Chaotic electrical activity of living β-cells in the mouse pancreatic islet

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Abstract

To test for chaotic dynamics of the insulin producing β-cell and explore its biological role, we observed the action potentials with the perforated patch clamp technique, for isolated cells as well as for intact cells of the mouse pancreatic islet. The time series obtained were analyzed using nonlinear diagnostic algorithms associated with the surrogate method. The isolated cells exhibited short-term predictability and visible determinism, in the steady state response to 10 mM glucose, while the intact cells did not. In the latter case, determinism became visible after the application of a gap junction inhibitor. This tendency was enhanced by the stimulation with tolbutamide. Our observations suggest that, thanks to the integration of individual chaotic dynamics via gap junction coupling, the β-cells will lose memory of fluctuations occurring at any instant in their electrical activity more rapidly with time. This is likely to contribute to the functional stability of the islet against uncertain perturbations.

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1. Introduction

Pancreatic β-cells in the islets of Langerhans control the blood glucose concentration by secreting insulin in response to the presence of extracellular glucose. In the mouse islet, for instance, glucose metabolism triggers rhythmic electrical activity of the β-cell, for a duration ranging from 10 to 60 s at a glucose concentration exceeding 7 mM [1,2]. This activity corresponds to a sequence of alternating cellular states consisting of a depolarizing plateau, on which a spike-train (bursting) of the action potential is superimposed, and an electrically repolarized silent state [3]. Ca\textsuperscript{2+} influx via voltage-activated Ca\textsuperscript{2+} channels evokes the spike-train [4, 5]. This is tightly coupled to insulin secretion [6]. About seventeen years ago, chaotic dynamics was suggested to be associated with the bursting phenomenon [7]. This idea has since been verified mainly through numerical studies based on the Hodgkin–Huxley type model of the ion channels [8–10]. It appears possible to prove mathematically that bursting dynamics is associated with chaos [11]. However, we are not aware of previous studies designed to test to observational data for the possible existence of chaotic dynamics in the electrophysiology of actual β-cells.

The action potential of an isolated (dispersed) mouse β-cell is known not to display the bursting patterns that typically appear in intact β-cells of the islet [1,12,13]. A single isolated β-cell usually generates random sequences of electrical spikes sustained typically for a few minutes [12]. Under particular conditions, isolated cells may display a short-term bursting dynamics ranging from 2 to 5 s [13]. For intact β-cells in the islet, which are electrically coupled with neighboring β-cells via gap junctions, there is significant experimental evidence to demonstrate synchronous electrophysiological activity [14–17]. The role of the electrical coupling in generating the bursting was investigated with a mathematical model [18]. Interestingly, there is no evidence indicating that other constituent cells of the islet, i.e., α- or δ-cells, are connected with β-cells in

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the islet [15,16]. This means that the electrical modulation of an intact β-cell in the islet is mediated only by its neighboring β-cells. Thus the intact β-cell can be a good platform for exploring the physiological role of cell-to-cell electrical coupling [19].

The present study aims at testing for the possible existence of chaotic dynamics underlying the electrophysiological activity of the β-cell. We examine the possible biological effects of the integration of such individual chaotic dynamics in the actual islet. To achieve this purpose, we resort to time series analysis [20,21] of action potentials recorded for isolated living mouse β-cells and intact β-cells in the islet. The difference in dynamical properties between the isolated and the intact cells is analyzed with the help of the surrogate method [22,23]. These methods have been shown to be reliable when handling short time series data, say no more than a few hundreds of data points [20,24–26]. We show that the electrical activity of the isolated cell seems to be governed by chaotic dynamics, while the intact cell in the islet displays marginally chaotic behavior of many degrees of freedom. We also examine how the dynamical behavior of the intact cell changes after the application of a gap junction inhibitor (carbenoxolone) [27] or a KATP-channel blocker (tolbutamide). These experiments allow us to determine whether or not a biologically significant effect is introduced to the islet by the integration of chaotic dynamics underlying individual β-cells [28].

2. Experimental procedures

2.1. Preparation of pancreatic islets and β-cells

We purchased NMRI (Naval Medical Research Institute) mice from a commercial breeder (Møllegaard, Kille Skensved, Denmark). Wild type mice obtained from the TTE2 embryonic stem cell [29] were kindly shared from the laboratory of the Department of Metabolic Disease at The University of Tokyo. The care and use of the animals were approved by the ethical committees of Lund University and Hirosaki University. The animals were anesthetized by cervical dislocation. Immediately afterwards the abdominal cavity was opened, and collagenase (2 mg, dissolved in Hanks’ buffer) was injected into the pancreatic duct. The islets were then isolated by gentle digestion for 25 min at 37 °C. The isolated islets were washed extensively in a collagenase-free solution, subsequently maintained in short-term tissue culture (<24 h) in RPMI 1640 containing 5 mM glucose and 10% (vol/vol) fetal calf serum (Flow Laboratories, Irvine, UK). The islets were then supplemented with 100 µg/ml streptomycin and 100 IU/ml penicillin (both from Northumbria Biologicals, Ltd, Cramlington, UK). Isolated single β-cells were prepared in much the same way as in [30].

2.2. Electrophysiology

Intact (superficial) β-cells in the islets were functionally identified by the ability to generate characteristic bursting patterns, in the presence of glucose concentrations greater than or equal to 10 mM [2,3,15]. The islets were immobilized by a wide-bore (diameter, 50–100 µm) suction pipette in the recording bath. Patch pipettes were pulled from borosilicate glass (the tip resistance was about 5 MΩ, when filled with the pipette solutions). In all the recordings, the electrical contact with the cell interior was established by an addition of 0.24 mg/ml of pore-forming antibiotic amphotericin B [31] (Sigma) to the pipette solution. Perforation required a few minutes. The voltage clamp was satisfactory, when the series conductance was greater than or equal to 40 pS (corresponding to a series resistance of 25 MΩ). The voltage error was less than 5 mV even for the maximum current [15]. We observed the action potential in 10 mM glucose using an EPC-9 patch clamp amplifier (HEKA Electronics, Lambrecht/Pfalz, Germany) and Pulse software (version 8.11; HEKA) with a sampling rate of 500 Hz.

3. Statistical test for chaotic dynamics

To test for chaotic dynamics, we applied the Takens “embedding” theorem [32,33] to the time series data, analyzing their dynamical properties in terms of short-term predictability [20] as well as of the parallelness of neighboring trajectories reconstructed in phase space [21]. The statistical significances of the estimated statistics were inferred by means of the surrogate method [22,23] in combination with the t-statistical test.

3.1. Embedding and mutual information

Given a time series \( \{ x(t) \}_{t=0}^{N-1} \), we apply the embedding theorem to reconstruct, in phase space, trajectories representing the time evolution of a system with delayed vectors that consist of lagged sequences of data points:

\[
\mathbf{x}(t) = (x(t), x(t - \Delta t), \ldots, x(t - (D - 1)\Delta t))
\]

where \( \Delta t \) is an appropriate time lag and \( D \) denotes the embedding dimension. The optimal time lag can be determined utilizing the mutual information as a function of the time lag [34]. The methodology for estimating the mutual information is as follows. Let \( U \) and \( V \) be the sets of realizations of the random variables \( u \) and \( v \), respectively. We can obtain the probability density functions \( P(u), P(v) \) and the joint probability density function \( P(u, v) \) by approximating the corresponding distribution functions with one-dimensional and two-dimensional histograms. Let us express the distribution functions as the histograms of \( M \) partitions and \( M \times M \) partitions. The information entropies \( H(U), H(V) \) and the joint information entropy \( H(U, V) \) are calculated from

\[
H(U) = - \sum_{i=1}^{M} P(u_i) \log_2 P(u_i),
\]

\[
H(V) = - \sum_{i=1}^{M} P(v_i) \log_2 P(v_i),
\]

\[
H(U, V) = - \sum_{i,j=1}^{M} P(u_i, v_j) \log_2 P(u_i, v_j).
\]
where \( u_t \) and \( v_t \) are the central values of the partitions. Thus, the average mutual information \( I(V; U) \) is estimated with

\[
I(V; U) = H(V) - H(V|U) = H(U) + H(V) - H(U, V).
\]

(5)

\( I(V; U) \) represents the amount of information that one can acquire about \( V \), given that \( U \) is known. In time series analysis, \( U \) and \( V \) correspond to the time series \( \{x(t)\}_{t=1}^{N-\tau} \) and its time-delayed counterpart \( \{x(t+\tau)\}_{t=1}^{N-\tau} \), respectively. In this case, \( I(V; U) \) is a measure of the spontaneous loss of information by the dynamical evolution in \( \tau \). Rapid decay of the mutual information with the time lag is a signature of chaos. The appropriate time lag for embedding can be determined from the \( I(V; U) \) plot. To acquire about \( \tau \) by a sum of delayed counterparts \( \{x(t)\}_{t=1}^{N-\tau} \)

3.2. Short-term predictability

Rapid decay of predictability with time, i.e., short-term predictability, despite the determinism governing the dynamical behavior, is an important signature of chaos. One can capture chaotic dynamics underlying a time series by detecting an exponential increase in the prediction error. This is the central idea of the Sugihara–May algorithm, briefly described below.

We make predictions \( T \) time steps into the future by means of function approximation of the dynamical behavior:

\[
x(t + T \Delta t) = F[x(t)] + \varepsilon(T \Delta t)
\]

(6)

where \( F \) is an approximation function and \( \varepsilon(T \Delta t) \) expresses random variables representing the prediction error. To construct the approximation function, we utilize the Sugihara–May predictor, which is a class of local nonlinear approximation technique. In this predictive method, we generate library examples as the pairs of \( x(t) \) and \( x(t + T \Delta t) \) representing the dynamical behavior from the first half of the time series. Then, forecasts \( x(t_p + T \Delta t) \) are made for \( x(t_p) \) generated from the remaining part of the series by a sum of \( x(t_k + T \Delta t) \) nonlinearily weighted by the distance to \( x(t_p) \) and \( x(t_k) \) \( (k = 1, \ldots, D + 1) \). Here, \( x(t_k) \) are \( D + 1 \) vectors pointing in the directions of the vertices of the smallest simplex including \( x(t_p) \) in \( D \)-dimensional Euclidean space.

\[
\hat{x}(t_p + T \Delta t) = \frac{\sum_{k=1}^{D+1} x(t_k + T \Delta t) \exp(-d_k)}{\sum_{k=1}^{D+1} \exp(-d_k)}.
\]

(7)

\[d_k = |x(t_p) - x(t_k)|.
\]

(8)

The accuracy of the prediction is measured in terms of the root mean squared (rms) error between the predicted and actual values normalized by the standard deviation of the library data (normalized rms), denoted by \( E(T \Delta t) \). If \( E(T \Delta t) = 0 \), the prediction is perfect, while it is no better than the average value of the series if \( E(T \Delta t) = 1 \). The dynamical nature of the system determines the scaling property of \( E(T \Delta t) \) with respect to \( T \Delta t \). Deterministic chaos occurs providing

\[
\log \frac{E(T \Delta t)}{E(\Delta t)} = \lambda(T - 1) \Delta t
\]

(9)

where \( \lambda > 0 \) is the largest Lyapunov exponent, which can be estimated from the initial slope of the semilog plot of \( E(T \Delta t)/E(\Delta t) \) against \( (T - 1) \Delta t \) [35].

3.3. Parallelness of neighboring trajectories in phase space

The diagnostic algorithm proposed by Wayland et al. [21] provides a direct measure indicating the degree of visible determinism in time series data. At the heart of this algorithm lies the idea that neighboring trajectories reconstructed in the phase space should point in similar directions if determinism is visible in the dynamical behavior. This method has been shown to be robust against noise contamination of data and to work well in distinguishing chaos from stochastic processes [24].

We generate delayed vectors by reconstruction of a times series. For a randomly chosen vector \( x(t_0) \), we seek its \( K \) nearest neighbors \( x(t_k) \), making the image \( x(t_k + T \Delta t) \) \( (k = 0, 1, \ldots, K) \) with an appropriately chosen time interval \( T \). We measure the degree of diversity in the directions of neighboring trajectories in terms of the translation error:

\[
E_{\text{trans}} = \frac{1}{K + 1} \sum_{k=0}^{K} \frac{||\mathbf{v}(t_k) - \langle \mathbf{v} \rangle||^2}{||\langle \mathbf{v} \rangle||^2},
\]

(10)

\[
\langle \mathbf{v} \rangle = \frac{1}{K + 1} \sum_{k=0}^{K} \mathbf{v}(t_k).
\]

(11)

\[
\mathbf{v}(t_k) = x(t_k + T \Delta t) - x(t_k).
\]

(12)

The displacement vectors \( \mathbf{v}(t_k) \) approximate the tangential vectors of individual trajectories. More visible determinism generates smaller \( E_{\text{trans}} \). To reduce the stochastic error of the estimates, we seek the median of \( E_{\text{trans}} \), for \( Q \) sets of \( M \) randomly chosen \( x(t_0) \), calculating the mean over the \( Q \) medians.

According to the previous numerical works [24,25], \( E_{\text{trans}} \) does not exceed \( \sim 0.1 \) for deterministic time series such as chaos, while \( E_{\text{trans}} \) lies over \( \sim 0.5 \) for correlated random noise with fractional power-law spectral indices lying between 0 and 2. For uncorrelated random noise, \( E_{\text{trans}} \) takes \( \sim 1 \) independently of the embedding dimension. If \( E_{\text{trans}} < 0.1 \) at a finite embedding dimension, the dynamical behavior can be said to be deterministic.

3.4. The surrogate method

The surrogate method permits assessing the significance of a statistic estimated from a single realization of time series. In this method, we first postulate a null hypothesis, in relation to the dynamical nature to be tested. Following the hypothesis, we synthesize surrogate data having the postulated dynamical property to simulate many realizations of the series. Then, an appropriate statistic is estimated for the original and surrogate
data. We assess the significance of the estimates with the \( t \)-statistical test to infer whether or not the null hypothesis is likely to underlie the original data [22,23].

In the present work, the null hypothesis is taken to be that the time series data of the action potentials represent stochastic processes, not low-dimensional chaos. Under this hypothesis, we generate surrogate time series by using a Fourier transform of the original time series followed by the inverse Fourier transform with phase randomization. In the surrogate data, the autocorrelation of the original data, i.e., the underlying linear autoregressive processes, is preserved, while the nonlinear determinism included in the original data, if any, has been lost. Hence, a significant difference in the statistics between the original and the surrogate data indicates that the null hypothesis should be rejected, and that nonlinear determinism is likely present in the original data.

We generated forty surrogate data from the original data, applying the \( t \)-statistical test to the estimates of the translation error. In the case of forty degrees of freedom, the critical value of the two-sided \( t \)-test static is 2.01 at 5% reliability. If \( t \geq 2.01 \), the null hypothesis can be rejected.

4. Results

In the steady state response to 10 mM glucose, the isolated \( \beta \)-cells of the NMRI mice generated random trains of spikes occurring repetitively during the stimulation. Fig. 1(A) shows a typical pattern. It seems to belong to the pattern of class I that was reported in [13]. These observations agree well with the previous ones of NMRI mice [12,36]. The intact \( \beta \)-cells of the islet exhibited intermittent bursting, as shown in Fig. 1(B).

The estimated mutual information exhibited an exponential decay with time both for the isolated cells (Fig. 2(A)) and for the intact \( \beta \)-cells (Fig. 2(B)). The rate of initial decay was significantly slower for the isolated cells than for the intact cells. The mutual information at a time lag of \( T = 10 \) (20 ms) was 1.11 ± 0.04 b for the isolated cells, and 0.78 ± 0.06 b for the intact cells (\( N = 7 \) observations, \( p < 0.01 \)). This means that the intact cells in the islet will lose memory of fluctuations occurring at any instant in their electrophysiological activity more rapidly with time than the isolated cells. Following Fraser’s prescription [34], we selected \( T = 10 \) as the time delay for embedding.

We conducted time series prediction with the Sugihara–May method [20]. Fig. 3(A) and (B) illustrate the prediction error one time step into the future as a function of the embedding dimension, for the isolated and the intact cells, respectively. From these estimates, we determined the minimal embedding dimension that achieves the minimum prediction error. Fig. 3(C) and (D) depict the prediction error at the minimal embedding dimension as a function of prediction-time step, for the isolated and the intact cells, respectively. The rate
of initial decay in predictability is slower for the isolated cells than for the intact cells. However, the rate is so steep that the scaling characteristics of chaos are smeared out. Hence, it is difficult to judge whether the underlying dynamics should be ascribed to deterministic chaos or to stochastic processes.

To test for chaotic dynamics in the electrical activity, we next estimated the degree of visible determinism with the diagnostic method of Wayland et al. [21]. In the isolated cells, five of the seven cells provided the minimum translation errors below 0.1 (Fig. 4(A)). The average over the minima was 0.08 ± 0.01 (\(N = 7\)).
7, Fig. 4(C)). On the other hand, the intact cells provided the minimum translation errors over 0.1 (Fig. 4(B)). Their sample average was 0.18 ± 0.02 (N = 7, Fig. 4(C)), significantly larger than that of the isolated cells (p < 0.01). These results suggest that the electrical activity of the isolated cells represent deterministic chaos, while those of the intact cells may not.

To assess the statistical significance, we applied the surrogate method to the time series data of randomly selected three cells. For both the isolated and the intact cells, the t-statistics estimated for the minimum translation error exceed the critical value at 5% (two-sided) confidence, as shown in Fig. 5(A) and (B). Hence, we can reject the null hypothesis for both the cases. This suggests the presence of deterministic dynamics underlying the electrical activity of the isolated as well as of the intact cells. From the present analysis, as a whole, we can conclude that the dynamics underlying the electrical activity of the isolated cells represent low-dimensional chaos. Such chaotic determinism may be also marginally visible for the intact cells of the islet, despite the many degrees of freedom.

Because the difference in the dynamical behavior between the intact and the isolated cells stems from interactions with neighboring cells via gap junctions in the islet, we next investigated the biological role of the gap junction with a gap junction inhibitor, carbenoxolone [27]. In this experiment, we used the wild type mice [29,37]. Six intact β-cells were subjected to carbenoxolone with 10 mM glucose when their bursting became stable. Then, all the cells ceased bursting in six to ten bursting phases. A slight hyperpolarization (∼6 mV) of the action potential was observed for two of the six cells during the interburst interval. For all the cells, the patterns of the action potential were similar to those of the isolated cells of the NMRI mice (Fig. 6).

We applied the Wayland test to the time series data corresponding to the fourth bursting following the application of carbenoxolone. The minimum translation error significantly
decreased down to 0.08 ± 0.01, from the corresponding value of 0.13 ± 0.01 that was observed before the application of carbenoxolone (p < 0.05, Fig. 7(C)). This suggests that determinism became more visible on the application of the gap junction inhibitor. This may reflect a phase transformation, from high-dimensional chaos to low-dimensional chaos. We also found that, for the islet of the wild type mice, the minimum translation error was significantly smaller (0.13 ± 0.01) than that of the NMRI mice (0.18 ± 0.02, p < 0.01).

We examined the possible existence of chaotic dynamics underlying the intact β-cells of the wild type mice to clarify its physiological role. The application of a $K_{ATP}$ channel inhibitor, tolbutamide (100 μM), to the intact β-cells of the islet was found to render the chaotic determinism more visible, when comparing with the steady state response to 10 mM glucose (Figs. 8 and 9). The application of tolbutamide causes the closing of the $K_{ATP}$ channels and the depolarization of the membrane potential. These effects mimic a stronger stimulation with a higher glucose concentration exceeding 10mM [38]. During the application of tolbutamide, the cells generated a continuous train of the spikes, as shown in Fig. 8. The minimum translation error during this phase was significantly smaller (0.08 ± 0.01) than that in the stable state to 10 mM glucose (0.13 ± 0.01, p < 0.01, Fig. 9(C)). These results indicate that the chaotic dynamics of an isolated cell can become more apparent on the application of tolbutamide.

5. Discussion

We have shown that the action potential of the living isolated single β-cells have dynamical properties of chaos in response to the 10 mM glucose stimulation (Figs. 3–5). The electrical activity of the β-cells became more complex to develop bursting in the islet (Fig. 5(B)). Such complex cooperative activity may be achieved by the interaction between β-cells connected to each other via gap junctions. This inference is consistent with the results shown in Figs. 6 and 7. In fact, the complexity of the electrical activity of the intact cells was lowered by the application of a gap junction inhibitor. Each intact cell seems to have more or less resumed the chaotic dynamics governing the electrical activity of an isolated cell, thanks to gap junction inhibition. Nevertheless, in Fig. 6, the intact cells still burst after the application of the inhibitor. This may be due to imperfect blocking of the gap junctions despite an optimized dose of carbenoxolone. In order to circumvent imperfect gap junction inhibition, we should have used, for example, a connexin-36 knock-out mouse [39].

The properties of the isolated β-cells appear to be different from those reproduced by the mathematical model of a single β-cell [10]. In the model, the parameter $V_5$, defined as the half-activation potential of the variable $S$ representing a slow dynamic, is selected as a control parameter to generate a bifurcation diagram. To mimic the chaotic dynamics, $V_5$ must be set within a narrow range (>1 mV) (for details, see Fig. 3 in [10]). Because of the heterogeneity of individual living β-cells [40], they are unlikely to have a similar value of $V_5$ within the narrow range in the islet. Furthermore, we have recently compared the degree of complexity between the electrical activities of actual living β-cells and those reproduced by the cell model of Mosekilde et al. [10], in terms of the permutation entropy as a variant of the Kolmogorov–Sinai entropy (Miyano et al., unpublished data). The permutation entropy of the actual
isolated cells was significantly higher than that of the cell model. These observations suggest that the living β-cell has an intrinsic mechanism for producing chaotic electrical activities stably and constantly in spite of their heterogeneity. The physiological role of chaos in living systems has been extensively discussed, for example, for the cardiovascular system [41–45] and the nervous system [46–51]. In the nervous system, chaotic dynamics was shown to exist in an isolated neuron during periodic electrical stimulations. However, in the central nervous system, there are many observations indicating the absence of chaos based on time series analysis. We conjecture that the underlying dynamics of the neural network is too complex for the diagnostic methods that can handle dynamical behavior of no more than ten degrees of freedom to capture its chaotic signature [52]. This may be the case with the intact β-cells of the islet responding to 10 mM glucose. In fact, the intact β-cells are connected to neighboring β-cells via gap junctions, and the total conductance of the patched cell is approximately ∼1 nS [15]. Thus, the electrical coupling between β-cells can achieve dynamics of many degrees of freedom, much greater than 10. This idea seems to be supported directly by the faster decay in the mutual information in the intact β-cells (Fig. 2). The integration of the individual cell dynamics may generate a high-dimensional chaotic attractor in the islet. We surmise that such a high-dimensional attractor may endow the islet with a functional stability against uncertain perturbations. That is, small fluctuations in the environment, as well as the spread in cell characteristics, would exert little influence on the synchronous bursting of the islet, thanks to dynamical instability inherent in high-dimensional chaos.

Physiological studies on the β-cell have unraveled the complex mechanism of glucose-induced insulin secretion [53]. Insulin secretion over the physiological range of blood glucose concentrations is biphasic, consisting of a rapidly initiated and transient first phase followed by a sustained second phase [54, 55]. During the first phase, insulin is released at a high rate. In contrast, through the second phase, whose bursting patterns were analyzed in this work, the release rate is lowered but kept constant. The silent phases of the bursting cycles allow preparing, at the expense of ATP, microgranules containing insulin to be secreted through the exocytotic fusion of the granules with the plasma membrane. The synchronous bursting, which is endowed with functional stability by the high-dimensional chaos, may serve to establish a common and steady rhythm that controls the cellular events preceding exocytosis for effective insulin secretion.

In the present work, we have analyzed the dynamical properties of the action potential that belongs to the fast subsystem in the mathematical model [56]. The present analysis could also be applied to the slow subsystem that generates slow oscillations of the membrane potential and the intracellular Ca\(^{2+}\) concentration in the living β-cells [57]. Although it is an issue of importance to test for chaos in the slow subsystem, it is outside the focus of this paper. To conduct such a study, we need data of a larger size over the characteristic time-scale of the slow dynamics.

In summary, we have shown that the complex dynamics underlying the electrical activity of the mouse pancreatic islet arises through the integration of chaotic dynamics of individual β-cells via gap junctions. The islet dynamics may generate a high-dimensional chaotic attractor to achieve the robustness of the islet against uncertain perturbations.
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