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Ca^{2+} wave dispersion and spiral wave entrainment in *Xenopus laevis* oocytes overexpressing Ca^{2+} ATPases

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Abstract

Complex, spatiotemporal patterns of intracellular Ca^{2+} release in *Xenopus* oocytes can be accounted for by the operation of two fundamental processes: Ca^{2+} release from the endoplasmic reticulum (ER) via the inositol 1,4,5-trisphosphate receptor (IP_3R) with its inherent dependency on cytosolic Ca^{2+}, and Ca^{2+} uptake via Ca^{2+} ATPases. Overexpression of sarco-endoplasmic reticulum Ca^{2+} ATPases (SERCAs) in *Xenopus* oocytes, increases IP_3-induced Ca^{2+} wave frequency and amplitude [1–3]. This effect can be attributed to an increased removal of cytoplasmic Ca^{2+} and more efficient refilling of Ca^{2+} stores. By overexpressing SERCA isoforms, we report here that Ca^{2+} waves exhibit dispersion [4–6]. At wavelengths greater than 60 μm, wave velocity is constant. However, wave velocity and amplitude progressively decreases at smaller wavelengths. Below λ ~20 μm, Ca^{2+} waves disperse and fail to propagate. In oocytes exhibiting both spiral and target patterns of Ca^{2+} release, spiral waves had higher frequencies and showed entrainment of the surrounding regions. These properties are characteristic of a classical excitable medium [4–6].

Keywords: Ca^{2+} oscillations; Inositol; Oocytes; Excitable media

1. Introduction and background

Inositol 1,4,5-trisphosphate (IP_3)-induced intracellular Ca^{2+} release plays a key role in the action of many hormone and neurotransmitter pathways [7–10]. Cell growth, differentiation, secretion and contraction are processes controlled by Ca^{2+} signaling. It is well established that the mechanism of Ca^{2+} release begins with G-protein or tyrosine kinase mediated activation of phospholipase C (PLC). At the plasma membrane, PLC, stimulates production of IP_3 which diffuses into the cytosol where it binds to the IP_3 receptor (IP_3 R), releasing Ca^{2+} from endoplasmic reticulum (ER) stores. Ca^{2+} signals produced by hormone activation are complex in spatial and temporal domains [11]. Oscillations in the Ca^{2+} response have been suggested to encode cellular functions [12]. Gu and Spitzer [13] have demonstrated that developmental changes in a K^+ current, neurite outgrowth, and secretion are dependent on the occurrence of Ca^{2+} oscillations and Ca^{2+} waves. Hajnoczky and Thomas [14] have shown that mitochondrial respiration depends on the frequency of Ca^{2+} waves in hepatocytes. Spatial control of gene expression has also been

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demonstrated in a mouse pituitary cell line (AtT20 cells) where transient increases in nuclear Ca^{2+} control transcription of genes that contain the cyclic AMP responsive element (CRE), while cytosolic Ca^{2+} transients are necessary for the activation of transcription via the serum-response element (SRE) [15]. Thus, in many cases spatial and/or temporal transients in Ca^{2+}, rather than a continuous global Ca^{2+} release are required to activate a cellular process.

2. Ca^{2+} release is an excitable process

In *Xenopus* oocytes, we have described complex spatiotemporal patterns of Ca^{2+} release using confocal microscopy [1–3,16–20]. Depending on the concentration of IP_3, we observe different patterns of Ca^{2+} release. At low IP_3 concentrations (10–50 nM), discrete sites of Ca^{2+} release are observed and have been referred to as Ca^{2+} 'puffs' [21]. In cardiac cells, where the analogous intracellular Ca^{2+} release channel is the ryanodine receptor, these discrete, elementary events are called Ca^{2+} 'sparks' [22]. At slightly higher concentrations of IP_3 (50–100 nM), abortive Ca^{2+} waves propagate asymetrically and travel only short distances (~10–50 μm). At high concentrations of IP_3 (>1–10 μM), we typically observe a large tide of Ca^{2+} release with no repetitive Ca^{2+} waves. It is only at intermediate concentrations of IP_3 (100 nM to 1 μM) that repetitive complex Ca^{2+} wave patterns are obtained [1,2]. Specifically, we observe propagating Ca^{2+} waves originating at multiple focal sites and generating broken, circular and spiral waves [16,18]. However, the probability of observing these focal sites is higher in the animal pole of the oocyte. Ca^{2+} waves annihilate each other upon collision, revealing an underlying refractory period during which Ca^{2+} release is temporarily inhibited [2]. Furthermore, the waves propagate with undiminished amplitude, suggesting a regenerative mechanism. These fundamental observations are characteristic of an excitable medium [23]. An excitable process is one that undergoes a large excursion away from steady state in response to a suprathreshold stimulus, and returns to steady state before it can respond to a new suprathreshold stimulus. When individual excitable processes are coupled by a common diffusible catalyst, a set of mathematical rules accounts for very complex spatiotemporal pattern formations. Spiral and circular waves are the trademark patterns of excitable media, and are observed in systems ranging from the classic Belousov–Zhabotinsky chemical reaction, to aggregating slime mold in *Dictyostelium discoideum* and electrical activity in neuronal and cardiac tissue [24–27]. Our original discovery [16] of propagating and annihilating spiral Ca^{2+} waves in *Xenopus* oocytes extended the framework of excitability to intracellular Ca^{2+} signaling. Importantly, this concept of Ca^{2+} excitability can also be successfully applied to other cell types as well as to intercellular Ca^{2+} signaling in tissues such as heart, liver, brain and more recently, in the retina [28–32,55].

3. Ca^{2+} -induced Ca^{2+} release (CICR) is the elementary excitable event

The fundamental property responsible for excitability is the Ca^{2+} dependency of the IP_3-bound IP_3R [18]. At low Ca^{2+} concentrations, the IP_3R ion channel is closed, however, its probability of opening increases with increasing cytosolic Ca^{2+} concentrations [33–36]. Consequently, Ca^{2+} ions released from the open IP_3R act to further increase the open probability of the channel. This positive feedback loop is referred to as Ca^{2+}-induced Ca^{2+} release (CICR). At high Ca^{2+} concentrations, the probability of channel opening decreases leading to inactivation [33–36]. It has been suggested that inhibition of the IP_3R may be mediated by an accessory protein called calmedin [37,38]. Both activation (channel opening) and inactivation (channel closing) of the IP_3R are faster at higher Ca^{2+} levels [35]. These strongly non-linear properties of the IP_3R constitute fundamental feedback mechanisms ultimately responsible for complex Ca^{2+} wave activity.

Ca^{2+} diffusion, together with the process of CICR serves to couple individual Ca^{2+} release sites (Ca^{2+} puffs or sparks) into an excitable medium which can propagate Ca^{2+} waves. However, wave propagation is only successful when the density of IP_3-bound IP_3Rs (excitable sites) is sufficiently high so that Ca^{2+} released from one receptor can diffuse to neighboring receptors. The amount of Ca^{2+} released and the distance to the nearest excitable IP_3R are rate limiting steps in this process. Reducing IP_3R channel inactivation will increase the amount of Ca^{2+} released and will

thereby increase the likelihood of continuous wave propagation. The distance to the nearest IP_3-bound IP_3R can also be decreased by increasing the concentration of IP_3 (assuming that the channels are not saturated). We suggest that the increasing occupation of IP_3Rs by IP_3 underlies the continuous progression from Ca^{2+} sparks/puffs to asymmetric abortive Ca^{2+} waves, and from the later to a continuous Ca^{2+} wave. The amount of Ca^{2+} released during a Ca^{2+} spark/puff appears to be too large to be attributed to Ca^{2+} release through a single receptor protein [39,40]. Thus, these events are presumably due to the activation of a few receptors in a cluster acting as a functional unit. Ca^{2+} release from single IP_3Rs or ryanodine receptors are referred to as blips and quarks, respectively [40]. If the Ca^{2+} release which initiates a Ca^{2+} wave originates from a cluster of receptors, then the distance between IP_3R clusters and the activation state of neighboring clusters will be important in determining whether wave propagation is successful.

4. The role of Ca^{2+} ATPases (SERCAs)

Once Ca^{2+} is released into the cytosol, resting Ca^{2+} levels are restored by pumping Ca^{2+} either across the plasma membrane [41] or back into the sarco-endoplasmic reticulum stores [42]. Here, we focus on the sarco-endoplasmic reticulum Ca^{2+}-ATPases (SERCAs). Three distinct genes have been cloned (SERCAs 1, 2 and 3) with alternatively spliced variants (SERCA 1a and 1b; SERCA 2a and 2b) [43–48]. Lytton et al. [49] have studied the Ca^{2+} sensitivity and transport capacities of all SERCAs by overexpression in *COS* cells. The SERCA 2b isoform is expressed in non-muscle and has the highest affinity for Ca^{2+} (K_D ~200 nM) while having also the lowest transport capacity of all ATPases. SERCAs 1 and 2a have comparable Ca^{2+} affinities (K_D ~400 nM) and are expressed in fast skeletal muscle and cardiac/slow twitch muscles, respectively. Finally, SERCA 3 which is particularly abundant in thymus, intestine and cerebellum, has the lowest sensitivity to cytosolic Ca^{2+} (K_D ~1 μM). SERCA 3 has a unique ER signaling target which is not shared by other isoforms and has been suggested to reside in a ER subcompartment which is chronically elevated with Ca^{2+} [50]. Preliminary experiments suggest that SERCA 2b and SERCA 3 are the isoforms endogenously expressed in *Xenopus* oocytes (J. Lytton, pers. commun.).

5. Overexpression of SERCA isoforms in *Xenopus* oocytes

As we mention above, injections of IP_3 at intermediate concentrations (~100–300 nM) elicit distinctive Ca^{2+} wave patterns. This activity is characterized by the appearance of an initial tidal wave of Ca^{2+} which is followed by oscillatory waves with a periodicity of ~10 s (Fig. 1). Overexpression of the fast twitch skeletal muscle SERCA1 isoform results in Ca^{2+} oscillations of higher frequency without a preceding tidal wave [1]. Two-three days following mRNA injections, a two–three-fold increase in frequency is observed (wave period ~4 s). In addition to changes in wave frequency, SERCA1 overexpression resulted in an ~two-fold increase in the amplitude of individual waves at peak activity [1].

6. Ca^{2+} wave dispersion and spiral entrainment in oocytes overexpressing SERCAs

In an excitable medium, wave dispersion occurs when consecutive waves propagate into regions which have recently been excited and hence are still refractory [4–6]. The frequency at which dispersion begins to occur provides an estimate of the refractory period of the underlying excitatory event. As the wave frequency increases beyond this value, an increasing number of refractory Ca^{2+} release sites is encountered and more time is needed to reach the excitation threshold. This leads to a continual decrease in wave velocity and amplitude as the frequency increases. Eventually, the number of active receptors decreases to a point where wave propagation cannot be supported and dispersion occurs.

The Ca^{2+} wave frequency in oocytes uninjected with mRNA is not sufficiently high to affect wave velocity. Fig. 1 shows a control oocyte in which the velocity of wave propagation remained constant at ~19.0 μm/s as the wavelength decreased from ~100 to 60 μm (average periodicity of ~10 s). Similar results were obtained in other oocytes (n = 48),

where the period between consecutive waves varied between 6–13 s and the wave velocity remained constant at ~20 μm/s. The wavelength in these oocytes varied from 60 μm to over 200 μm. Similarly, when IP_3-induced Ca^{2+} wave activity is measured 2–3 days after SERCA1 mRNA injections, we also observed no variance in velocity over the measured wave frequencies. The wave velocity averaged 21.5 μm/s with period of ~4 s [1]. These data indicated that the underlying refractory period must be less than 4 s.

We were able to further increase the Ca^{2+} wave frequency up to five-fold over control oocytes when we changed the expression vector for the SERCA1 to include the 5′ and 3′ untranslated regions of *Xenopus* β-globin gene [3]. In addition, we waited longer (5–7 days after mRNA injections) before Ca^{2+} wave activity was induced by IP_3 injections and analyzed. These procedures increased oocyte SERCA1 expression such that the Ca^{2+} wave periods decreased to between 1.5 and 3 s. At these wave frequencies, we observed a progressive reduction in both wave amplitude and velocity (Fig. 2), which is indicative of wave dispersion. It has previously been reported that SERCA 1 and SERCA 2a have similar biophysical properties

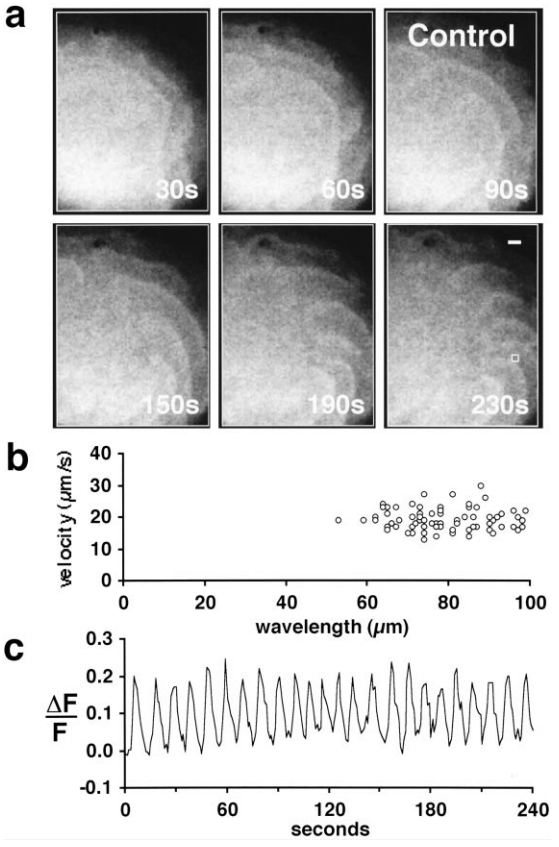

Fig. 1. Ca^{2+} wave activity in a control oocyte does not show the dispersion phenomenon. (a) Ca^{2+} activity was induced by a 50 nl bolus injection of IP_3 (final concentration ~300 nM). Confocal images of Ca^{2+} waves are shown for images taken at times indicated. The scale bar in frame 230 s is 50 μm. (b) Scatter plot of wave velocities as a function of wavelength. Average velocity is 18.8 μm/s. (c) Line plot of Ca^{2+} wave intensity for the 5×5 pixel square shown in frame 230 s. Ca^{2+} concentration is expressed as $\Delta F/F_{rest}$, where $\Delta F = F - F_{rest}$. The wave period during these measurements averaged ~10 s.

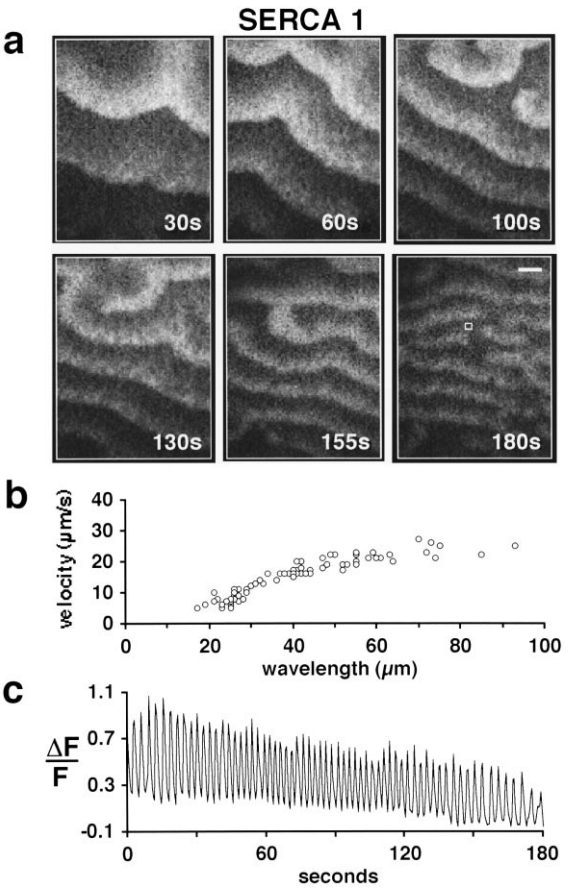

Fig. 2. Repetitive Ca^{2+} wave activity in an oocyte overexpressing SERCA 1 shows wave dispersion. (a) Images of repetitive Ca^{2+} waves at high magnification (40× objective lens). IP_3 concentration is ~300 nM (final). Scale bar is 20 μm. (b) Scatter plot of wave velocities shows a decrease in velocity as the wavelength decreases. (c) Line plot of Ca^{2+} concentration for the 5×5 pixel square shown in frame 180 s. The wave period is ~2.8 s during the first 60 s and ~3.1 s during the final 60 s.

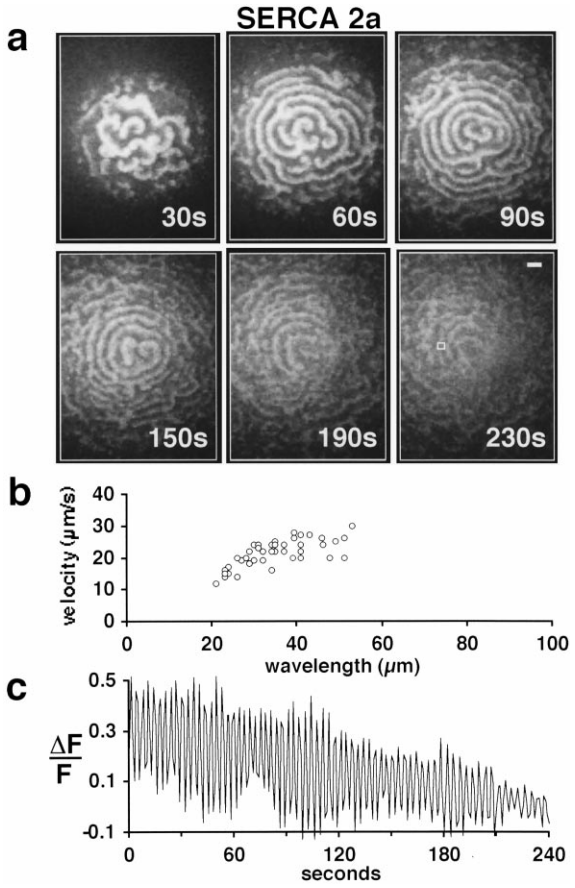

Fig. 3. Ca^{2+} wave dispersion in an oocyte overexpressing SERCA 2a. (a) Individual confocal images of Ca^{2+} wave activity. IP_3 concentration is ~300 nM (final). Scale bar is 50 μm. (b) Scatter plot of wave velocities. (c) Line plot of Ca^{2+} concentration for the 5×5 pixel square shown in frame 230s. The wave period is 3.3 s during the first 120 s and 3.5 s during the final 120 s.

when overexpressed in COS cells [49]. Similar to SERCA1 expressing oocytes, Ca^{2+} wave dispersion was detected (Fig. 3). These data indicate that the refractory period value of the underlying excitatory event is approximately 3 s.

We also investigated IP_3-induced Ca^{2+} waves in oocytes expressing high levels of SERCA 2b, using the same protocols as for SERCAs 1 and 2a. Interestingly, the IP_3-induced Ca^{2+} wave frequencies were not as high as those observed in SERCA 1 or 2a expressing oocytes, consistent with the lower transport capacity of SERCA 2b [49]. Ca^{2+} wave periods varied between 2 and 4 s. However, SERCA 2b expressing oocytes still exhibited Ca^{2+} wave dispersion with interwave periods as high as 4 s (Fig. 4). These data suggest that the refractory period may be as long as 4 s. One explanation of these data is that the underlying refractory event cannot begin to reset until Ca^{2+} levels return to baseline levels. Since SERCA 2b has a lower transport capacity, cytoplasmic Ca^{2+} following a wave returns to baseline more slowly. Hence, the overall time that is needed for recovery is longer. Alternatively, the higher amplitude of SERCA 2b vs. SERCA 2a and 1 Ca^{2+} waves (cf Figs. 2, 3 and 4) may cause IP_3Rs to inactivate for longer periods of

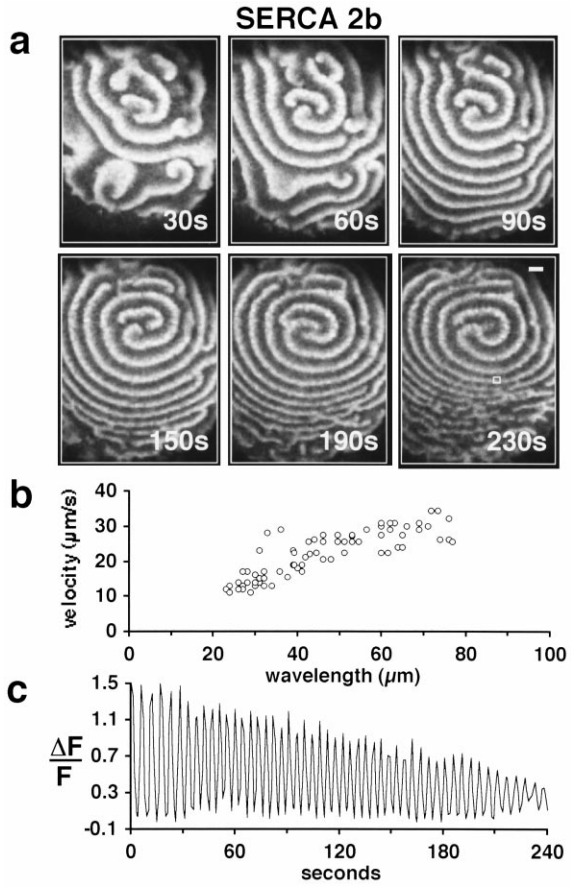

Fig. 4. Ca^{2+} wave dispersion in an oocyte overexpressing SERCA 2b. (a) Images of repetitive Ca^{2+} waves are collected under the same conditions in Fig. 3. (b) Scatter plot of wave velocities shows a reduction in wave velocity as the wavelength decreases. (d) Line plot of Ca^{2+} concentration (5×5 pixel square shown in frame 230 s) shows a decrease in wave amplitude as a function of time. The wave period is 4.6 s during the first 120 s and 4.8 s during the final 120 s.

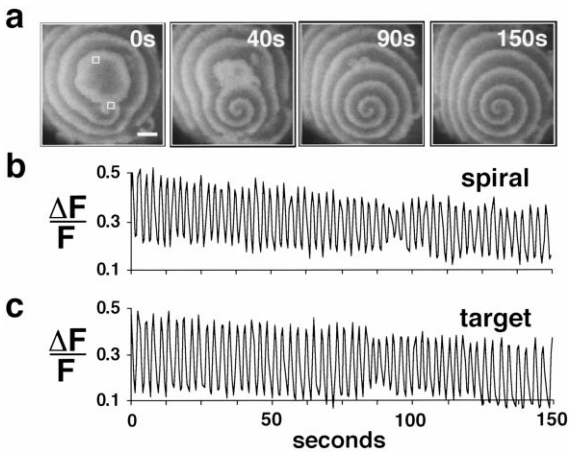

Fig. 5. Spiral wave entrainment in an oocyte overexpressing SERCA 2b. (a) Images of IP_3-induced Ca^{2+} wave activity. Oocyte was injected with IP_3 (300 nM final) 3 min before the first image shown (labeled at time = 0 s). Scale bar is 100 μm. (b) Line plots of Ca^{2+} wave intensity at the 5 × 5 pixel squares shown in frame 0 s for the spiral pattern (b, period ~2.56 s) and for the target pattern (c, period ~2.68 s). Ca^{2+} intensity is expressed as $\Delta F/F$. Intensity measurements were made at 0.5-s intervals.

time. Finch et al. [35] have reported a Ca^{2+} dependence for IP_3R inactivation.

In some oocytes overexpressing SERCAs, IP_3 injections resulted in the simultaneous presence of both spiral and target patterns of Ca^{2+} waves. For the oocyte shown in Fig. 5, the spiral wave had a periodicity of ~2.564 s while the target pattern had a period of ~2.679 s. Over time, the spiral wave in this oocyte spatially dominated the entire area. The same phenomenon, called entrainment, was observed and analyzed in a second oocyte with slightly slower wave frequencies. In this oocyte, the spiral and target patterns had periods of 3.278 s and 3.448 s, respectively. As with the first oocyte (Fig. 5), the spiral pattern enveloped the entire oocyte within 3 min. This entrainment can be attributed to the slightly higher frequency of the spiral wave over the target wave pattern.

7. Discussion

The classic role attributed to the endoplasmic reticulum (ER) Ca^{2+} ATPases has been that of refilling and maintaining intracellular Ca^{2+} stores. Our data demonstrate that Ca^{2+} pumps also dynamically modulate the release of Ca^{2+} into the cytosol. Overexpression of SERCA isoforms in the oocyte, increased wave amplitudes and frequencies for SERCAs 1, 2a and 2b when compared to control oocytes (non-mRNA injected). We suggest that the increase in wave amplitude is due to an increase in the Ca^{2+} store content. Thus, when an IP_3R channel opens, the Ca^{2+} flux is larger due to a larger driving force. This increased Ca^{2+} flux contributes to an increase in wave frequency since less time is now required for cytosolic Ca^{2+} levels to exceed excitation threshold levels. We previously defined excitation threshold as the point at which more Ca^{2+} is released via CICR than is re-sequestered by the Ca^{2+} ATPases into the Ca^{2+} stores. Hence, the positive feedback of CICR results in a large non-linear increase in cytosolic Ca^{2+} [2].

An interesting consequence of increased wave frequencies is that Ca^{2+} wave dispersion can now be observed in oocytes. For all three SERCA subtypes (1, 2a and 2b), we observed a dependence of wave velocity on wave spacing. The minimal distance between waves that we observe is ~20 μm. Interestingly, the drop off in wave velocity appears linear for some oocytes (Figs. 3 and 4). This may be due to the limitation in spatial resolution since higher magnification shows a non-linear fall off (Fig. 2). Alternatively, a linear relationship between wavelength and velocity is suggestive of the kinematic waves described by Jafri and Keizer [51]. Model simulation by these authors indicate that the diffusion of Ca^{2+} may play only a minor role in Ca^{2+} wave propagation and under certain conditions, Ca^{2+} waves may be primarily kinematic in nature, dependent on the phase differences between oscillators at different spatial points. Consistent with this model, Hagan [52] theoretically proved the existence of spiral wave solutions for reaction-diffusion systems close to a Hopf bifurcation. Finally, we have determined experimental boundaries in which Ca^{2+} wave dispersion occurs. In *Xenopus* oocytes, it is clear that Ca^{2+} wave dispersion is supported when the system oscillates with a periodicity lower than 4 s.

The existence of a refractory period leads to the prediction of Ca^{2+} wave entrainment. In this phenomenon, high frequency waves overtake low frequency waves (Fig. 5). Spiral entrainment has potentially important implications for the encoding of signals in biological systems. Specifically, a Ca^{2+} signal

encoded in the temporal domain (frequency) can be transduced into a spatial domain. Consequently, mechanisms which alter the expression levels of Ca^{2+}-ATPases [53,54] are predicted to greatly affect IP_3-mediated Ca^{2+} signaling.

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