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[Ca^{2+}] oscillations in a model of energy-dependent Ca^{2+} uptake by the endoplasmic reticulum

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Abstract

Active Ca^{2+} transport in living cells necessitates controlled supply of metabolic energy. Direct coupling between sarco/endoplasmic reticulum (ER) Ca^{2+} ATPases (SERCA) and intracellular energy-generation sites has been well established experimentally. On the basis of these experimental findings we propose a pump-driven model to investigate complex dynamic properties of a cell system. The model describes the pump process both by the Ca^{2+} ATPase itself and by a suitable description of the glycolysis. The associated set of differential equations shows a rich behavior, the solutions ranging from simple periodic oscillations to complex patterns such as bursting and spiking. Recent experimental results on calcium oscillations in *Xenopus laevis* oocytes and on dynamic patterns of intracellular Ca^{2+} concentrations in electrically non-excitable cells are well described by corresponding theoretical results derived within the proposed model. The simulation results are further compared to spontaneous [Ca^{2+}] oscillations in primitive endodermal cells.

Keywords: Intracellular calcium oscillations; Ca^{2+} dynamics; Ca^{2+} transport; Ca^{2+}ATPase; Glycolysis

1. Introduction

One of the most essential demands of a cellular system is to keep intracellular [Ca^{2+}] at a sufficiently low level of about 0.1 μM. As calcium ions play a central role in the regulation of many vital cell functions such as growth, differentiation, intracellular transport, secretion, metabolism, cell contraction, and motility (Orrenius et al., 1989), disruption of intracellular Ca^{2+} homeostasis can lead to uncontrolled changes in these processes, which may result in severe toxicity (Orrenius et al., 1989; Berridge et al., 1998). To maintain a low concentration in the cytosol, calcium is removed from the cytosol by Ca^{2+}-ATPase enzymes. Ca^{2+} ATPase transports Ca^{2+} against its concentration gradient by utilizing the metabolic energy derived from hydrolysis of adenosine triphosphate (ATP) (de Meis et al., 1970; de Meis, 1981; Inesi, 1985). It has been previously suggested that glycolytic enzymes within the plasma membrane make glycolytically derived ATP immediately available to energy-demanding transport systems in the membranes (Schrier, 1966). Evidence for a coupling between glycolysis and ion transport has been provided by experiment. If glycolysis is blocked, Ca^{2+} transport is interrupted (Paul et al., 1989; Yu and Inesi, 1995; Zu et al., 1995). Further, experiments have shown that glycolytic enzymes such as hexokinase and phosphofructokinase may be used as ATP-regenerating systems by Ca^{2+} ATPase (Montero-Lomeli and de Meis, 1992; Ramos and de Meis, 1999). Moreover, Lien

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et al. (1995) have observed that intracellular [Ca^{2+}] is modulated by glucose via endoplasmic reticulum (ER) Ca^{2+} ATPase. This property implies a functional coupling between glycolysis and Ca^{2+} transport (Lien et al., 1995). Such an organization should affect intracellular [Ca^{2+}] in a far more complex manner than has been previously believed. Interestingly, complex dynamic patterns of intracellular [Ca^{2+}] have been observed in a variety of different cell types either after hormonal stimulation or spontaneously (Allen et al., 1984; Cuthbertson and Chay, 1991; Gray, 1988; Jacob et al., 1988; O'Sullivan et al., 1989; Woods et al., 1987; Yule and Callacher, 1988) (for a review see also Carafoli (2002) and Jacob (1990)). Fig. 1 displays representative traces of intracellular Ca^{2+} oscillations in primitive endodermal cells (Sauer et al., 1998). The addition of thapsigargin, an ER Ca^{2+}-ATPase blocker, abolishes the oscillatory activity, thus demonstrating the participation of Ca^{2+} ATPase in [Ca^{2+}] oscillations.

Hormonal stimulation is associated with Ca^{2+} release from intracellular calcium stores (Ehrlich, 1995; Marks, 1997; Mikoshiba, 1997). Thus, most models assume the oscillations to arise from a feedback mechanism between intracellular Ca^{2+} and/or inositol 1,4,5 trisphosphate (IP_3) with Ca^{2+}-channel receptors, the ryanodine receptor and the IP_3 receptor, leading to periodic channel opening of intracellular Ca^{2+} stores. Specific models for periodic Ca^{2+} release have been developed to take account of the respective effects of different types of Ca^{2+}-channels (Berridge and Galione, 1988; Cuthbertson and Chay, 1991; Goldbeter, 1996; Meyer and Stryer, 1988; De Young and Keizer, 1992; Schuster et al., 2002). However, [Ca^{2+}] oscillations are a common phenomenon in electrically non-excitable cells, and even though Ca^{2+}-release mechanisms are cell-type specific, the basic principles underlying [Ca^{2+}] dynamics are not. Yet all cell types which display [Ca^{2+}] oscillations contain Ca^{2+} ATPase and glycolytic enzymes. Thus, we were motivated to investigate whether or not the dynamics of Ca^{2+} ATPases could principally account for periodic behavior on a more unified basis. To address this question, we investigated the stability of the coupled system of Ca^{2+} ATPase and glycolytic enzymes. We will demonstrate that both stable resting levels and different types of oscillations of intracellular [Ca^{2+}] can be understood in terms of an appropriate pump model.

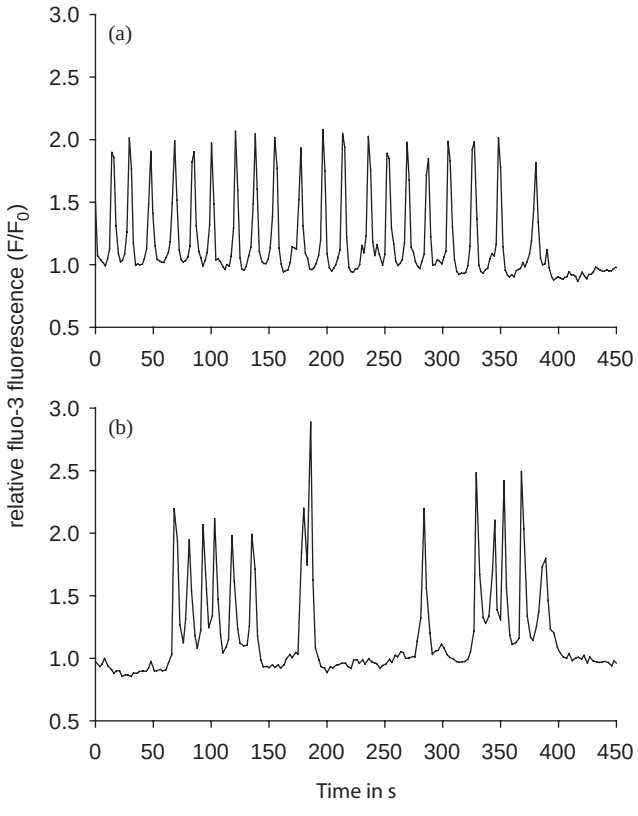

Fig. 1. Spontaneous [Ca^{2+}] oscillations. Representative traces of [Ca^{2+}] oscillations recorded in cell layers of the primitive endoderm at the periphery of embryoid bodies, which are cultivated from pluripotent murine embryonic stem cells. The characteristics of [Ca^{2+}] oscillations are different in individual cells. Shown are traces of periodic oscillations (a) as well as of bursting behavior (b). Intracellular Ca^{2+} has been recorded by confocal laser scanning microscopy after staining of embryoid bodies with the Ca^{2+}-sensitive dye fluo-3,AM (Sauer et al., 1998).

In Section 2, we introduce the model and derive a system of differential equations that describe the dynamics of the model system. In Section 3, we investigate the dynamics of the system using stability analysis and numerical methods under the condition of both constant glucose concentrations ([Glc]) and variable [Glc]. The oscillatory solutions of the system are explored in detail, and the dependencies on the system parameters that control the Ca^{2+} influx and the pump strength are elaborated. The simulation results are compared with available experimental data on Ca^{2+} waves observed in *Xenopus laevis* oocytes (Camacho and Lechleiter, 1993; Falcke et al., 2003). In Section 4, the model results are compared with spontaneous Ca^{2+} oscillations that occur in primitive endodermal cells (Sauer et al., 1998). Finally, in Section 5 the model results are summarized and discussed against the background of experimental data and existing models.

2. Model

The catalytic cycle of Ca^{2+} ATPase contains two distinct enzyme conformations, E_1 and E_2, and several intermediate reactions. The form E_1 faces the external surface of the membrane of the intracellular store, the ER, and has a high affinity for Ca^{2+} ($\approx 1\ \mu M$ at pH 7) (de Meis, 1981; de Meis et al., 1970; Inesi, 1985). In the form E_2, Ca^{2+} binding sites face the interior of the Ca^{2+} store and have a low affinity for Ca^{2+} (about