An Electrical Model for the Cytoplasmic Calcium Wave in Fertilized Eggs

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Abstract. The calcium wave subsequent to fertilization of the egg is analyzed in terms of an electrical equivalent circuit. The circuit consists of a switch, a capacitor, an inductor, and a resistor. The switch symbolizes a series of chemical reactions initiated by the sperm that lead to the development of the calcium wave. Its closure signifies the onset of the calcium wave. The capacitor and inductor represent the endoplasmic reticulum. The capacitive component of the endoplasmic reticulum controls the release of calcium ions, while the inductive component regulates the sequestration of calcium ions. The resistor represents the inductor and cytoplasm and has very low resistance. The analysis of the circuit shows that the period of calcium oscillations is proportional to the size of the egg. It agrees with measurements on various types of eggs.

Key words: Cytoplasmic calcium wave, Fertilization of eggs

1. Introduction

One of the major goals of embryonic research is to elucidate the signal transduction pathways and the mechanisms of morphogenesis [1]. During embryonic development great amounts of information are transmitted to and from various regions within the fertilized egg. In the eggs of all species reported, one of the most obvious events soon after fertilization is a transient increase in the cytosolic calcium ion concentration. The transient increase propagates as a wave from the sperm-entry point to the opposite side or, for a few cases, from the periphery inward from the cortical endoplasmic reticulum. This event signifies the onset of development. The origin of the calcium wave has been studied extensively. Examples of papers summarizing these studies are given in [2–5]. Physical or mathematical models describing the calcium wave or oscillations are lacking. Recently, the theory of chaos was applied to analyze the intracellular calcium oscillations in various cells [6]. The present paper describes a simple physical model to account for calcium oscillations in eggs soon after fertilization.

2. Calcium Wave and Oscillations

A wave of Ca^{2+} emanates from the sperm-entry point of the fertilized egg after the initial membrane depolarization caused by the sperm-egg interaction. Its concentration becomes many times higher than the resting concentration. The concentration

Figure 1. The equivalent circuit for the calcium-wave process.

peak propagates radially toward the opposite side of the sperm-entry point at a speed of 5–10 $\mu\text{m/s}$. When it reaches the opposite pole, it is reflected backward toward the sperm-entry point. The back and forth propagation eventually fades away; and at any given time the Ca^{2+} concentration is uniform throughout the egg. However, the concentration remains variable and oscillates at a well defined frequency of 10–20 Hz [7, 8]. For some eggs the Ca^{2+} wave is solitary. For example, after the appearance of the calcium wave at the sperm-entry point of the *Xenopus* egg, the peak of the wave reaches a maximum value of about 1.2 μM , which is about three times the resting concentration [9]. It propagates toward the future posterior pole at a speed of about 8 $\mu\text{m/s}$. As the wave propagates, the Ca^{2+} concentration near the sperm-entry point slowly returns to the resting level in about 10 minutes. No more massive release of calcium ions is observed at the sperm-entry point.

The interaction between the sperm and egg triggers a series of chemical reactions. One of the byproducts of these reactions is diffusible inositol trisphosphate. Inositol trisphosphate molecules are thought to chemically induce the opening of Ca^{2+} channels along the endoplasmic reticulum near the sperm-entry point [10]. While inositol trisphosphate can initially open the first Ca^{2+} channels, the subsequent opening of Ca^{2+} channels during wave propagation is likely to involve the calcium-induced calcium release mechanism. The initial release of Ca^{2+} causes a chain reaction of Ca^{2+} release from the endoplasmic reticulum away from the sperm-entry point. The release process then spreads and propagates toward the opposite side. This process gives rise to the calcium wave. It has been shown that most, if not all, of the calcium ions involved come from internal stores rather than from the external medium [11, 12]. The oscillation of the cytoplasmic Ca^{2+} concentration is believed to be due to a periodic release and sequestration of Ca^{2+} by the endoplasmic reticulum [13–15].

3. Electrical Circuit Model

The electromagnetic mechanism underlying the release and sequestration of calcium ions can be understood in terms of an electric circuit shown in Figure 1. The circuit has four elements: a switch denoted by S, a capacitor of capacitance C, an inductor of inductance L, and a resistor of resistance R. The values of C, L, and R are taken to be constant, and they do not vary with time. The combination of the capacitor and inductor describes the action of the endoplasmic reticulum; and the resistor represents both the inductor and the cytoplasm. In the model calcium ions are stored in the capacitor. The switch closes in the presence of inositol trisphosphate. Once the switch is closed, calcium ions leak out of the capacitor and pass through the inductor and the resistor. As the ions travel through the inductor, an electromotive force is generated in the inductor. When the capacitor is empty, the electromotive force of the inductor pumps the calcium ions back to the capacitor. Once the capacitor is filled with calcium ions, it leaks again. Subsequently, the inductor pumps the calcium ions back to the capacitor again. The calcium ions move in and out of the capacitor in a regular manner. According to the model the calcium ions undergo damped harmonic motion through the proposed circuit. The damped harmonic motion requires that $4L > R^2 C$. Therefore,

$$Q(t) = \frac{1}{2} Q_0 e^{-\frac{R}{2L}t} \cos \left[\sqrt{\frac{1}{LC} - \frac{R^2}{4L^2}} t \right] + \frac{1}{2} Q_0, \quad (1)$$

where Q_0 is the charge due to Ca^{2+} stored in the capacitor before the switch is closed at time $t = 0$ and $Q(t)$ is the charge stored in the capacitor at any time t . The resistor is related to the dissipation of the energy generated by the movement of calcium ions. A larger resistance implies a smaller fraction of calcium ions would be returned to the endoplasmic reticulum. If all the released calcium ions are returned, R would be zero. It is assumed that R is close to zero. This assumption satisfies the requirement for the cyclic behavior of the calcium ions and the sequestration of most of the released calcium ions.

The period of the calcium oscillation can be determined using Equation 1. As a good approximation, assume that $R = 0$. At time $t = 0$, the capacitor has a charge of Q_0 . After one period of time (T) has elapsed, the capacitor has charge Q_0 again, or $Q(T) = Q_0$. From Equation 1, $\cos \sqrt{\frac{1}{LC}} T = 1$, and $T = 2\pi\sqrt{LC}$. If R is zero, the concentration of calcium ions in the cytoplasm would oscillate indefinitely. The oscillation eventually stops because R is not equal to zero. The number of oscillations is dependent on the type of egg. In eggs where solitary calcium waves are observed, the period of the wave is usually large. For example, for the *Xenopus* egg the period is about 10 minutes. This implies that the flow of calcium ions is nearly critically damped. The model can qualitatively account for the periodic variation in the calcium ion concentration in fertilized eggs.

4. Discussion

An electrical circuit is used to describe the movement of calcium ions in and out of the endoplasmic reticulum. In this analysis, the endoplasmic reticulum has two compartments. One compartment is capacitive and the other is inductive. The former is in charge of storing calcium ions, while the latter is in charge of sequestering calcium ions from the cytoplasm. After the endoplasmic reticulum is activated by inositol trisphosphate, calcium ions stored in the capacitive compartment are released. They travel to the inductive compartment and also to the cytoplasm. When the calcium ion concentration of the inductive compartment reaches a critical level, the sequestration of the cytoplasmic calcium ions begins. The sequestration is an active process where excess cytoplasmic calcium ions are pumped back to the endoplasmic reticulum. In this model the pumping force comes from the electromotive force of the inductor. As the capacitor discharges, the motion of the charges energizes the inductor and determines the electromotive force for the sequestration later. The net result is that calcium ions move in and out of the endoplasmic reticulum in an orderly fashion. During each calcium oscillation the endoplasmic reticulum uses energy for active transport of cytoplasmic calcium back to its store. The energy used in the sequestration of calcium ions can be viewed as energy dissipated by the resistor in the circuit.

The resistor in the model leads to an incomplete sequestration of the excess calcium ions in the cytoplasm. According to Equation 1, the amount of charge or calcium ions pumped back to the capacitor or the endoplasmic reticulum is $Q(T) = \frac{1}{2} Q_0 e^{-\frac{R}{2L}T} + \frac{1}{2} Q_0$, which is less than Q_0 . Therefore, a very small amount of calcium ions released from the endoplasmic reticulum does not return back after each calcium oscillation. These calcium ions could be released to the external medium at the peak of the calcium oscillations.

Table 1. The duration of calcium waves observed in various cells

Group	Genus	Cell width (μm)	Temperature ($^{\circ}\text{C}$)	Duration (s)
Echinoderms	<i>Scaphechinus</i>	105	23	11
Tunicates	<i>Phallusia</i>	140	20	11
Hemichordates	<i>Saccoglossus</i>	400	23	50
Bony fishes	<i>Hypomedusa</i>	730	211	91
Bony fishes	<i>Gasterosteus</i>	960	20	120
Bony fishes	<i>Carassius</i>	1100	21	180
Amphibians	<i>Xenopus</i>	1300	22	160
Amphibians	<i>Xenopus</i>	1300	22	130

Data taken from Jaffe (1991)

Figure 2. Variation of the duration of calcium oscillation with cell width. Descriptions of the data are tabulated in Table 1.

Oscillations in the calcium ion concentration have been observed in many different fertilized eggs and their periods are different [16]. Thus far, there is no model which could correlate the various periods. The circuit model shows that the period, $T \approx 2\pi\sqrt{LC}$, where L is the inductive component and C is the capacitive component of the endoplasmic reticulum. The endoplasmic reticulum lies on the periphery of the egg. It is expected that L and C are proportional to the diameter (d) of the egg. Consequently, $T \propto d$. The release and sequestration of calcium ions are dependent on temperature. Therefore, to test the hypothesis that the period of the calcium wave is proportional to the size of the cell only the measurements taken at temperatures between 20 and 23°C are used. These measurements are tabulated in Table 1 and plotted in Figure 2. Figure 2 shows a linear relationship as predicted by the model. Therefore a simple electric circuit can account for the general features of calcium oscillation.

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