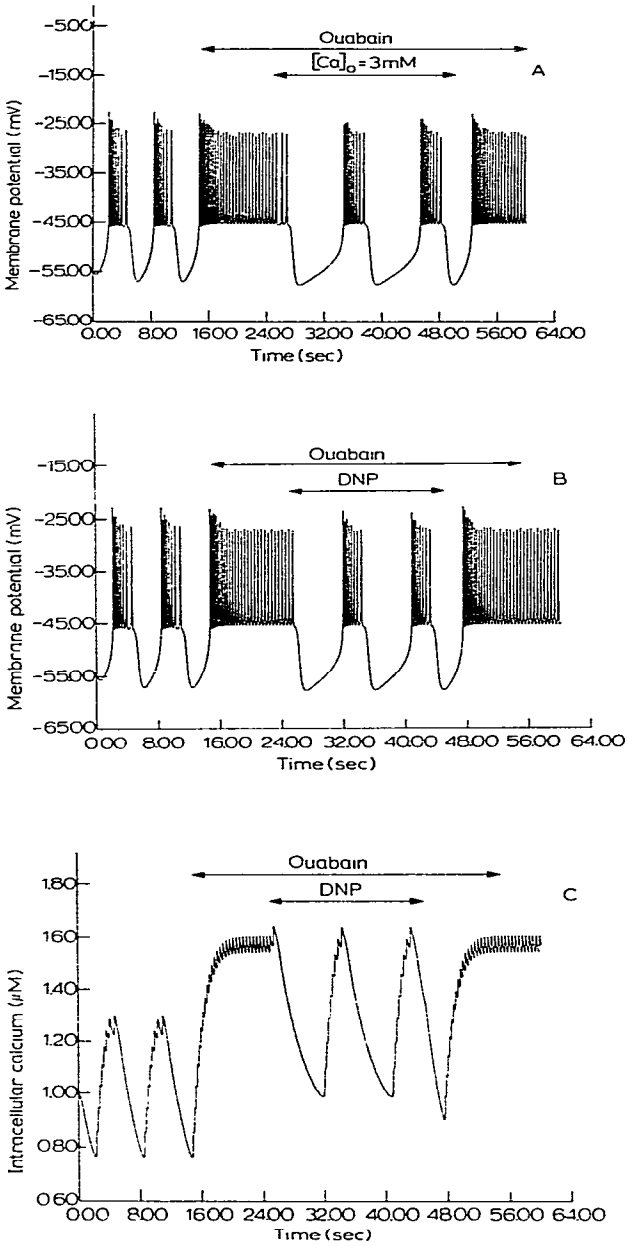

Fig. 5. The effect of external Ca^{2+} (A) and DNP (B and C) on spiking activity induced by an addition of ouabain. We used the value $[Qu]/K_{Qu} = 1.5$ (see eq. 3) and $I_{DNP} = 0.03\ \mu A/cm^2$ (see eq. 21) in this computation.

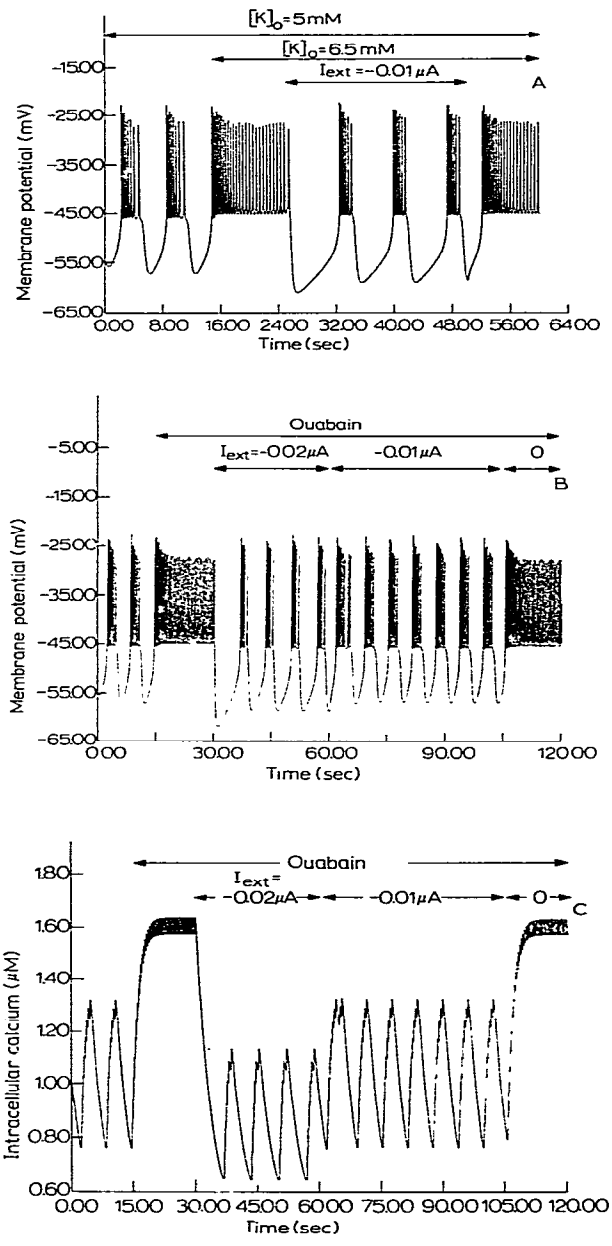

Fig. 6. A restoration of bursting by an injection of hyperpolarization current. The spiking was induced by an addition of K^+ (A) or ouabain (B and C). The currents shown here are in $\mu A/cm^2$.

tude and prolonged duration. It may also be seen that the spike frequency is elongated at lower glucose concentration and that the potential at the foot of each spike becomes depolarized as the glucose concentration increases. This response of membrane potential to TEA also agrees well with the experimental results of Atwater et al. (see fig. 4 of ref. 28).

Fig. 5 shows changes of the membrane potential as ouabain, an Na^+-K^+ pump inactivator, is added to a β-cell exhibiting glucose-induced bursting activity. Note that an increase in external calcium (fig. 5A) or addition of DNP (fig. 5B), an agent which releases Ca^{2+} from the mitochondria, results in the restoration of bursting activity. Consistent with fig. 7 of ref. 18, ouabain has the effect of abolishing the bursting activity, while DNP and $[Ca^{2+}]_0$ have the opposite effect. Fig. 5C shows changes of intracellular calcium which occur in response to additions of ouabain and DNP to an external medium.

Fig 6 shows the restoration of the silent phase by an injection of hyperpolarizing current as continuous spike activity is elicited by increasing extracellular K^+ level (fig. 6A) or by an addition of ouabain (fig. 6B). Addition of ouabain or increase in $[K^+]_0$ inhibits the silent phases; injection of a hyperpolarizing current restores them. With a termination of current injection, the original spiking pattern is restored as shown in this figure. This is consistent with the experimental finding of Ribalet and Beigelman on β-cells (see fig. 8 of ref. 18). Fig. 6C illustrates changes of the intracellular calcium in response to applied external currents when the depolarization phase is induced by an addition of ouabain.

Since in β-cells, quinidine causes shortening and eventual suppression of the silent phases between bursts, it has been proposed [19] that this agent inhibits the Ca-sensitive K^+ permeability which is responsible for membrane repolarization. Fig. 7 shows the effects of quinidine and Ca^{2+} on electrical activity elicited by the addition of glucose. Note that our simulation result agrees with the experimental result of Ribalet and Beigelman (see fig. 10 of ref. 19).

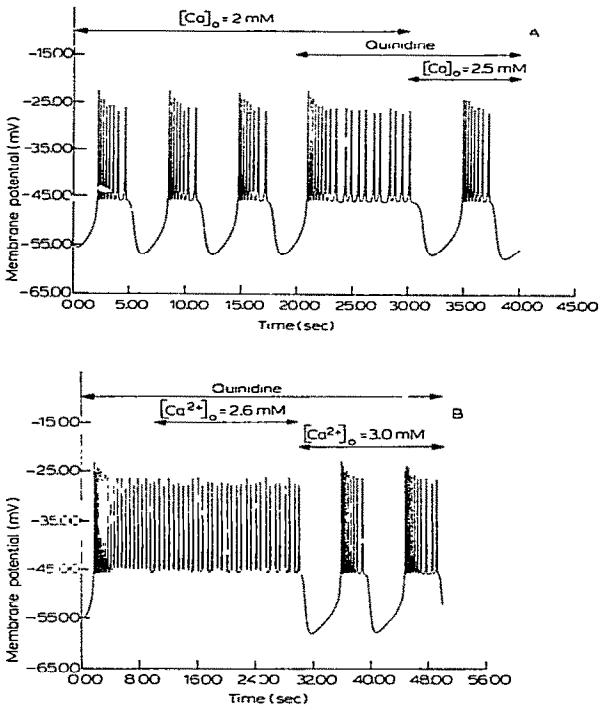

Fig. 7. The effect of quinidine and of varying concentration of Ca^{2+}. The concentration of quinidine divided by its dissociation constant (i.e., $[Qu]/K_{Ou}$ in eq. 11) was taken to be 1/23 in A and 1/11 in B.

8. Discussion

This analysis was carried out to explore the effect of the external variation of Ca^{2+}, Na^+ and K^+ on the bursting behavior of excitable cells [5,7]. We were able to extend the model of Chay and Keizer [8] to include the moderating effect of external variation of these ions. Our model is an approximation to a highly complex process that is taking place in the excitable cells, such as the β-cell, barnacle muscle fibers and cardiac purkinje fibers [30]. Despite its limitations, the general features of our simulations are in good agreement with the experimental observations on the β-cell.

Our model, however, displays much quicker responses to an external variation of ions. For

example, according to our model oscillations in membrane potential approach a new 'steady state' in only a few milliseconds after Na^+ is removed from an external medium (see fig. 3), but experimentally about 10 s are required [6]. This may be because eqs. 8 and 9 are only approximations and a diffusion process may be important, as pointed out by Scriven [29]. Our model also displays much faster responses to agents such as quinidine and ouabain. This may be because the formation of a receptor complex is not a very fast process and that it therefore takes a few seconds until eqs. 11 and 3 are applicable.

Our model describes intracellular calcium changes inside the cell in response to electrical activity and external variation of K^+, Na^+ and Ca^{2+}. Based on our model, intracellular Ca is a primary agent, but not the only one, which triggers bursting. A Hodgkin-Huxley-type gating mechanism results in fast spiking, as well as bursting, through the voltage-sensitive Ca channel.

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