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A theoretical study of effects of cytosolic Ca^{2+} oscillations on activation of glycogen phosphorylase

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Abstract

Taking into account the Ca^{2+}-stimulated degradation of inositol 1,4,5-trisphosphate (IP_3) by a 3-kinase, we have theoretically explored the effects of both simple and complex Ca^{2+} oscillations on the regulation of a phosphorylation–dephosphorylation cycle process involved in glycogen degradation by glycogen phosphorylase *a*-form, respectively. For the case of simple Ca^{2+} oscillations, the roles of cytosolic Ca^{2+} oscillations in the regulation of active phosphorylase depend upon the maximum rate of IP_3 degradation by the 3-kinase, V_{M5}. In particular, the smaller the values of V_{M5} are, the lower the effective Ca^{2+} threshold for the activation of glycogen phosphorylase will be. For the case of complex Ca^{2+} oscillations, the average level of fraction of active phosphorylase is nearly independent from the level of stimulation increasing in the bursting oscillatory domain. Both simple and complex Ca^{2+} oscillations can contribute to increase the efficiency and specificity of cellular signalling, and some theoretical results of activation of glycogen phosphorylase regulated by Ca^{2+} oscillations are close to the experimental results for gene expression in lymphocytes.

Keywords: Calcium oscillations; Fraction of glycogen phosphorylase; Frequency encoding

1. Introduction

A large variety of cell types display calcium (Ca^{2+}) oscillations after stimulation by an extracellular agonists such as hormones and neurotransmitters [1–5]. Cytosolic Ca^{2+} oscillations mediate a diverse array of cell functions. For instance, Ca^{2+} oscillations play important roles in regulating gene expression [8]. Experimental results show that Ca^{2+} oscillations reduce the effective Ca^{2+} threshold for activating transcription factors, thereby increasing signal detection at low levels of stimulation. In addition, specificity is encoded by the Ca^{2+} oscillation frequency.

Phosphorylation–dephosphorylation cascades represent one of the most exquisite modes of cellular regulation. A prototypic example of phosphorylation–dephosphorylation cascade involved in metabolic regulation is the one controlling the balance between glycogen synthesis and degradation. The coordinated changes in the phosphory-

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lation status of glycogen synthase and glycogen phosphorylase are under hormonal control through the activation of protein kinases by cyclic AMP and cytosolic Ca^{2+}. A bicyclic cascade model for the control of glycogen phosphorylase and glycogen synthase by glucose have been proposed by Cárdenas and Goldbeter [6]. This model has proven to be consistent with experimental findings concerning the sequential changes in the activity of glycogen phosphorylase and glycogen synthase observed following the addition of supra-threshold amounts of glucose.

Recently, Gall et al. [7] have studied theoretically the effects of Ca^{2+} oscillations on the activation of glycogen phosphorylase controlled by the phosphorylation–dephosphorylation cycle based on bicyclic cascade model proposed by Cárdenas and Goldbeter [6] in hepatocytes. First, by modelling periodic sinusoidal variations in the intracellular Ca^{2+} concentration, they have shown that Ca^{2+} oscillations reduce the threshold for the activation of the enzyme; Second, by using signal-induced Ca^{2+} oscillation model based on Ca^{2+}-induced Ca^{2+} release (CICR), they have found that Ca^{2+} oscillations can potentiate the response to a hormonal stimulation, and Ca^{2+} oscillations in hepatocytes could contribute to increase the efficiency and specificity of cellular signalling, as shown experimentally for gene expression in lymphocytes [8]. The Ca^{2+} oscillation types considered by Gall et al. [7] are simple periodic Ca^{2+} oscillations since the variation of activity of inositol 1,4,5-trisphosphate 3-kinase in the model of Ca^{2+} was neglected. However, in some cell types, particularly in hepatocytes, complex Ca^{2+} oscillations reminiscent of the bursting-like behavior displayed by many excitable cells have been observed in response to stimulation by specific agonist [9,10]. As these cells are not electrically excitable, it is likely that these complex Ca^{2+} oscillations rely on the interplay between two intracellular mechanisms capable of destabilizing the steady state. Some theoretical models have been proposed to account for such complex Ca^{2+} oscillations [11–14].

Now a question to be raised is how the complex Ca^{2+} oscillations affect the activation of glycogen phosphorylase, or what are the effects of complex Ca^{2+} oscillations on the phosphorylation–dephosphorylation cycle controlling the activation of glycogen phosphorylase? In this paper, combining the model for control of glycogen phosphorylase activity of Ref. [7] with the model for cytosolic Ca^{2+} oscillations of Ref. [14], we will explore theoretically the possible role of both simple and complex Ca^{2+} oscillations in the regulation of a phosphorylation–dephosphorylation cycle process involved in glycogen degradation by glycogen phosphorylase. This process plays a vital role in the regulation of glycaemia, providing glucose for the organism between feeding in hepatocytes (for review see Ref. [15]).

2. Model

The function of glycogen phosphorylase is to govern glycogen degradation. The enzyme acts as a sensor of blood glucose level, liberating glucose from stored glycogen as needed. The dynamics of the Ca^{2+}-associated phosphorylation–dephosphorylation cycle involves the glycogen phosphorylase: glycogen phosphorylase is converted from the inactive *b*-form into the active *a*-form by phosphorylase kinase, and inactivated by a phosphatase. Phosphorylase kinase is a hexadecamer composed of four different subunits ($\alpha_4\beta_4\gamma_4\delta_4$). The δ subunit is identical to calmodulin and mediates the Ca^{2+}-sensitivity of phosphorylase kinase [16].

The model used for the activation of liver glycogen phosphorylase by Ca^{2+} oscillations by Gall et al. [7] is based on the bicyclic cascade model proposed by Cárdenas and Goldbeter [6] for the control of glycogen phosphorylase and glycogen synthase by glucose. When the dynamics of phosphorylation–dephosphorylation cycle controlling the activation of glycogen phosphorylase by cytosolic Ca^{2+} is only considered, then the kinetic equation governing the time evolution of fraction of active glycogen phosphorylase (X) is given by

$$\frac{dX}{dt} = V_{p1}(Z)\frac{1-X}{K_{p1}(Z)+1-X} - \frac{V_{pM2}(1+\alpha G/(K_{a1}+G))X}{K_{p2}/(1+G/K_{a2})+X}, \quad (1)$$

with the Ca^{2+}-dependent terms

$$V_{p1}(Z) = V_{pM1}\left(1 + \gamma \frac{Z^4}{K_{a5}^4 + Z^4}\right), \quad (2)$$

$$K_{p1}(Z) = \frac{K_1^1}{1 + Z^4/K_{a6}^4}, \quad (3)$$

where Z represents the concentration of cytosolic Ca^{2+} and G represents the intracellular concentration of glucose. In above model, it is assumed that glucose activates phosphorylase phosphatase (of maximum rate V_{pM2} and normalized Michaelis constant K_{p2}) by decreasing the K_m of enzyme, with an activation constant K_{a2}, and further activates the enzyme by enhancing its maximum rate by a multiplicative factor α, with an activation constant K_{a1}. Moreover, the model is a typical Ca^{2+}-dependent system, it is also assumed that Ca^{2+} activates the phosphorylase kinase (of maximum rate V_{pM1} and normalized Michaelis constant K_{p1}) by decreasing the K_m of the enzyme, with an activation constant K_{a6}, and further activates the enzyme by enhancing its maximum rate by a multiplicative factor γ, with an activation constant K_{a5}. The values of parameter are $G = 10.0$ mM, $K_1^1 = 0.1$, $K_{p2} = 0.2$, $K_{a1} = K_{a2} = 10$ mM, $K_{a5} = K_{a6} = 0.5$ μM, $\alpha = \gamma = 9$, $V_{pM1} = 1.5$ min^{-1}, $V_{pM2} = 0.6$ min^{-1}.

In hepatocytes, repetitive Ca^{2+} oscillations can be obtained by the application of Ca^{2+}-mobilizing agonists, acting through the phosphoinositide signalling pathway [3]. Each transient rise with 3 s from basal Ca^{2+} ($\sim$100 nM) level to a peak of at least 600 nM and has a duration of approximately 7 s. The oscillation period varies, from 0.3 to 4 min depending on the agonist concentration. Here, we employ a model of Ca^{2+} oscillations which was previously proposed by Borghans et al. [13] to account for complex intracellular Ca^{2+} oscillations based on the mechanism of CICR [17,18]. Recently, Houart et al. [14] have investigated in detail the various complex dynamic behaviors of this model. The key species in this Ca^{2+} model are the cytosolic Ca^{2+} (its concentration is represented by Z), the Ca^{2+} sequester in an internal store (its concentration is represented by Y), and the inositol 1,4,5-trisphosphate (IP_3) (its concentration is represented by A) which is another important intracellular messenger. Then, the time evolution of these species can be described by following differential equations:

$$\frac{dZ}{dt} = V_{in} - V_2 + V_3 + k_f Y - kZ, \quad (4)$$

$$\frac{dY}{dt} = V_2 - V_3 - k_f Y, \quad (5)$$

$$\frac{dA}{dt} = \beta V_4 - V_5 - \epsilon A, \quad (6)$$

with

$$V_{in} = V_0 + V_1 \beta, \quad (7)$$

$$V_2 = V_{M2} \frac{Z^2}{K_2^2 + Z^2}, \quad (8)$$

$$V_3 = V_{M3} \frac{Z^m}{K_Z^m + Z^m} \frac{Y^2}{K_Y^2 + Y^2} \frac{A^4}{K_A^4 + A^4}, \quad (9)$$

$$V_5 = V_{M5} \frac{A^p}{K_5^p + A^p} \frac{Z^n}{K_d^n + Z^n}. \quad (10)$$

In these equations, V_0 refers to a constant input from the extracellular medium and V_1 is the maximum rate of stimulus-induced influx of Ca^{2+} from the extracellular medium. Parameter β reflects the degree of stimulation of the cell by an agonist and thus only varies between 0 and 1. The rates V_2 and V_3 refer, respectively, to pumping of cytosolic Ca^{2+} into the internal stores and to the release of Ca^{2+} from these stores into the cytosol in a process activated by cytosolic calcium. V_{M2} and V_{M3} denote the maximum values of these rates. Parameters K_2, K_Y, K_Z and K_A are threshold constants for pumping, release and activation of release by Ca^{2+} and by IP_3. k_f is a rate constant measuring the passive, linear leak of Y into Z. k relates to the assumed linear transport of cytosolic Ca^{2+} into the extracellular medium. V_4 is the maximum rate of stimulus-induced synthesis of

Table 1
Parameter values corresponding to the simple oscillations and the various types of complex oscillatory behavior in the Ca^{2+} oscillations model

Parameters	Simple oscillation	Bursting	Chaos	Quasiperiodicity
n	4.0	2.0	4.0	4.0
m	2.0	4.0	2.0	2.0
p	2.0	1.0	1.0	2.0
β	0.5	0.46	0.65	0.51
K_2 (μM)	0.1	0.1	0.1	0.1
K_5 (μM)	1.0	1.0	0.3194	0.3
K_A (μM)	0.2	0.1	0.1	0.2
K_d (μM)	0.4	0.6	1.0	0.5
K_Y (μM)	0.2	0.2	0.3	0.2
K_Z (μM)	0.5	0.3	0.6	0.5
k (min^{-1})	10.0	10.0	10.0	10.0
k_f (min^{-1})	1.0	1.0	1.0	1.0
ϵ (min^{-1})	0.1	1.0	13.0	0.1
V_0 ($\mu M\ min^{-1}$)	2.0	2.0	2.0	2.0
V_1 ($\mu M\ min^{-1}$)	2.0	2.0	2.0	2.0
V_{M2} ($\mu M\ min^{-1}$)	6.0	6.0	6.0	6.0
V_{M3} ($\mu M\ min^{-1}$)	20.0	20.0	30.0	20.0
V_4 ($\mu M\ min^{-1}$)	2.0	2.5	3.0	5.0
V_{M5} ($\mu M\ min^{-1}$)	5.0	30.0	50.0	30.0

IP_3. V_5 is the rate of phosphorylation of IP_3 by the 3-kinase, it is characterized by a maximum value V_{M5} and a half-saturation constant K_5, and the 3-kinase is stimulated by Ca^{2+} is taken into account through a term the Hill form, with a threshold Ca^{2+} level equal to K_d. Parameters m, n and p are Hill coefficients.

The model (Eqs. (4)–(6) with Eqs. (7)–(10)) for cytosolic Ca^{2+} shows not only simple periodic Ca^{2+} oscillations, but also some complex oscillatory phenomena. The dynamic behavior of this model in parameter space has been investigated by Houart et al. [14], and it was shown that the complex Ca^{2+} oscillatory behaviors include bursting, chaos and quasiperiodicity. Four sets of parameter values corresponding to the simple oscillations and the complex oscillatory behaviors are listed in Table 1. In order to study, the effects of both simple and complex Ca^{2+} oscillations on the dynamics of the phosphorylation–dephosphorylation loop, numerical simulations are needed. Eqs. (1), (4)–(6) are simulated by using a simple forward Eular algorithm with a time step of 0.001 min. In each calculation, the time evolution of the system lasted 1000 min after transient behavior was discarded.

3. Effects of Ca^{2+} oscillations on activation of glycogen phosphorylase

Intracellular Ca^{2+} oscillations take the form of abrupt spikes, sometimes preceded by a gradual increase in cytosolic Ca^{2+}. When the parameter values for cytosolic Ca^{2+} model are the first column in Table 1, the model for cytosolic Ca^{2+} shows a simple periodic Ca^{2+} oscillations. Under the regulation of Ca^{2+} oscillations, the fraction of active phosphorylase, X, also shows simple oscillation behavior. Fig. 1a shows the time courses of fraction of active phosphorylase at a constant value of stimulation level ($\beta = 0.5$) for different maximum rate of IP_3 degradation by the 3-kinase, V_{M5}. As can be expected from the regulations considered, the peak in cytosolic Ca^{2+} precedes the peak in fraction of active phosphorylase (data not shown).

It is well known that [14] intracellular Ca^{2+} oscillations occur in a range bounded by two critical values (i.e. two supercritical Hopf bifurcation points) of the stimulation level β, and there are different relationships between the frequency of Ca^{2+} oscillations and the level of stimulation for distinct values of V_{M5} as shown in Fig. 1b. For

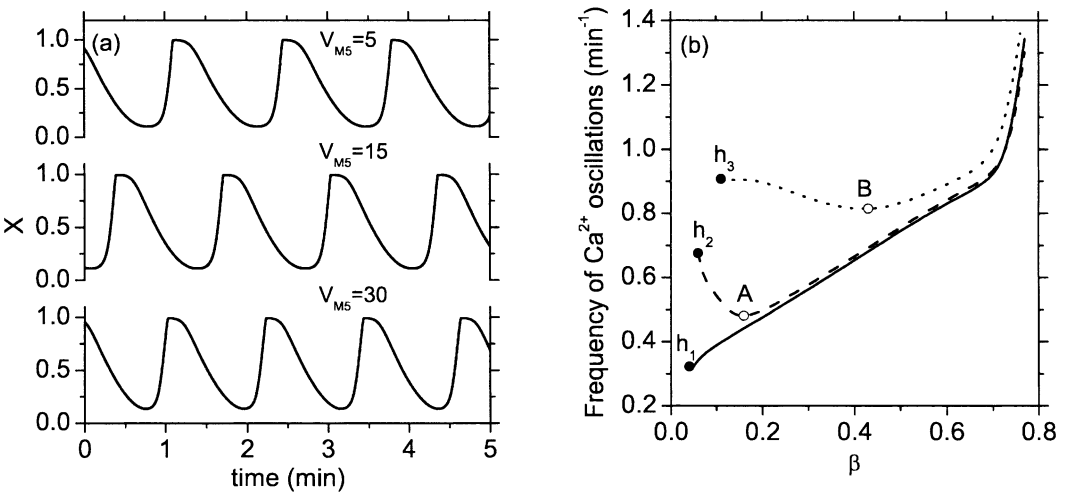

Fig. 1. (a) Temporal evolution of fraction of active phosphorylase regulated by simple Ca^{2+} oscillations at a fixed stimulation level $\beta = 0.5$ for different V_{M5}. (b) Different relationships between the frequency of Ca^{2+} oscillations and the level of stimulation for $V_{M5} = 5$ μM min^{-1} (solid line), $V_{M5} = 15$ μM min^{-1} (dash line) and $V_{M5} = 30$ μM min^{-1} (dot line). h_1, h_2 and h_3 correspond to the smaller supercritical Hopf bifurcation points of Ca^{2+} kinetics for different V_{M5}, and *A* and *B* correspond to the smallest frequency of Ca^{2+} oscillations, respectively. The other parameter values are given by the first column in Table 1.

small values of V_{M5}, the frequency of Ca^{2+} oscillations is increased with stimulation level β. However, for large values of V_{M5}, the frequency of Ca^{2+} oscillations is decreased with stimulation level β firstly, and the frequency of Ca^{2+} oscillations reaches a minimum with β increasing (the point *A* for $V_{M5} = 15$ μM min^{-1} and the point *B* for $V_{M5} = 30$ μM min^{-1} in Fig. 1b), and then goes up with β. It means that, for large values of V_{M5}, there is a smallest frequency of Ca^{2+} oscillations (or the largest oscillation period) with the variation of β. In this calcium oscillations model, increasing the level of stimulation triggers a rise first in the rate of synthesis and then in the rate of degradation of IP_3 (due to the enhanced stimulation of the 3-kinase by Ca^{2+}) [14]. This is why qualitatively distinct relationships between the level of stimulation and the frequency of Ca^{2+} oscillations for different parameter values can be obtained.

The effects of stimulation β on the fraction of active phosphorylase for distinct values of V_{M5} are shown in Fig. 2a. It can be found that, for small values of V_{M5}, the average fraction of phosphorylated phosphorylase jumps mutationally from low level to high value at the bifurcation point of Ca^{2+} kinetics ($\beta = 0.04$ at h_1). However, for large values of V_{M5}, the average fraction of phosphorylated phosphorylase, $\langle X \rangle$, is still at small level even when cytosolic Ca^{2+} begins to oscillate ($\beta = 0.06$ at h_2 and $\beta = 0.11$ at h_3), and $\langle X \rangle$ is gradually increased after Ca^{2+} begins to oscillate. The fraction of active phosphorylase in different response to cytosolic Ca^{2+} oscillations at smaller bifurcation point of Ca^{2+} kinetics for different value of V_{M5} have been plotted in Fig. 2b. The relation between average fraction of active phosphorylase and stimulation level β shows a step-increasing phenomenon for different value of V_{M5}. During the regime of Ca^{2+} oscillations, our results also show that, in the low level of stimulation β, although the frequency of Ca^{2+} oscillations for $V_{M5} = 5$ μM min^{-1} is smaller than that for $V_{M5} = 15$ or 30 μM min^{-1} (as shown in Fig. 2a), yet the average fraction of active phosphorylase for $V_{M5} = 5$ μM min^{-1} is larger than that for $V_{M5} = 15$ or 30 μM min^{-1}. In the high level of stimulation β, the average fraction of active phosphorylase for $V_{M5} = 5$ μM min^{-1} will be smaller than that for $V_{M5} = 15$ or 30 μM min^{-1}.

When the active phosphorylase is stimulated by

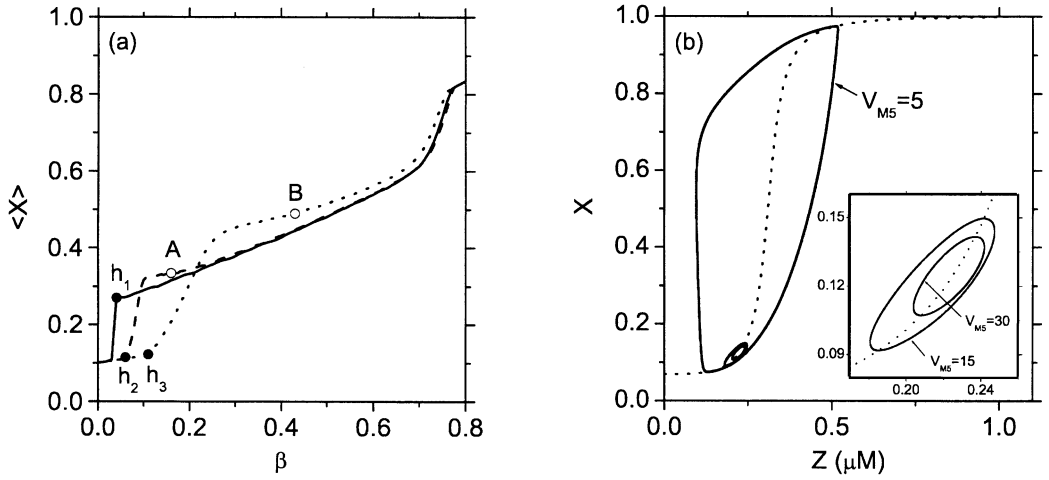

Fig. 2. Effect of a hormonal stimulation on the fraction of active phosphorylase. (a) $\langle X \rangle$ vs. β for $V_{M5} = 5$ μM min^{-1} (solid line), $V_{M5} = 15$ μM min^{-1} (dash line) and $V_{M5} = 30$ μM min^{-1} (dot line), respectively. Points h_1, h_2, h_3, A and B correspond to these as in Fig. 1b. (b) Kinetics of the phosphorylation–dephosphorylation cycle at the beginning of cytosolic Ca^{2+} oscillation (i.e. at points h_1, h_2 and h_3, respectively). The dot line in (b) in the phosphorylase level regulated by a sustained elevation of Ca^{2+} concentration (by setting $dX/dt = 0$ in Eq. (1)).

a sustained Ca^{2+} level at the steady-state, the relation between the fraction of active phosphorylase and the concentration of Ca^{2+} has a steep sigmoidal nature [7], this result is a direct consequence of the saturation of the converter enzymes by their substrates, leading to a phenomenon known as 'zero-order ultrasensitivity' [19], and of the cooperativity in the kinase activation by Ca^{2+} [20]. Fig. 3a shows the similar steep sigmoidal nature for distinct values of V_{M5}. Ca^{2+} oscillations

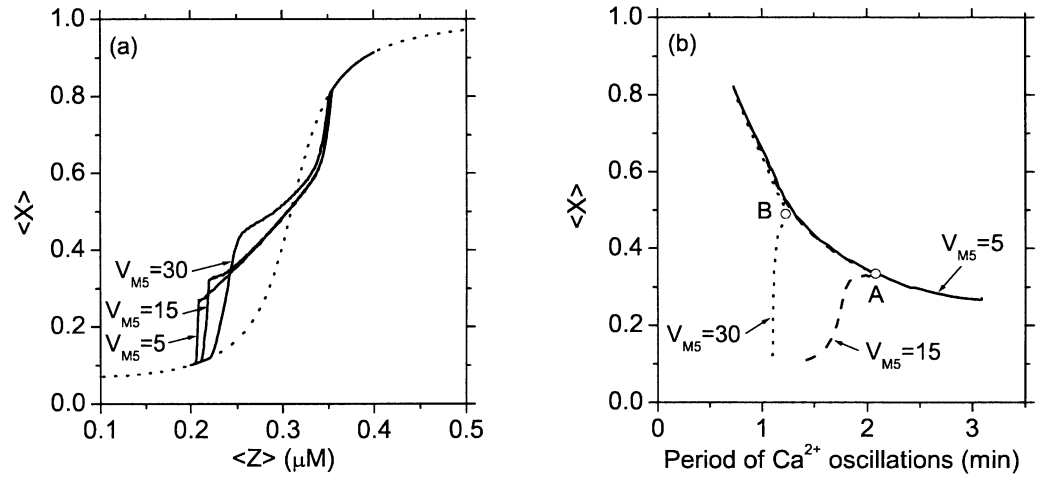

Fig. 3. Effects of cytosolic Ca^{2+} oscillations on the fraction of active phosphorylase. (a) Average fraction of active phosphorylase as a function of average Ca^{2+} concentration for different V_{M5}, the dot line by the response of $\langle X \rangle$ to the regulation by a sustained Ca^{2+} concentration. (b) Average fraction of active phosphorylase as a function of period of Ca^{2+} oscillations, A and B correspond to these as marked in Fig. 1b, and period of Ca^{2+} oscillations at A or B is the largest for a given V_{M5}.

reduce the threshold for the activation of the enzyme. The threshold depends on the parameter value of V_{M5}. The smaller the value of V_{M5} is, the lower the effective Ca^{2+} threshold for the activation of glycogen phosphorylase will be. It is also shown that, when the periodic Ca^{2+} oscillations exist for distinct values of V_{M5}, the $\langle X \rangle$ levels are larger than those obtained with an equivalent stimulation by a steady Ca^{2+} concentration in the low level of β but the $\langle X \rangle$ levels are smaller than those obtained with an equivalent stimulation by a steady Ca^{2+} concentration in the high level of β.

Different relationships between the average fraction of active phosphorylase and the period of Ca^{2+} oscillations for distinct values of V_{M5} are shown in Fig. 3b. For small values of V_{M5}, the average fraction of active phosphorylase is decreased with the period of Ca^{2+} oscillations increasing (see solid line in Fig. 3b). For large values of V_{M5}, when the stimulation level is high (upper the point *A* or *D* in Fig. 3b), the average fraction of active phosphorylase is decreased with the period of Ca^{2+} oscillations increasing, however, when the stimulation level is low (lower the point *A* or *B*), the average fraction of active phosphorylase is increased with the period of Ca^{2+} oscillations increasing. In fact, this distinct relationships between the average fraction of active phosphorylase and the period of Ca^{2+} oscillations for different values of V_{M5} could be easily understood through the variations of frequency of Ca^{2+} oscillations with the level of stimulation (Fig. 1b).

When the parameter values of Ca^{2+} model take the second, third and fourth column in Table 1, cytosolic Ca^{2+} shows complex oscillation behaviors [14]: bursting, chaos and quasiperiodicity, respectively. The time series of fraction of active phosphorylase regulated by different types of Ca^{2+} oscillations are shown in Fig. 4. The active phosphorylase also shows the same complex oscillation behaviors in the regulation of Ca^{2+} oscillations, and the peak in cytosolic Ca^{2+} concentration slightly precedes the peak in active phosphorylase fraction for all complex oscillation types.

The effects of complex Ca^{2+} oscillations on the average fraction of active phosphorylase are shown

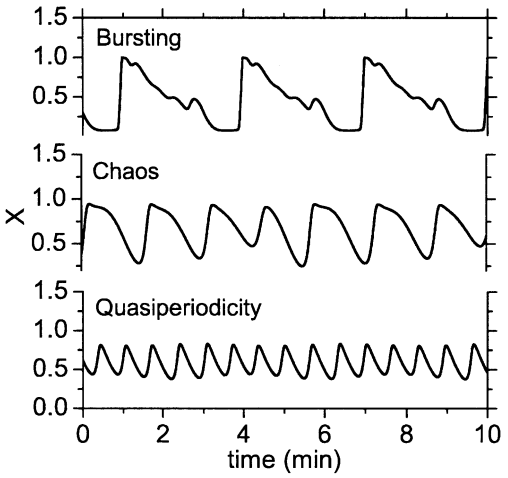

Fig. 4. Temporal evolution of fraction of active phosphorylase regulated by complex calcium oscillations: bursting, chaos and quasiperiodicity. The parameter values are given by the second, third and fourth column in Table 1, respectively.

in Fig. 5. The variation of $\langle X \rangle$ with β is different for various complex Ca^{2+} oscillatory types (Fig. 5a). In both chaotic and quasiperiodic types, $\langle X \rangle$ levels are increased with the level of stimulation β increasing. Moreover, $\langle X \rangle$ for the quasiperiodic type is always larger than that for chaotic type in the regime of Ca^{2+} oscillations. However, for the case of bursting Ca^{2+} oscillations, $\langle X \rangle$ level is gently decreased with β during the regime of Ca^{2+} oscillations. Therefore, the average level of fraction of active phosphorylase is nearly independent from the level of stimulation β increasing in the oscillatory domain. On the other hand, Fig. 5b shows that both bursting and quasiperiodic Ca^{2+} oscillation types can reduce the threshold for the activation of the enzyme. However, chaos Ca^{2+} oscillations can hardly reduce the threshold (by comparing curves (b) and (c) with the open dots), and the effect of chaos Ca^{2+} oscillations on the average fraction of active phosphorylase is so weak that it barely distinguish the $\langle X \rangle$ for case of chaos Ca^{2+} oscillations and that for case of the steady-state.

In the case of bursting Ca^{2+} oscillations, the period of cytosolic Ca^{2+} oscillations is increased with the level of stimulation [14]. The relationships both the $\langle X \rangle$ and the frequency of cytosolic Ca^{2+}

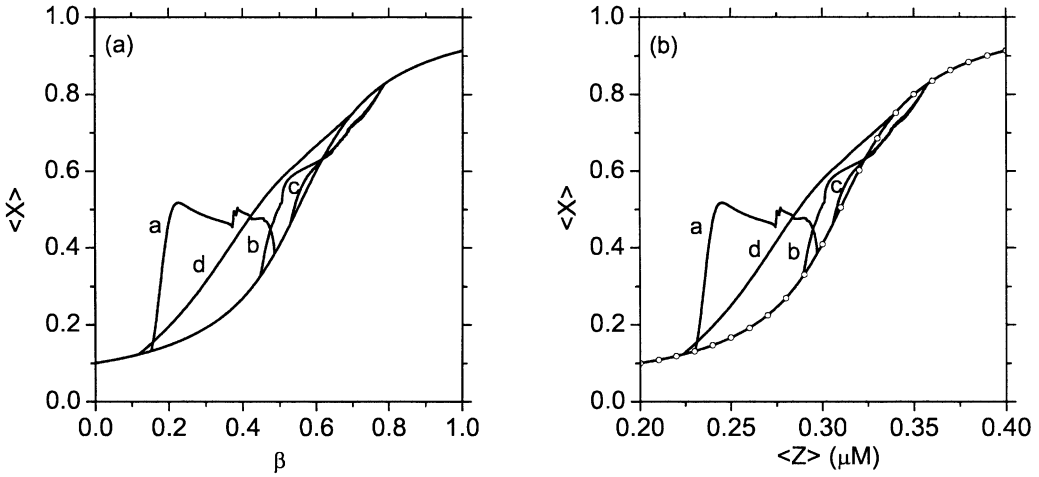

Fig. 5. Effect of complex Ca^{2+} oscillation on the fraction of active phosphorylase. (a) $\langle X\rangle$ vs. β for complex Ca^{2+} oscillations: bursting (curve a), chaos (curve b, $\epsilon = 11\ min^{-1}$), chaos (curve c, $\epsilon = 13\ min^{-1}$) and quasiperiodicity (curve d). (b) $\langle X\rangle$ vs. $\langle Z\rangle$ for different Ca^{2+} oscillation types: bursting (curve a), chaos (curve b, $\epsilon = 11\ min^{-1}$), chaos (curve c, $\epsilon = 13\ min^{-1}$) and quasiperiodicity (curve d). The open circles are the response of $\langle X\rangle$ to the regulation by a sustained Ca^{2+} concentration.

oscillations with the level of stimulation are shown in Fig. 6a, respectively. With the increase of β, the concentration of cytosolic Ca^{2+} is increased, and a step increase of the average fraction of active phosphorylase occurs before the Ca^{2+} begin to oscillate (Fig. 6a). However, after Ca^{2+} oscillating, $\langle X\rangle$ has small-amplitude increasing with the increase of stimulation level β first, then $\langle X\rangle$ is decreased, and there are small-amplitude increase of $\langle X\rangle$ at some medial values of β

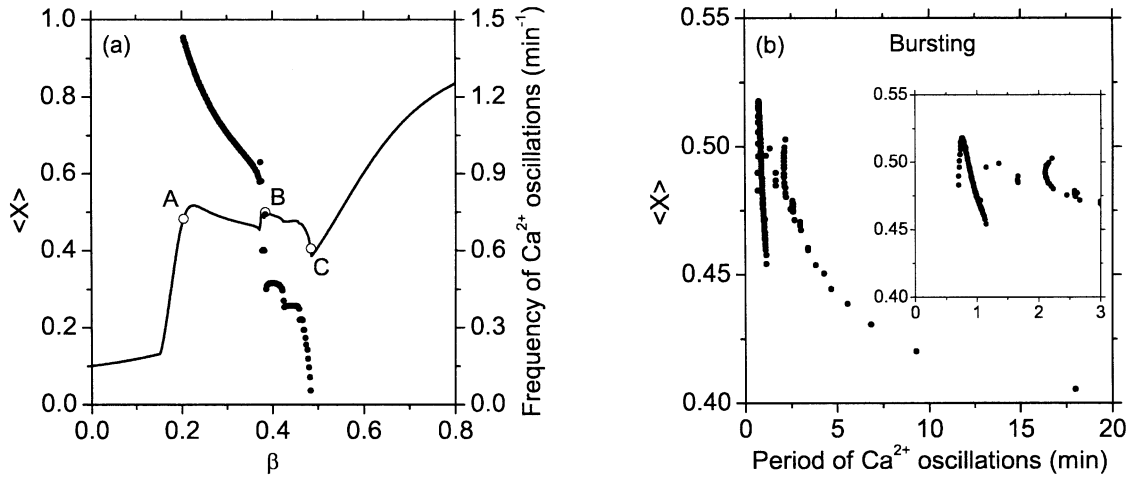

Fig. 6. Effects of bursting Ca^{2+} oscillations on the fraction of active phosphorylase. (a) The relationship between average fraction of active phosphorylase (solid line) and frequency of Ca^{2+} oscillations (solid circle) as a function of β. Points *A* and *C* (open circles) correspond to the two supercritical Hopf bifurcation points of Ca^{2+} dynamics. Note that some frequencies of bursting Ca^{2+} oscillations jump located *B* (open circle). (b) Average fraction of active phosphorylase as a function of the period of bursting Ca^{2+} oscillations.

between two bifurcation points. Thus, the decrease of frequency of Ca^{2+} oscillations with β makes the average level of fraction of active phosphorylase nearly independent from the level of stimulation β increasing in the oscillatory domain. Finally, the average fraction of active phosphorylase as a function of the period of bursting Ca^{2+} oscillations is shown in Fig. 6b. In general, the average fraction of active phosphorylase is decreased with the period of bursting Ca^{2+} oscillations increasing, but small-amplitude increase occurs during the beginning of bursting Ca^{2+} oscillation and at some medial values of β between two bifurcation points (as shown by the insert in Fig. 6b), respectively.

4. Conclusions

Previous theoretical investigations for the control of glycogen phosphorylase activity suggested that simple Ca^{2+} oscillations decrease the effective Ca^{2+} threshold for the activation of glycogen phosphorylase [7]. Furthermore, the level of activity of the phosphorylase kinase oscillates in phase with Ca^{2+} oscillations, from the point of view of the intrinsic time-scales of phosphorylase kinase activation, that is corroborated by experimental observations on pancreatic acinar cells [21]. Based on the model for control of glycogen phosphorylase activity of Ref. [7] and the model for cytosolic Ca^{2+} oscillations of Ref. [14], we have explored theoretically the possible effects of both simple and complex Ca^{2+} oscillations on the regulation of a phosphorylation–dephosphorylation cycle process involved in glycogen degradation by glycogen phosphorylase *a*-form, respectively.

In the case of simple Ca^{2+} oscillations, the effects of cytosolic Ca^{2+} oscillations on the fraction of active phosphorylase depend upon the maximum rate of IP_3 degradation by the 3-kinase, V_{M5}. Our results showed that, at the smaller bifurcation point of Ca^{2+} kinetics, the step increase of the average fraction of active phosphorylase for small value of V_{M5} is mutational, but that for large values of V_{M5}, is gradual. The smaller the values of V_{M5} are, the lower the effective Ca^{2+} threshold for the activation of glycogen phosphorylase will be. There are different relationships between the period of Ca^{2+} oscillations and the level of average fraction of active phosphorylase for distinct values of V_{M5}.

In the case of complex Ca^{2+} oscillations, the variation of $\langle X \rangle$ is different for various complex Ca^{2+} oscillatory types. The most interesting result is the prediction that, in the case of bursting Ca^{2+} oscillations, $\langle X \rangle$ level is gently decreased with β instead of increased during the regime of Ca^{2+} oscillations. Therefore, the average level of fraction of active phosphorylase is nearly independent, from the level of stimulation β increasing in the oscillatory domain for the case of bursting Ca^{2+} oscillations. It is also predicted that the average fraction of active phosphorylase is decreased with the period of bursting Ca^{2+} oscillations increasing.

In conclusion, both simple and complex cytosolic Ca^{2+} oscillations can decrease the effective Ca^{2+} threshold for the activation of glycogen phosphorylase, i.e. the Ca^{2+} oscillations could contribute to increase the efficiency and specificity of cellular signalling, as shown experimentally for gene expression in lymphocytes [8]. It should be pointed out that some theoretical results of this present study, for instance, the effects of average Ca^{2+} concentration on the average fraction of glycogen phosphorylase, the relationships between the average fraction of glycogen phosphorylase and the period of Ca^{2+} oscillations, are very close to the experimental results for gene expression in lymphocytes. Thus, it would be highly interesting to investigate if similar experimental techniques could be used to measure the effects of Ca^{2+} oscillations on the glycogenolysis.

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