THEORY OF THE EFFECT OF EXTRACELLULAR POTASSIUM ON OSCILLATIONS IN THE PANCREATIC β-CELL

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ABSTRACT Based on the observation that potassium ions are compartmentalized near the surface of pancreatic β-cells in mouse islets (Perez-Armendariz, E.M., I. Atwater, and E. Rojas 1985, *Biophys. J.* 48:741–749), we present a theoretical treatment of the effect of external potassium on oscillations in the pancreatic β-cell. Our model includes the effects of ionic diffusion, the Ca^{2+}-activated K^+ channel, voltage-gated K^+ and Ca^{2+} channels, and some of the effects of glucose. It is described by four ordinary differential equations. Numerical integration of these equations allows us to examine the effect of glucose, external K^+, quinine, and tetraethylammonium ion (TEA) on the oscillations in membrane potential, intracellular Ca^{2+}, and compartmentalized K^+. The results are in good agreement with experiment.

INTRODUCTION

The voltage across the plasma membrane of the mouse pancreatic β-cell is observed to oscillate in a series of bursts when whole islets are perfused with glucose concentrations of the order of 10 mM (Dean and Matthews, 1970). A key to understanding this phenomenon was the discovery of a Ca^{2+}-gated K^+ permeability in the plasma membrane (Atwater et al., 1979). Based on this discovery of the existence of voltage-gated channels for both K^+ and Ca^{2+} in the β-cell (Ribalet and Beigelman, 1979), we have recently proposed a minimal mathematical model for these oscillations (Chay and Keizer, 1983). The model consists of the following: potassium channels with a conductance that is activated by the binding of intracellular Ca^{2+}; Hodgkin-Huxley–like conductances for K^+ and Ca^{2+} (Ca^{2+} replaces Na^+ in the Hodgkin-Huxley model); and a sink for intracellular Ca^{2+} that is activated by glucose. The sink for Ca^{2+} corresponds to the fact that one action of glucose is to induce uptake of Ca^{2+} into intracellular stores, possibly mitochondria (Andersson, 1983; Rorsman et al., 1984; Bergsten and Hellman, 1984). This model is the minimal one that gives rise to burst oscillations. Numerical calculations with the model (Chay and Keizer, 1983; Lee et al., 1983) are in good agreement with experimental measurements of the voltage oscillations and predict, as well, oscillations in the intracellular Ca^{2+} concentration. Because of its high intracellular concentration, changes in K^+ within the β-cell were neglected in our minimal model. Since changes in extracellular K^+ concentration are not required to model the voltage oscillations, extracellular K^+ was not included as a variable in our minimal model.

A recent and seemingly paradoxical experimental observation on mouse islets convinced us that it would be of interest to include changes in extracellular K^+ in our model. Using $^{86}Rb^+$ as a marker for the K^+ efflux in the β-cell, a substantial increase in $^{86}Rb^+$ efflux was observed when the glucose concentration in the perfusion medium of rat or mouse islets was increased from 8.3 to 16.7 mM or higher (Lebrun et al., 1982, 1983). This seems paradoxical since, according to one of the prevailing hypotheses (Atwater et al., 1980), glucose contributes to a decrease in permeability of Ca^{2+}-activated K^+ channels. Indeed, this decreased permeability is supposed to be responsible for the depolarization of the membrane at the onset of each burst. The $^{86}Rb^+$ efflux experiments have been offered as "evidence that glucose ... does not inactivate the Ca^{2+}-sensitive modality of K^+ extrusion" (Lebrun et al., 1983).

This apparent paradox can be resolved qualitatively within the context of our minimal model. The resolution is based on a comparison of the time scale on which the $^{86}Rb^+$ efflux measurements are made, with the time scale on which the Ca^{2+}-activated K^+-channel opens and closes. According to our calculations, the intracellular Ca^{2+} concentration both decreases and increases during a burst on a time scale the order of 10 s. This means that the Ca^{2+}-gated K^+ permeability is turned on and off on this time scale. The $^{86}Rb^+$ measurements, on the other hand, are made every minute and so measure the efflux averaged over several bursts. In our minimal model glucose produces an average increase in the intracellular Ca^{2+} concentration under conditions of steady state bursting. This tends to open up the Ca^{2+}-activated K^+ channel on the average, increasing K^+ efflux. Furthermore, the depolarization of

the membrane potential during a burst opens up the voltage-gated K^+ channel. Thus the minimal model qualitatively predicts a net average increase in K^+ efflux, even though the Ca^{2+}-gated K^+ channel opens and closes during each burst.

Shortly after it occurred to us how to resolve the $^{86}Rb^+$ efflux data using our minimal model, Atwater (private communication) informed us that sustained oscillations had been observed in the concentration of extracellular K^+ in mouse pancreatic islets (Perez-Armendariz et al., 1985). As both of these experiments depend on the efflux of K^+ into the extracellular medium, we decided to elaborate our minimal model by adding extracellular K^+ as a variable. Here, we show how that can be accomplished and compare our numerical results with experiment. Before doing so, we recapitulate the ideas that go into our minimal model, discussing its strengths and weaknesses in greater detail.

CRITIQUE OF THE MINIMAL MODEL

Our minimal model (Chay and Keizer, 1983) was devised to explain the steady voltage bursting of β-cells that occurs 10 min or so after an islet is perfused with 6–17 mM glucose. This, however, is not the only glucose-stimulated electrical activity that is observed in the β-cell. In addition to the steady behavior, there is a rich transient activity immediately after exposure to glucose. This activity has been correlated (Meissner, 1976) with the nadir observed in the insulin release rate from the β-cell (Hedeskov, 1980; Wollheim and Sharp, 1981). The origin of this transient electrical activity in terms of ion channels has so far eluded electrophysiologists. As a consequence, we made no effort to include that transient phenomena in our minimal model. The minimal model includes only those ion channels that were generally acknowledged to be crucial to the bursting phenomenon, namely, voltage-regulated Ca^{2+} and K^+ channels (Ribalet and Beigelman, 1979) and Ca^{2+}-activated K^+ channels (Atwater et al., 1979). Glucose appears in our minimal model in its role as a trigger for the uptake of glucose into intracellular stores. This phenomenon is well documented experimentally (Andersson, 1983; Rorsman et al., 1984). According to our numerical work (Chay and Keizer, 1983), this minimal collection of effects reproduces a broad range of experimental observations on the steady state of bursting.

The minimal model is not, of course, complete. Indeed, it cannot produce transient behavior when glucose is added to the β-cell in the presence (Atwater et al., 1979) or absence (Meissner, 1976) of quinine. There are many other aspects of β-cell metabolism that are missing or incomplete in our minimal model. For example, the treatment of Ca^{2+} handling in the cytosol of the β-cell is primitive. Our minimal model includes only the uptake of Ca^{2+} by intracellular stores and rapid association with binding sites in the cytoplasm. The effect of the Ca^{2+}-ATPase pump, the Na^+-Ca^{2+} exchange mechanism, and other known Ca^{2+} regulatory mechanisms (Wollheim and Sharp, 1981) are not explicitly included. The minimal model also neglects the effect of intracellular pH, which is thought to be important in insulin release (Pace, 1984), and which inhibits the Ca^{2+}-activated K^+ channel in cultured rat neonatal β-cells (Cook et al., 1984).

The minimal model also neglects the effect of external potassium on the oscillations. This effect has been studied in many laboratories (Meissner, 1976; Atwater et al., 1978; Cook et al. 1981*b*). Complementary to those measurements are measurements of potassium efflux from the β-cell (Lebrun et al., 1982, 1983; Henquin, 1981). Several recent experiments suggest that glucose is directly involved in modulating potassium efflux. A channel that conducts K^+ in the absence of glucose has been found in cultured rat β-cells using the cell-attached membrane patch technique (Ashcroft et al., 1984). This so-called G-channel has a constant conductance of ~50 pS, and is completely inhibited by 20 mM glucose. Since the conductance of this channel is substantially reduced in the presence of even 10 mM glucose, it is doubtful that this channel has a major effect on the bursting activity of the β-cell. Other experiments (Cook and Hales, 1984), relying on unattached patches of membrane from cultured rat neonatal β-cells, have demonstrated the existence of a K^+ channel that is strongly inhibited by ATP in submillimolar concentrations. Since ATP is a metabolic product of both glycolysis and oxidative phosphorylation, the existence of this channel implies a potential regulatory role for glucose. It is possible that this channel is identical to the G-channel. The ATP effect, however, is unlikely to be important for steady state bursting. Indeed, during steady state glycolysis, overall cystolic concentrations of ATP are in the millimolar range (Newsholme and Start, 1973), well above the concentrations at which ATP has a regulatory effect on this channel.

Other reasons suggest that these channels are not needed to explain steady state bursting activity in the β-cell. Calculations by ourselves and others using the minimal model (Rinzel, J., private communication) have explored the dependence of the burst oscillations on the parameter k_{Ca}. This parameter governs the uptake of Ca^{2+} into intracellular stores. Under physiological conditions, the only features of the oscillations that change appreciably when k_{Ca} is increased are the oscillation period and the relative duration of the spiking and silent phases (Chay and Keizer, 1983). This aspect of the calculation is in good agreement with experiment (Meissner, 1976). Furthermore, we find that increasing k_{Ca} increases the duration of the spiking phase, as is also found experimentally (Meissner and Schemlz, 1974; Cook et al., 1981*a*). The effect of increasing k_{Ca} on the period is more complicated: When k_{Ca} corresponds to glucose concentrations just above the bursting threshold (~5–8 mM), the period is somewhat longer than it is at values of k_{Ca} corresponding to the intermediate range 10–16 mM. If k_{Ca} is made even larger

(Rinzel, J., private communication), the period lengthens again. For k_{Ca} above a critical value, only continuous spiking is observed. Experimentally, low to intermediate glucose concentrations show great variability from one cell to another in their effect on the oscillation period (Cook et al., 1981*a*). Other experiments, however, which cover a more extensive range of glucose concentrations, support the results of our calculations. These experiments (Meissner and Schmelz, 1974; Beigelman et al., 1977) show that just above threshold the period is longer than throughout the intermediate range of glucose concentrations, and that the period lengthens again at concentrations just below the onset of continuous spiking.

Overall, there is reasonable, qualitative agreement between our calculations on the effect of glucose and the results of our experiment. This suggests to us that the dominant effects of glucose on steady state bursting are already included in the minimal model. While the newly discovered glucose-inhibited channels may well be important in explaining other properties of the β-cell, their effect does not appear to be crucial for explaining steady state bursting.

One effect that does seem to be important for steady state bursting is compartmentalization of potassium ions in the extracellular space (Perez-Armendariz et al., 1985). Although our model provides a reasonable representation of bursting behavior without this elaboration, the inclusion of a compartmentalized extracellular space is necessary for understanding K^+ efflux measurements. In the following sections we extend our minimal model to include the effect of extracellular K^+ ions compartmentalized around the β-cell. In our calculations the compartmentalized space is assigned a volume per cell that is one-eighth that of the β-cell itself. This volume is about an order of magnitude larger than the tip of the microelectrode used to detect external K^+ (Perez-Armendariz et al., 1985). Our calculations exhibit burst oscillations of K^+ that agree well in terms of size, shape, and period with those observed experimentally (Perez-Armendariz et al., 1985). Experimentally, one finds oscillations of K^+ concentrations with amplitudes that range in different experiments from ~1–0.1 mM. In our calculations this implies a range of extracellular volumes up to the size of the β-cell itself. Whether these compartments are intrinsic in intact islets, or are created by insertion of the microelectrode, remains to be seen.

COMPARTMENTALIZED K^+ IONS

We assume that in an islet the β-cell is surrounded by an unstirred layer, as suggested by Perez-Armendariz et al., (1985). The environment of the unstirred layer must be quite different from the perfusion medium, both because of the charge of the membrane surface and because of the flux of K^+ ions from the membrane during the electrical activity in the β-cell. This microenvironment serves as a model of the K^+ gradient that thus develops between the β-cell and medium. The variation of the concentration of compartmentalized K^+ ions with time depends on the following three processes taking place in the layer: diffusion between the medium and the layer; the electrical activity of the membrane, which results in a gain of K^+ ions coming from the cell through the voltage- and calcium-sensitive K^+-channels; and the Na/K pump, which results in the loss of K^+ ions. This is expressed by the following equations:

$$\frac{d[K]}{dt} = (I_K - 2\,I_{Na/K})/v_c F + J_{Diff}, \tag{1}$$

where [K] is the concentration of compartmentalized K^+ ions, F the Faraday constant, the quantity v_c is the effective volume of the compartmentalized space per β-cell, I_K the current carried by K^+ ions due to the membrane electric activity, J_{Diff} the flux of diffusing K^+ ions, $I_{Na/K}$ the current due to the Na/K pump. The factor 2 in front of $I_{Na/K}$ is a result of the 3:2 Na/K exchange ratio.

The flux J_{Diff} in Eq. 1 may be expressed in terms of the two K^+ concentrations

$$J_{Diff} = k_D[K]_o - k_D\, e^{-\psi}[K], \tag{2}$$

where $[K]_o$ is the K^+ concentration of the external medium and k_D is the diffusion rate constant of K^+ ions from the medium to the layer. Because of the difference in electrochemical potential of K^+ in the perfusion medium and the compartment, the rate constants for diffusion out of the compartment and into the compartment must be different (Keizer, 1976). Their ratio is given by $e^{-\psi}$ where ψ is the electrical potential difference between the perfusion medium and the compartment divided by RT/F. One effect of the electrochemical potential difference is to make the steady state concentration of compartmentalized K^+ differ from $[K]_o$. This has been observed experimentally by Perez-Armendariz et al. (1985), and in our calculations we have estimated the value of the ψ from results in their Fig. 7 *A*.

The K^+ current, I_K, in Eq. 1 consists of the current carried by K^+ ions through the Ca^{2+}-sensitive K^+-channel, $I_{K,Ca}$, and that carried by K^+ ions through the voltage-sensitive K^+-channel, $I_{K,V}$:

$$I_K = -I_{K,Ca} - I_{K,V}. \tag{3}$$

According to our minimal model (Chay and Keizer, 1983), $I_{K,Ca}$ is represented by

$$I_{K,Ca} = \bar{g}_{K,Ca}\frac{[Ca]/K_{dis}}{1 + ([Ca]/K_{dis})}(V_K - V). \tag{4}$$

Here, [Ca] is the intracellular calcium concentration and K_{dis} is an apparent dissociation constant of Ca^{2+} ions from

the Ca^{2+}-sensitive K^+-channel. In our model, $I_{K,V}$ is written as

$$I_{K,V} = \bar{g}_{K,V}\, n^4\, (V_K - V), \tag{5}$$

where n is the probability of opening of the voltage-sensitive K^+-channel. In Eqs. 4 and 5, V_K is the resting potential of K^+ ions, and $\bar{g}_{K,Ca}$ and $\bar{g}_{K,V}$ are the maximum conductances of the Ca^{2+}- and voltage-sensitive channels, respectively.

In Eq. 5, the probability of opening of the voltage-sensitive K^+-channel, n, is described by the dynamic expression given by Hodgkin and Huxley (1952)

$$dn/dt = \lambda[n_\infty - n]/\tau_n, \tag{6}$$

where λ is a proportionality constant, n_∞ is n at the steady state, and τ_n a relaxation time. In our model the voltage dependencies of n_∞ and τ_n have the same form as the original Hodgkin-Huxley equations, but V is replaced by $V_n - V$.

The equilibrium potential of K^+, V_K, in Eqs. 4 and 5 follows the Nernst equation (Plonsey, 1969)

$$V_K = (RT/F)\, ln\{[K]/[K]_{in}\}, \tag{7}$$

where R is the gas constant, T is the absolute temperature, and $[K]_{in}$ the intracellular potassium concentration, which is assumed to change little under the conditions that we investigate here.

The intracellular calcium concentration in Eq. 4 varies with time due to calcium ions coming into the cell through the voltage-sensitive Ca^{2+}-channel and the loss of intracellluar Ca^{2+} ions into intracellular stores stimulated by glucose. Thus, according to the rate law, the time derivative of the intracellular Ca^{2+} concentration may be represented by

$$f^{-1}\frac{d[Ca]}{dt} = \frac{3}{4\pi r^3 F} I_{Ca} - k_{Ca}[Ca], \tag{8}$$

where f is the fraction of free intracellular calcium ions, k_{Ca} is the rate constant for glucose-stimulated uptake of intracellular Ca^{2+} ions, and I_{Ca} is the inward Ca^{2+} current coming from the voltage-sensitive Ca^{2+}-channel. In our model, this is expressed by

$$I_{Ca} = \bar{g}_{Ca}\, m^3 h\, (V_{Ca} - V), \tag{9}$$

where V_{Ca} is the Ca^{2+} Nernst potential, $\bar{g}_{Ca}$ the maximum conductance of the voltage-sensitive Ca^{2+}-channel, and m and h are the probabilities of the activation and inactivation of the Ca^{2+}-channel, respectively.

Our present model differs from the original Chay-Keizer model in that the activation and inactivation dynamic variables, m and h, of the voltage-sensitive Ca^{2+}-channel are replaced by their respective steady state values, i.e.,

$$m = m_\infty \tag{10}$$

and

$$h = h_\infty. \tag{11}$$

We have found (Chay, 1984) that this changes the results of our earlier calculations very little, but that it greatly reduces the time required for the computation. The voltage dependencies of m_∞ and h_∞ are the same as in the original Hodgkin-Huxley equations (Hodgkin and Huxley, 1952) except that V is shifted along voltage axis by a fixed amount V_m, i.e., V in the Hodgkin-Huxley expression is replaced by $V_m - V$.

The time derivative of the membrane potential V appearing in the above equations is given by the following expression (Plonsey, 1969):

$$4\pi r^2 C_m\, dV/dt = g_{Ca} m_\infty^3 h_\infty (V_{Ca} - V) + g_{K,V} n^4 (V_K - V) + g_{K,Ca}\frac{[Ca]/K_{dis}}{1 + [Ca]/K_{dis}}(V_K - V) + g_L(V_L - V) - I_{Na,K}, \tag{12}$$

where C_m is the membrane capacitance, and V_L and g_L are the Nernst potential and conductance of the channels responsible for ion leaks, respectively.

Once again, the present model contains four dynamic variables: (*a*) the concentration of compartmentalized K^+ ions; (*b*) the membrane potential, V, whose variation with time is expressed as the sum of ionic currents carried by outward K^+ ions, inward Ca^{2+} ions, the leak current of an unknown nature, and the current owing to the Na/K pump activity; (*c*) the probability of opening of the voltage-dependent K^+ gate, n; (*d*) the intracellular Ca^{2+} concentration. The four differential Eqs. 1, 6, 8, and 12 govern the time dependence of these variables.

It is possible to solve these four differential equations numerically, and we have done so on a DEC 10 computer (Digital Equipment Corp., Marlboro, MA) using a Gear algorithm (Hindmarsh, 1974). The magnitude of the absolute and relative error tolerances required in the integration code was set at 10^{-7}. The parametric values used in our computations are listed in Table I. When other values were used for our computations, they have been listed in the figure captions.

The value of C_m was obtained from Rojas (private communication) and the radius of the β-cell, r, is approximately that in Dean (1973). The values of T, $[K]_{in}$, $[K]_o$, k_D, and V_{Ca} correspond closely to the experimental conditions of Perez-Armendariz et al. (1985). In particular the value of k_D^{-1} is the time required for the external potassium ions to diffuse into the islet, which was measured to be 4.2 s. Other parameter values are the same as in our previous work (Chay and Keizer, 1983) with the following exceptions.

The value of λ was adjusted to give a spiking frequency compatible with experiment. The values of the conductances were adjusted to obtain the proper magnitude of the voltage in the silent and active phases. In this work the value of $\bar{g}_{K,Ca}$ is smaller than that used previously (Chay

TABLE I
PARAMETER VALUES OF THE MODEL

Parameter	Numerical value
C_m	1 μF · cm^{-2}
$\bar{g}_{K,Ca}$	50 pS
$\bar{g}_{K,V}$	7.5 nS
$\bar{g}_{Ca}$	8 nS
g_L	30 pS
$(RT/F)ln\{[K]_{in}/1\ mM\}$	125 mV
V_{Ca}	100 mV
V_L	−40 mV
V_n	−30 mV*
V_m	−50 mV*
K_{dis}	1 μM
r	6 μm
f	7×10^{-3}
T	310 K
k_D	0.25 s^{-1}
ψ	0.1
v_c	113 μ^3
$[K^+]_o$	5 mM
λ^{-1}	3
k_{Ca}	0.02 (ms)$^{-1}$

*Shifts in the voltage dependence of m_∞ and n_∞ assumed by Hodgkin and Huxley (1952).

and Keizer, 1983) by a factor of ~0.1. This adjustment makes the theoretical value of the spiking period closer to the experimental one, and corresponds more closely to the value of $\bar{g}_{K,Ca}$ = 60 pS estimated by Atwater et al. (1983). The volume of the compartmentalized space per β-cell, v_c, was chosen to be one-eighth that of the β-cell volume. If this volume were distributed in a spherical shell around the β-cell, it would have a width of 0.24 μm. This value was necessary for the computed amplitude of the [K] oscillations to be ~1 mM, as found by Perez-Armendariz et al. (1985). The values of ψ were chosen so that the computed steady state values of [K], obtained in the absence of glucose, would agree approximately with those of Fig. 7 *A* of Perez-Armendariz et al. (1985). For simplicity we have set the current in the Na^+/K^+ pump equal to zero.

In our model, the parameter f controls the length of the period, i.e., the larger the value of f, the shorter the bursting period becomes. We have chosen f = 0.007, which gives a bursting frequency compatible with experiment. Also in our model K_{dis} controls the magnitude of the concentration of intracellular Ca^{2+} ions. As previously (Chay and Keizer, 1983) a value of 1 μM was chosen for K_{dis}, and [Ca] oscillates in the vicinity of 1 μM. We have defined V to be the potential difference between the

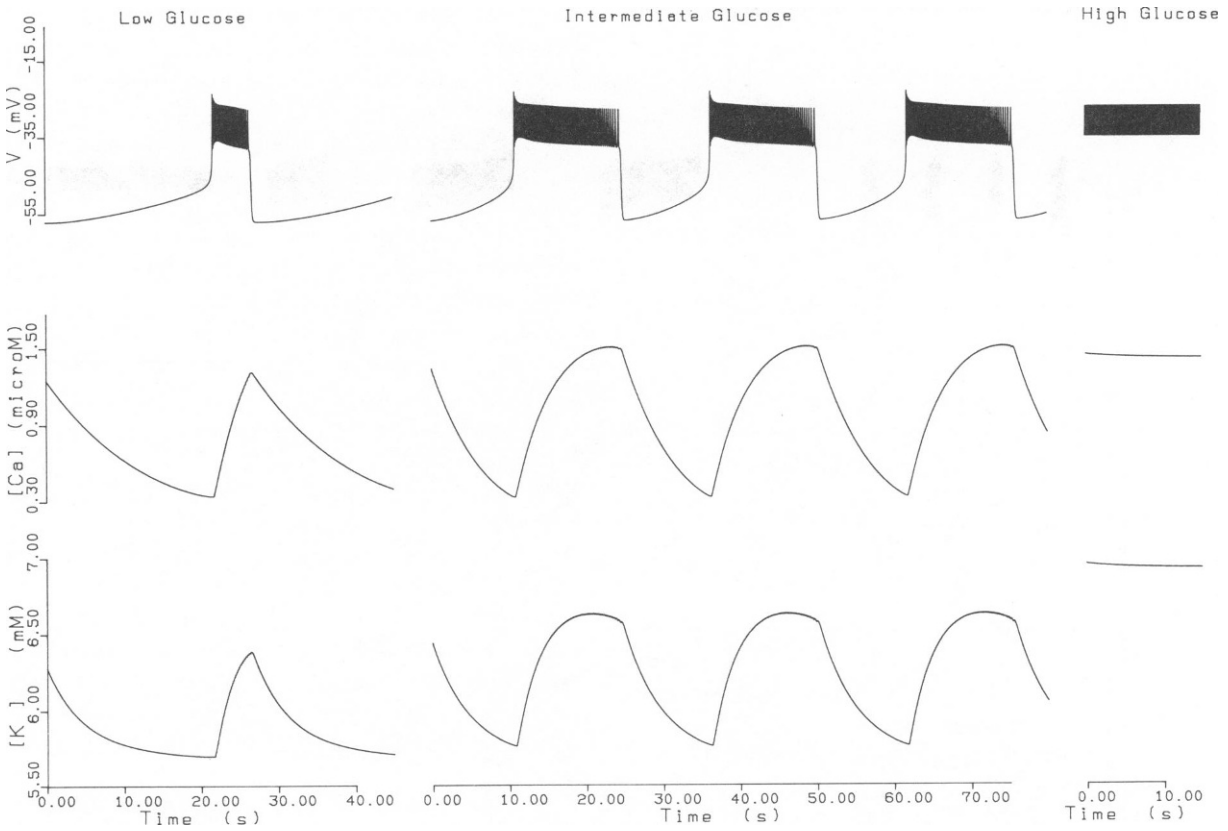

FIGURE 1 The oscillatory pattern caused by variation of glucose. The plot on the left column was obtained with k_{Ca} = 0.01 (ms)$^{-1}$, the middle column with k_{Ca} = 0.02 (ms)$^{-1}$, and the right column with k_{Ca} = 0.03 (ms)$^{-1}$. The first row shows the variation of membrane potential (in millivolts) with time (in seconds), the second row the intracellular calcium concentration (in millimolar) with time, the last row the compartmentalized K^+ ion concentration (in millimolar) with time.

intracellular medium and the intercellular space. Thus, to compare our results given in the figures that allow follow to experimental measurements of the membrane potential, one needs to add to V the potential difference between the intercellular space and the perfusion medium. In our calculations this is $-RT/\psi F$. The value of this term is 16 mV for $[K]_o = 2$ mM, 2.7 mV for $[K]_o = 5$ mM, and -2.7 mV for $[K]_o = 7$ mM.

NUMERICAL RESULTS: K^+ OSCILLATIONS

Using the model and techniques described in the preceding section we have integrated the differential equations for the concentration of intracellular calcium, [Ca], the concentration of intercellular potassium, [K], the membrane potential, V, and the probability, n, that the voltage sensitive K^+ channel is open. The time course of the solutions for parameter values corresponding to low, intermediate, and high glucose concentrations (all at 5 mM external K^+) are given in Fig. 1. The membrane potential exhibits the typical pattern of bursts, which includes a long silent phase of polarization followed by a rapid depolarization and K^+/Ca^{+2} action potentials in the active phase. These oscillations are limit cycles of the sort that are thought to typify many biological oscillators (Pavlidis, 1973). The effect of added glucose is to increase the duration of the active phase until, at high glucose concentration, the silent phase is completely abolished. In our expanded model the oscillations in intercellular K^+ are seen to follow a pattern similar to the intracellular Ca^{2+}. During the active phase [Ca] and [K] both rise to a maximum, while they both fall during the silent phase.

Fig. 2 shows the results of our calculation for the same intermediate glucose concentration as in Fig. 1, but at 2, 5, and 7 mM external K^+. The pattern of the resulting oscillations in [Ca], [K], and V depends on the electrochemical potential effect on [K] discussed in the previous section. This effect, as manifested by the increased steady state value of [K] over the value of $[K]_o$ (Perez-Armendariz et al., 1985), is less pronounced at higher values of external K^+. As explained in the previous section, this is reflected in our calculations by asymmetry in the effective rate constants for diffusion between the external medium and the intercellular space.

NUMERICAL RESULTS: K^+ FLUXES

Since both the voltage-gated and Ca^{2+}-activated K^+ channels are included in our model, we can obtain the instantaneous fluxes of K^+ ion through these channels from our calculations. We express the fluxes in nano amperes per cm^2 of β-cell surface using the definitions

$$J_{K,V} = g_{K,V}(V_K - V)/4\pi r^2 \qquad (13)$$

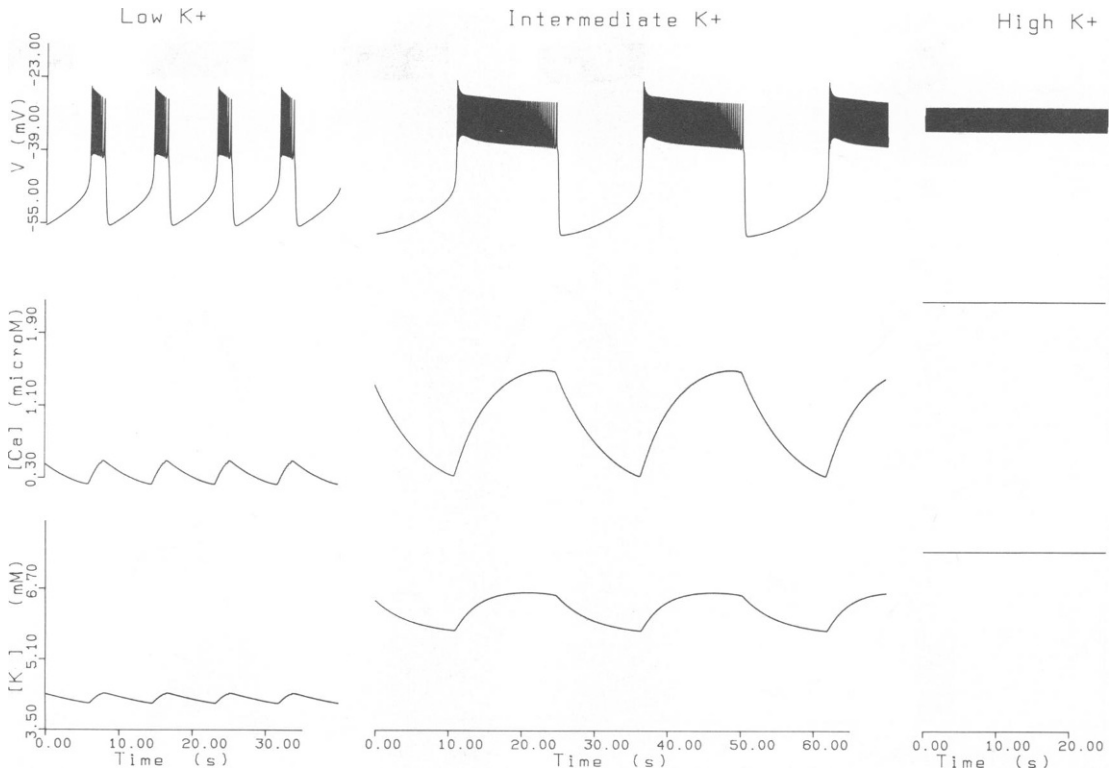

FIGURE 2 Effect of external K^+ concentration on the bursting mode shown in the middle column of Fig. 1. Here, the parametric values used for the computation were the same as those in the middle column of Fig. 1, with the following changes: low K^+ was computed with $[K]_o = 2$ mM and $\psi = 0.6$, the middle column the same condition as that of Fig. 1, and high K^+ was computed with 7 mM external K^+ concentration and $\psi = -0.1$.

and

$$J_{K,Ca} = g_{K,Ca}(V_{Ca} - V)/4\pi r^2, \quad (14)$$

where the g's are the conductance of the channels discussed in the section Compartmentalized K^+ Ions and r is the radius of a β-cell, taken as 6 μm. By adding these two fluxes together we obtain, $J = J_{K,V} + J_{K,Ca}$, the total K^+ flux from the β-cell.

The time course of the fluxes for the low, intermediate, and high glucose concentrations used in Fig. 1 are shown in Fig. 3. Since the fluxes in Eqs. 13 and 14 are defined in terms of the three variables [Ca], $[K]_o$, and V which, themselves, exhibit limit cycle oscillations, the fluxes also oscillate in a similar pattern. Notice that the fluxes are of the order of 10^2 nA cm^{-2}. This is within the range of values estimated using other experimentally measured parameters (Perez-Armendariz et al., 1985).

We have also calculated the time average values of the fluxes. These were obtained by numerically integrating the instantaneous fluxes, e.g.,

$$\bar{J} \equiv \int_0^\tau J(t)dt/\tau, \quad (15)$$

where τ represents either the bursting period or, in the case of continuous spiking, a time long compared with the duration of a spike. These results are tabulated for low, intermediate, and high glucose concentrations in Table II. To simplify comparison with experiments, the average fluxes in Table II are expressed as pmol cm^{-2} · s^{-1}, using the conversion factor nA·cm^{-2} = 0.0104 pmol cm^{-2} · s^{-1}. Notice as a check on our numerical work that the separate values of $\bar{J}_{K,V}$ and $\bar{J}_{K,Ca}$ add to the total average value of the flux, $\bar{J}$, to within a few percent.

EFFECT OF QUININE AND TEA ON K^+ FLUX

The effect of quinine on K^+ channels in the membrane of the β-cell seems to be relatively complex. It is known from a variety of experiments that it reversibly blocks the Ca^{2+}-activated K^+ channels (Atwater, et al., 1979) even in concentrations as low as 5 μM. However, it also appears to prolong the action potential spikes, perhaps through interaction with the voltage-gated K^+ channels. Thus we have chosen to mimic the addition of quinine by setting the conductance of the Ca^{2+}-activated K^+ channel, $\bar{g}_{K,Ca}$, equal to zero, and by decreasing by two-thirds the parameter, λ, in Eq. 6. This has the effect of increasing by a factor of 1.67 the time constant for the relaxation probability of opening, n, for the voltage-gated K^+ channel. The results of these calculations are shown in Figs. 4 and 5, where the value K^+ external was set equal to 5 mM. With the effect of quinine

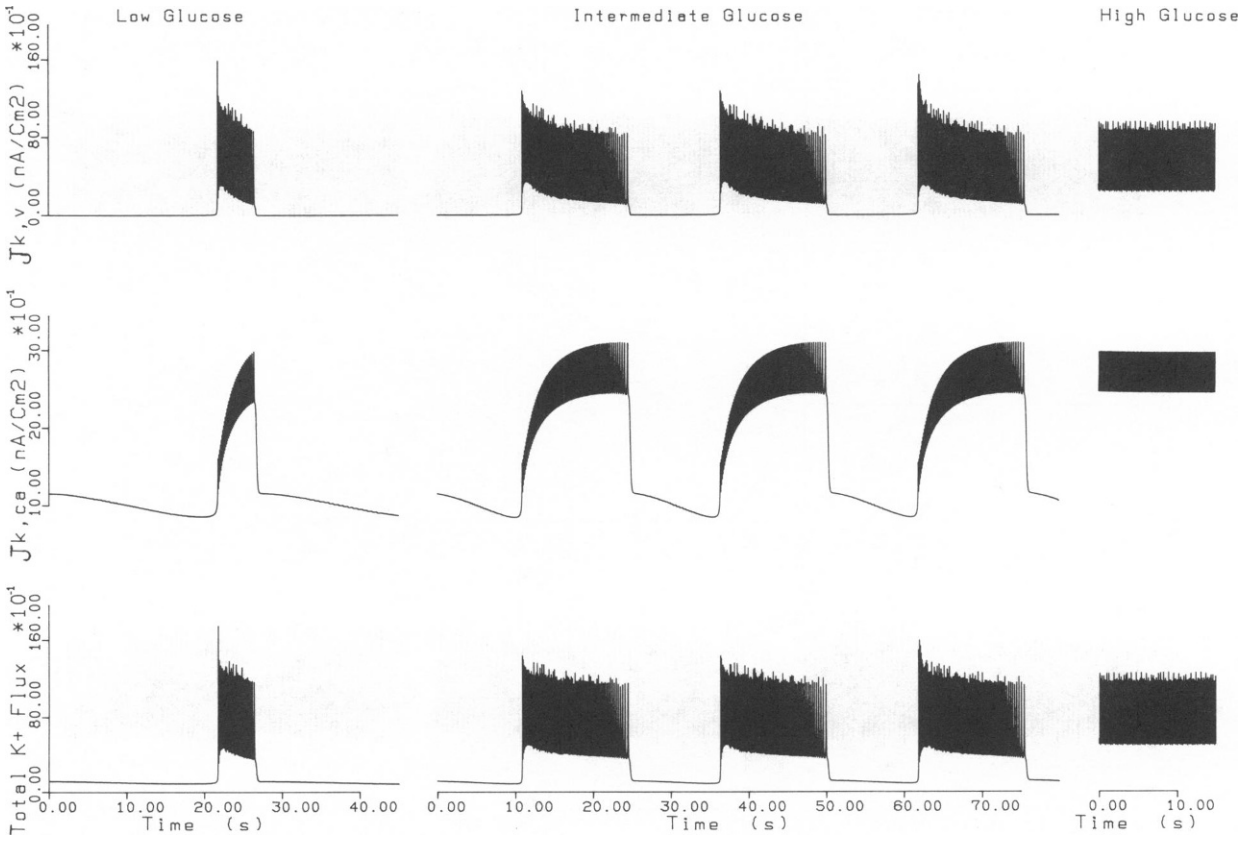

FIGURE 3 The fluxes of K^+ through the Ca^{2+}-sensitive K^+-channel (*top*), voltage-sensitive K^+ channel (*middle*), and the sum of the two (*bottom*) as defined by Eqs. 13–15. Conditions are as in legend to Fig. 1.

TABLE II
AVERAGE POTASSIUM ION FLUXES (pmol · cm^{-2} · s^{-1})

Flux	Low glucose $k_{Ca} = 0.01(ms)^{-1}$	Intermediate glucose $k_{Ca} = 0.02(ms)^{-1}$	High glucose $k_{Ca} = 0.03(ms)^{-1}$	External medium
$\bar{J}_{K,V}$	0.84	2.28	5.18	
$\bar{J}_{K,Ca}$	1.24	1.86	2.80	$[K]_o = 5$ mM
$\bar{J}$	2.07	4.15	7.88	
$\bar{J}_{K,V}$	0.35	0.91	1.35	TEA
$\bar{J}_{K,Ca}$	0.91	0.89	0.83	$[K]_o = 5$ mM
$\bar{J}$	1.24	1.76	2.18	
$\bar{J}_{K,V}$	6.01	6.01	6.01	quinine
$\bar{J}_{K,Ca}$	0	0	0	$[K]_o = 5$ mM
$\bar{J}$	6.01	6.01	6.01	
$\bar{J}_{K,V}$		0.80		
$\bar{J}_{K,Ca}$		1.14		$[K]_o = 2$ mM
$\bar{J}$		1.86		
$\bar{J}_{K,V}$		5.28		
$\bar{J}_{K,Ca}$		3.11		$[K]_o = 7$ mM
$\bar{J}$		8.50		

mimicked in this fashion, changing the glucose concentration has no effect on the oscillations. The instantaneous K^+ fluxes are shown in Fig. 5 and their time averages are given in Table II.

Tetraethylammonium ion (TEA) is known to inhibit the voltage-gated conductance of K^+ in the β-cell (Atwater et al., 1979). One of its effects is to prolong the K^+/Ca^{+2} action potential. We have previously modeled its effect by increasing the value of τ_n (Chay and Keizer, 1983). In the present calculations this is accomplished by decreasing the parameter λ by a factor of one-third over that in Table I. The results of our calculations at 5 mM external K^+ and

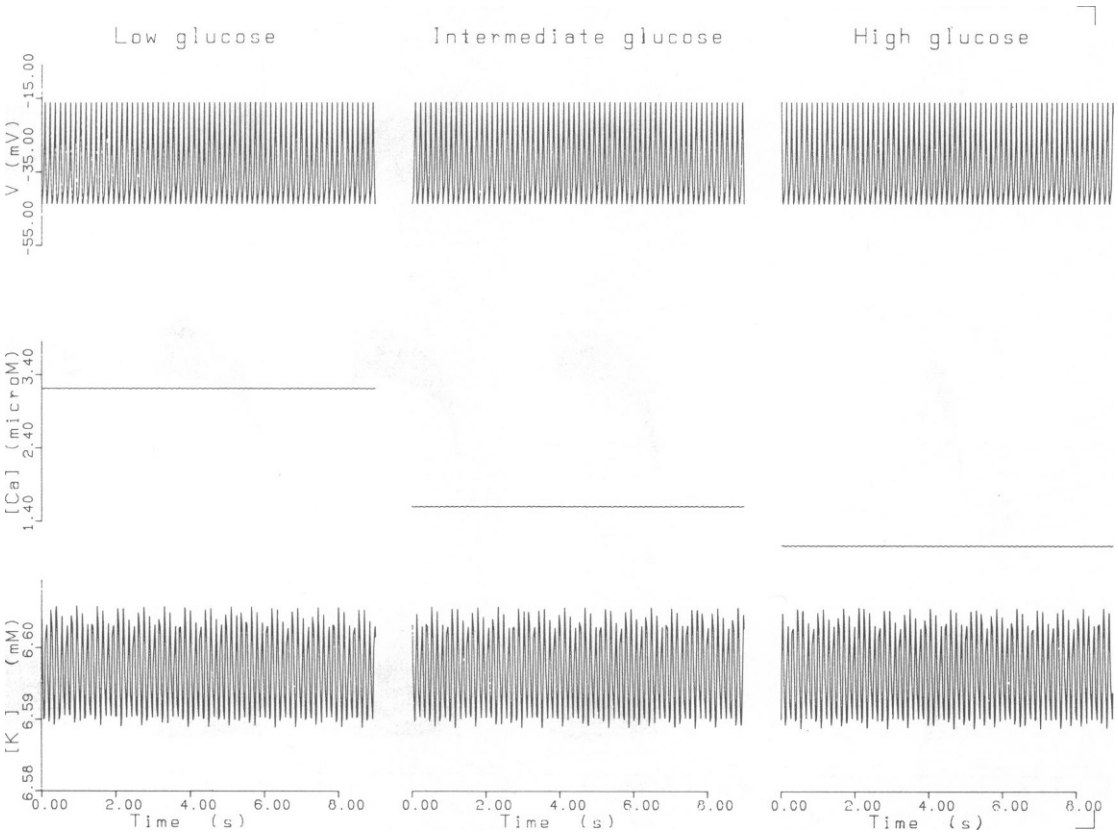

FIGURE 4 Effect of quinine on the electrical pattern, the intracellular Ca^{2+}, and compartmentalized K^+ concentrations. The parametric values used for this computation are the same as those in Fig. 1, except $\bar{g}_{K,Ca}$ was set at zero and λ^{-1} was increased from 3 to 5.

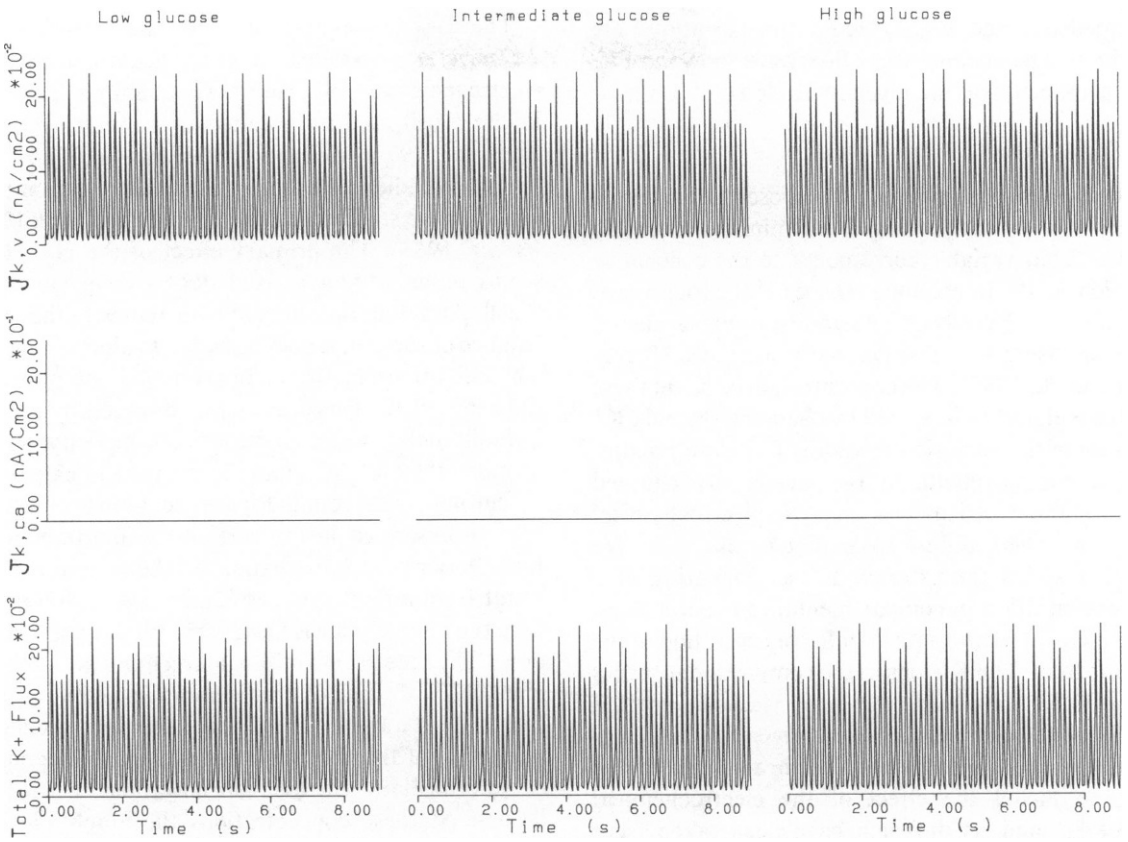

FIGURE 5 The fluxes of K^+ as defined in Eqs. 13–15 for the simulated effect of quinine described in the legend of Fig. 4.

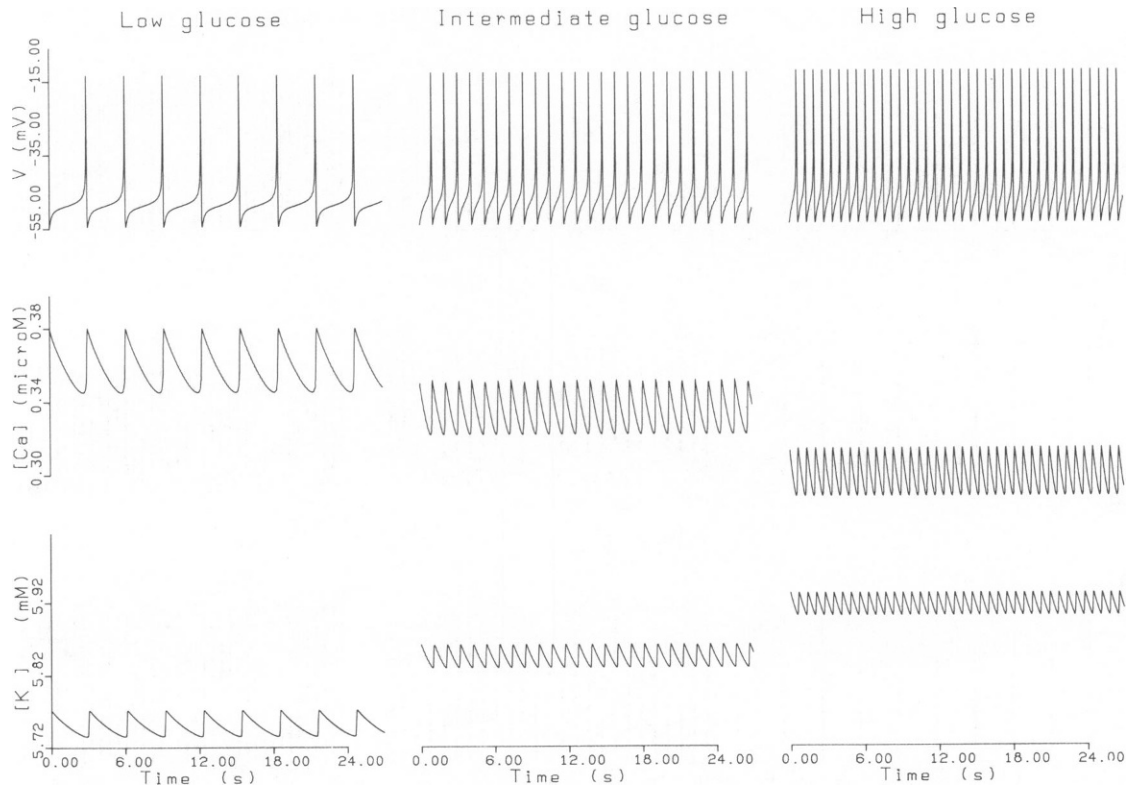

FIGURE 6 Effect of TEA on the oscillation pattern shown in Fig. 1. In this calculation we used the same parametric values as those of Fig. 1 except λ was decreased by a factor of one-third; i.e., $\lambda^{-1} = 9$.

low, intermediate, and high glucose concentrations are given in Fig. 6. The instantaneous fluxes are shown in Fig. 7, and the average fluxes are given in Table II.

DISCUSSION

To examine the effect of external K^+ on oscillations in the pancreatic β-cell we have enlarged our minimal model by one variable. That variable corresponds to the concentration of K^+ ions in the intercellular spaces of the islet tissue. Spaces of this sort have been inferred from experimental measurements using K^+-sensitive microelectrodes (Perez-Armendariz et al., 1985). The concentration of K^+ in these intercellular regions can be varied by changing the bulk K^+ concentration in the perfusion medium. The close proximity of these compartments to the electrically charged membrane of the β-cell means that the electrochemical potential of K^+ there differs from that in the bulk. We have, thus, modeled the external K^+ as consisting of a variable concentration in compartmentalized space, adjacent to the membrane and a fixed bulk concentration in the perfusion medium. The K^+ ions in the compartment spaces exchange with K^+ ions inside the β-cell via voltage-gated and Ca^{2+}-activated channels, and exchange with the perfusion medium via passive diffusion. The parameters that we have used to model the effect of the electrochemical potential of K^+ and its diffusion have been taken from experiment (Perez-Armendariz et al., 1985).

There is one important K^+ ion transport mechanism that we have not included in our calculations, namely the electrogenic Na^+/K^+ pump. This pump is known to exist in the β-cell, and is inhibited by ouabain (Atwater and Meissner, 1975; Meissner and Henquin, 1984). Ouabain inhibition induces a continuous volley of action potentials and we have studied its effect in previous work (Chay and Keizer, 1983). The primary effect of the Na^+/K^+ pump seems to be adding a fixed depolarizing current to the β-cell. Although this current contributes to the overall K^+ balance of the cell, it does not seem to alter strongly the K^+ ion oscillations in the compartmentalized space—unless the external K^+ concentration is changed by more than a few millimolar. Thus, for reasons of simplicity, we have not included the Na^+/K^+ pump in the present calculations.

Our numerical results for the oscillations of intercellular K^+ are described in the section Compartmentalized K^+ Ions. In our model, oscillations in the membrane potential result from a limit cycle oscillation that involves, in addition, the intercellular K^+ and intracellular Ca^{2+} concentrations. Thus the period of the intercellular K^+ oscillations is identical with that of the membrane potential, although the shape is quite different. Like the Ca^{2+} oscillation, the amplitude of the K^+ oscillation is appreciable only at low or intermediate glucose concentrations where bursting occurs. At these concentrations the amplitude is of the order of 1 mM (Fig. 1). At the beginning of a burst the K^+ concentration in the intercellular space rises rapidly, peak-

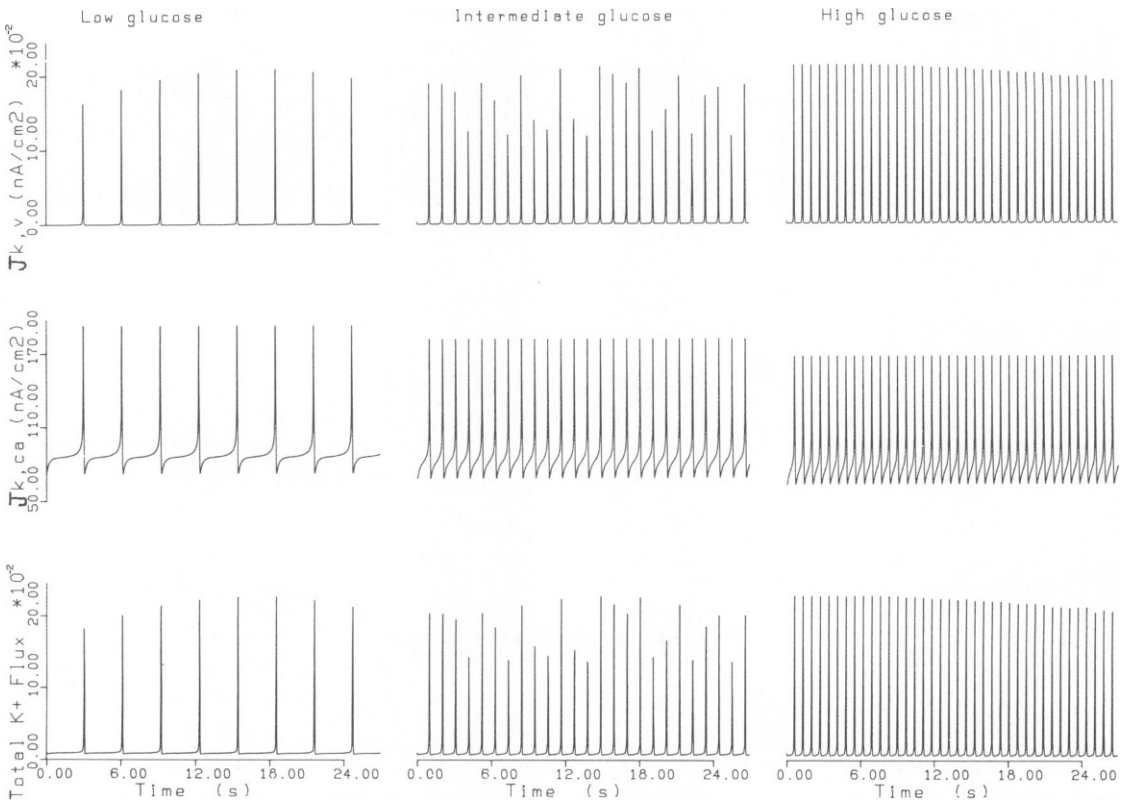

FIGURE 7 The fluxes of K^+ as defined in Eqs. 13–15 for the simulated effect of TEA described in the legend to Fig. 6.

ing before the burst ends. This increase is caused by the action-potential spikes during which K^+ flows out of the cell into the intercellular space. Since diffusion into the bulk is slow, the intercellular K^+ concentration rises. It achieves a maximum when the frequency of the action potentials decreases near the end of the burst. At the end of the burst the potential falls abruptly, terminating the action potentials and significantly decreasing the flux of K^+ through both the voltage- and calcium-gated channels, as shown in Fig. 3. The slow decrease of intercellular K^+ during this part of the oscillation is caused by its loss through diffusion into the perfusion medium. The amplitude and period of the calculated K^+ oscillations is similar to that observed experimentally with a K^+-selective microelectrode (Perez-Armendariz et al., 1985).

The K^+-selective microelectrode seems to provide a direct measurment of K^+ at the surface of the β-cell. The measurement of K^+ fluxes, using $^{86}Rb^+$ as a marker is less direct because it is a slower measurement that averages over several bursts. In addition, some K^+ channels do not transport Rb^+, although in the β-cell this is not a serious problem (Henquin, 1981). The $^{86}Rb^+$ measurements do not track the K^+ concentration, but rather the flux of K^+ ions out of the islets. Our results for the K^+ fluxes at various glucose concentations are given as a function of time in Fig. 3, and averaged over time in Table II. We have calculated the K^+ fluxes from both the voltage- and calcium-gated channels and the total flux. Naturally, the flux through the voltage-gated K^+ channel spikes rapidly as that channel opens and closes during its action potential phase. The net flux of this channel, however, tends to decrease during this part of the period since a small repolarization of the membrane occurs during the burst (Fig. 1). The flux of the Ca^{2+}-activated channel exhibits smaller spikes during the action potential phase since we have ignored the dependence of its conductivity on the membrane potential. The gradual increase of its flux during spiking is caused by the increase in Ca^{2+} ion concentration (Fig. 1) associated with the inward Ca^{2+} current during the action potentials. Notice that during the silent phase the voltage-gated channels are inactive and that the outward K^+ flux is carried entirely by the Ca^{2+}-activated channels.

The results in Table II give the average total K^+ flux, and exhibit quite clearly the phenomena of glucose-induced K^+ extrusion found in $^{86}Rb^+$ tracer experiments (Lebrun et al., 1983). According to our calculations, the total K^+ flux from the β-cell increases by a factor of ~ 2 when the glucose concentration is raised from a low value ($\sim$7–9 mM) to an intermediate value ($\sim$13 mM), and another factor of 2 when raised to a high value ($\sim$20 mM). As the data in Table II show, this is caused chiefly by an increase in the flux from the voltage-gated K^+ channel, although the flux from the Ca^{2+}-activated channel increases, too. The net glucose-induced K^+ flux is, thus, compatible with the existence of Ca^{2+}-activated K^+ channels. As Fig. 3 illustrates, those channels are the only ones carrying K^+ current during the silent phase. They are slowly deactivated during this period as the Ca^{2+} concentration is lowered by intracellular processes. The decreased permeability of the membrane to K^+, in turn, causes the voltage to rise (Fig. 1), ultimately reaching a value that initiates the burst of action potentials. Viewed in this way, there is no conflict between the initiation of a burst by a decreasing K^+ permeability and the increased average flux of K^+ induced by glucose: The glucose simply increases the duration of the burst, during which most of the K^+ ions are extruded.

Changes in the concentration of K^+ ion in the perfusion medium affect the glucose-induced electrical activity of the β-cell (Atwater, et al., 1980; Cook, et al., 1981*b*). We restrict our comparison with experiment to a narrow range of external K^+ concentrations since we have neglected the effect of the Na^+/K^+ pump, which adds a depolarizing current that depends on external K^+ concentration. For external K^+ between 4 and 7 mM the effect of glucose experimentally is to induce burst oscillations with a frequency of $\sim$3/min. Below this concentration range the number of bursts increases until it reaches a value of nearly 25/min at 0.5 mM. Similar results have been observed by others (Ribalet and Biegelman, 1979). Our calculations exhibit this general pattern, as shown in Fig. 2. Notice the predicted effect of external K^+ on the intercellular K^+ oscillations. When $[K]_o$ is low, intercellular K^+ oscillations are diminished in amplitude, but rise at a rate comparable to the oscillations at intermediate external K^+. The appearance of the intercellular K^+ oscillations at low K^+ is similar to those observed experimentally at high external Ca^{2+} (Perez-Armendariz et al., 1985), which, like low K^+, has the effect of shortening the duration of the burst.

TEA and quinine have potent effects on both the electrical activity of the β-cell and $^{86}Rb^+$ efflux measurements. Experimentally, 5 μM quinine has been shown to inhibit the glucose-induced efflux of K^+ from rat islets (Lebrun et al., 1982). Indeed, raising the glucose concentration from 8.3 to 16.7 mM causes no measureable increase in the $^{86}Rb^+$ efflux rate. Our numerical calculations, in which the conductance of the calcium-gated channel is set equal to zero, were used to model these experiments. With this channel blocked, Table II shows that the average K^+ flux is independent of glucose concentration. Furthermore, the time course of the oscillations shown in Figs. 4 and 5 indicates that quinine abolishes the silent phase, leading to sustained spiking, independent of glucose. This phenomenon is the same as that found experimentally (Atwater et al., 1979). In our calculations the only effect of glucose on the β-cell is an indirect one, operating by activation of Ca^{2+} uptake into intracellular stores (Rorsman et al., 1984). Thus, it is reasonable that quinine, which acts by blocking the control point of Ca^{2+} in our molecular mechanism, would eliminate any effect of glucose on the oscillations.

According to our calculations TEA tends to decrease the average K^+ flux from the β-cell. Nonetheless, it does not block the glucose-induced efflux as does quinine. As shown in Figs. 6 and 7, TEA reduces the active phase of a burst from a volley of action potentials to a single, rather slow action potential. It also decreases the duration of the silent phase and depolarizes the membrane potential during the silent phase slightly, in agreement with experiment (Atwater et al., 1979). In the presence of TEA glucose still maintains a control effect, operating indirectly through the Ca^{2+}-activated K^+ channel. Just as in the absence of TEA, Fig. 6 illustrates that increased glucose decreases the duration of the silent phase, which increases the flux through both K^+ channels as shown in Fig. 7. The net result is a glucose-induced K^+ flux as given in Table II.

It is worth remarking that the absolute fluxes, which we calculate at low glucose concentration, depend strongly on the presence or absence of TEA and quinine. The experimental results of $^{86}Rb^+$ fluxes, expressed as percent of total $^{86}Rb^+$ in the islet at any given time, show almost no sensitivity to TEA and 5 μM quinine at 8 mM glucose, where the voltage-gated K^+ channels are not operative (Lebrun et al., 1982).

CONCLUDING REMARKS

It appears from our calculations that the idea of intercellular K^+ ions, compartmentalized in a layer close to the β-cell surface, provides a relatively accurate, quantitative description of the effect of external K^+ on steady state oscillations in the pancreatic β-cell. In our model the time dependence of the intercellular K^+ concentration oscillates in synchrony with the membrane potential, and is coupled both to it and to the intracellular Ca^{2+} concentration. Our results for average K^+ fluxes from the β-cell yield a glucose-induced increase in K^+ efflux. This induced efflux is, in fact, a consequence of the existence of a Ca^{2+}-activated K^+ permeability that triggers an increased extrusion of K^+ through voltage-gated K^+ channels. It is important to appreciate this point: The net effect of the coupled transport processes that occur in the β-cell produce an enhanced efflux of K^+ in response to glucose, even though glucose, itself, triggers this effect by transiently reducing the efflux of K^+. Thus we find no paradox between the existence of Ca^{2+}-activated K^+ channels and $^{86}Rb^+$ efflux experiments (Lebrun et al., 1982). The $^{86}Rb^+$ simply tracks the net K^+ flux, whereas the Ca^{2+}-activated K^+ channels serve as a trigger for bursts of enhanced K^+ efflux through voltage-gated channels.

In our calculations we have assumed that the conductance Ca^{2+}-activated K^+ channels is 50 pS/cell and independent of voltage. The value of 50 pS is estimated from the measured permeability of the β-cell membrane to K^+ in the absence of glucose (Atwater et al., 1983). In our interpretation of the $^{86}Rb^+$ efflux experiments we have, in addition, assumed that the Ca^{2+}-activated K^+ channels are nonselective in their permeability to alkali metal ions (Rosario and Rojas, 1984). Nonselective, voltage independent channels of this sort have been reported in mouse and rat pancreatic acini, rat heart, and mouse neuroblastoma cells (Petersen and Maruyama, 1984).

After the submission of the present work for publications, a patch-clamp study of the Ca^{2+}-activated K^+ channel from the neonatal rat β-cell appeared in print (Cook et al., 1984). There the single channel conductance of the neonatal channel is reported to be 244 pS. Whether or not the Ca^{2+}-activated K^+ channel in neonatal cells is the same as in mature cells remains to be seen. Nonetheless, in the range of 1–3 μM Ca^{2+} ion the percent open time of the neonatal channel is close to zero. Thus, even if there are as many as 50 of these channels per cell—which is the density of the large Ca^{2+}-activated K^+ channel in pig pancreatic acini (Peterson and Maruyama, 1984)—the value of 50 pS/cell, which we have used for the conductance of this channel, seems to be in the correct range.

We also note that the percent open time of the neonatal channel depends sigmoidally on membrane potential at concentrations of Ca^{2+} in the range of 10–30 μM (Cook et al., 1984). At lower Ca^{2+} this sigmoidal dependence on membrane potential appears to be shifted to potentials significantly depolarized with respect to those that operate during bursting. Thus, the lack of a voltage dependence in our calculations for the conductance of the Ca^{2+}-activated K^+ channels may not be a serious shortcoming. The effect of pH on these channels, on the other hand, appears to be significant (Cook et al., 1984). The greatest effect of pH may be during the transient period before the β-cell settles down into steady bursting. We plan to include the effect of pH in an expanded version of our model, and to investigate its consequences for the behavior of the β-cell.

We would like to thank Drs. I. Atwater, E. Rojas, and P. Lebrun for their advice and encouragement during the progress of this work.

Joel Keizer is supported by National Institutes of Health GM 30688-03 and Teresa Ree Chay is supported by the National Science Foundation PCM82 15583.

Received for publication 2 April 1985 and in final form 11 June 1985.

REFERENCES

Andersson, T. 1983. Glucose-induced retention of intracellular ^{45}Ca in pancreatic islets. *Am. Physiol. Soc.* 245:C343–C347.

Ashcroft, F. M., D. E. Harrison, and S. J. H. Ashcroft. 1984. Glucose induces closure of single potassium channels in isolated rat pancreatic β-cells. *Nature (Lond.).* 312:446–448.

Atwater, I., and H. P. Meissner. 1975. Electrogenic sodium pump in β-cells of islets of Langerhans. *J. Physiol. (Lond.).* 247:56P–58P.

Atwater, I., C. M. Dawson, B. Ribalet, and E. Rojas. 1979. Potassium permeability activated by intracellular calcium ion concentration in the pancreatic β-cell. *J. Physiol. (Lond.).* 288:575–588.

Atwater, I., C. M. Dawson, A. Scott, G. Eddlestone, and E. Rojas. 1980. In Biochemistry Biophysics of the Pancreatic β-cell. G. T. Verlag, New York. 100–107.

Atwater, I., B. Ribalet, and E. Rojas. 1978. Cyclic changes in potential and resistence of the β-cell membrane induced by glucose in islets of Langerhans from mouse. *J. Physiol. (Lond.).* 278:117–139.

Atwater, I., L. Rosario, and E. Rojas. 1983. Properties of the Ca-activated K^+ channel in pancreatic β-cells. *Cell Calcium* 4:451–462.

Bergsten, P., and B. Hellam. 1984. Glucose inhibits insulin release when not promoting the entry of calcium into the β-cell. *Biochem. Biophys. Res. Commun.* 125:875–881.

Biegelman, P., B. Ribalet, and I. Atwater. 1977. Electrical activity of mouse pancreatic beta-cells. II. Effects of glucose and arginine. *J. Physiol. (Paris).* 73:201–217.

Chay, T. R. 1985. Chaos in a three-variable excitable cell model. *Physica D.* 16:233–242.

Chay, T. R., and J. Keizer. 1983. Minimal model for membrane oscillations in the pancreatic β-cell. *Biophys. J.* 42:181–190.

Cook, D. L. 1984. Electrical pacemaker mechanisms of pancreatic islet cells. *Fed. Proc.* 43:2368–2372.

Cook, D. L., and N. Hales. 1984. Intracellular ATP directly blocks K^+ channels in pancreatic B-cells, *Nature (Lond.).* 311:271–273.

Cook, D. L., W. E. Crill, and D. Porte. 1981*a*. Glucose and acetylcholine have different effects on the plateau behavior of pancreatic islet cells. *Diabetes.* 30:558–561.

Cook, D. L., M. Ikeucki, and W. Fujimoto. 1984. Lowering pH_i inhibits Ca^{2+}-activated K^+ channels in pancreatic B-cells. *Nature (Lond.).* 311:269–271.

Cook, D. L., D. Porte, and W. E. Crill. 1981*b*. Voltage dependence of rhythmic plateau potentials of pancreatic islet cells. *Am. J. Physiol.* 240:E290–E296.

Dean, P. M. 1973. Ultrastructural morphology of the pancreatic β-cell. *Diabetologia.* 9:115–119.

Dean, P. M., and E. K. Matthews. 1970. Glucose-induced electrical activity in pancreatic islet cells. *J. Physiol. (Lond.).* 210:255–264.

Hedeskov, C. J. 1980. Mechanisms of glucose induced insulin secretion. *Physiol. Rev.* 60:442–509.

Henquin, J. C. 1981. The potassium permeability of pancreatic islet cells: mechanisms of control and influence on insulin release. *In* Biochemistry Biophysics of the Pancreatic β-Cell, G. T. Verlag, New York. 66–73.

Hindmarsh, A. C. 1974. Ordinary differential equations systems solver. Report UCID-30001. Lawrence Livermore Laboratory. Livermore, CA.

Hodgkin, A., and A. F. Huxley. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.).* 117:500–544.

Keizer, J. 1976. Dissipation and fluctuations in nonequilibrium thermodynamics. *J. Chem. Phys.* 64:1679–1687.

Lebrun, P., W. J. Malaisse, and A. Herchuelz. 1982. Paradoxical activation by glucose of quinine-sensitive potassium channels in the pancreatic β-cell. *Biochem. Biophys. Res. Commun.* 107:350–356.

Lebrun, P., W. J. Malaisse, and A. Herchuelz. 1983. Activation, but not inhibition, by glucose of Ca^{2+}-dependent K^+ permeability in the rat pancreatic β-cell. *Biochim. Biophys. Acta.* 731:145–150.

Lee, Y. S., T. R. Chay, and T. Ree. 1983. On the mechanism of spiking and bursting in excitable cells. *Biophys. Chem.* 18:25–34.

Meissner, H. P. 1976. Electrical characteristics of the beta-cells in pancreatic islets. *J. Physiol.* (Paris). 72:757–767.

Meissner, H. P., and J. C. Henquin. 1984. The sodium pump of mouse pancreatic β-cells: electrogenic properties and activation by intracellular sodium. *In* Electrogenic Transport: Fundamental Properties and Physiological Implications. M. P. Blaustein and M. Lieberman, editors. Raven Press, NY. 295–306.

Meissner, H. P., and H. Schmelz. 1974. Membrane potential of beta-cells in pancreatic islets. *Pflügers Arch. Eur. J. Physiol.* 351:195–206.

Newsholme, E. A., and C. Start. 1973. Regulation in Metabolism. John Wiley and Sons, London. 109 and 323.

Pace, C. S. 1984. Role of pH as a transduction device in triggering electrical and secretory responses in islet β-cells, *Fed. Proc.* 43:2379–2384.

Pavlidis, T. 1973. Biological Oscillations: Their Mathematical Analysis. Academic Press, New York.

Perez-Armendariz, E. M., I. Atwater, and E. Rojas. 1985. Glucose-induced oscillatory changes in extracellular potassium concentration in mouse islets of Langerhans. *Biophys J.* In press.

Petersen, O. H., and Y. Maruyama. 1984. Calcium-activated potassium channels and their role in secretion. *Nature (Lond.).* 307:693–697.

Plonsey, R. 1969. Bioelectric Phenomena. McGraw-Hill Book Co. New York.

Ribalet, B., and P. M. Beigleman. 1979. Cyclic variation of K^+ conductance in pancreatic β-cell: Ca^{2+} and voltage dependence. *Am. J. Physiol.* 237:C127–C133.

Rorsman, P., H. Abrahamsson, E. Gylfe, and B. Hellman. 1984. Dual effects of glucose on the cytosotic Ca^{2+} activity of mouse pancreatic β-cells. *FEBS (Fed. Eur. Biochem. Soc.) Lett.* 170:196–200.

Rosario, L., and E. Rojas. 1984. Monovalent cation permeability sequence in the Ca^{2+}-activated K^+-channel of pancreatic B-cells from mouse. *Am. J. Physiol.* In press.

Wollheim, C. B., and G. W. G. Sharp. 1981. Regulation of insulin release by calcium. *Physiol. Rev.* 61:914–974.