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PLCζ and the initiation of Ca^{2+} oscillations in fertilizing mammalian eggs

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ABSTRACT

Mammalian eggs undergo a prolonged series of low frequency Ca^{2+} oscillations at fertilization. These Ca^{2+} oscillations are the immediate cause of egg activation. The Ca^{2+} oscillations in mouse eggs have been shown to be driven by increased $InsP_3$ production. Substantial evidence now indicates that a sperm-derived phospholipase C-zeta (PLCζ) is the key molecule that causes these Ca^{2+} oscillations at fertilization. The fertilizing sperm is envisaged to introduce this essential molecule into the egg following gamete fusion. This review summarizes our current knowledge of how sperm PLCζ causes these oscillations and why it is so much more effective at triggering $InsP_3$ production and Ca^{2+} oscillations in eggs, than other somatic isoforms of PLC. The molecular features of PLCζ and how they relate to the pattern of Ca^{2+} oscillations seen at fertilization are considered. We also discuss the evidence that PLCζ does not hydrolyze the conventional source of $PI(4,5)P_2$ in the plasma membrane to make $InsP_3$, but instead uses a distinct pool of $PI(4,5)P_2$ present on intracellular vesicles. This leads us to suggest that sperm PLCζ may be targeted to these cytoplasmic vesicles by directly interacting with a specific but as yet unidentified egg PLCζ-binding protein.

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1. Ca^{2+} oscillations and mammalian egg activation

The sperm is the trigger for egg activation and embryo development in most animals and, in all the cases studied a signal from the sperm produces an acute rise in the intracellular free Ca^{2+} concentration within the egg [1]. The form of the Ca^{2+} rise can be a single large increase that crosses the egg from the point of sperm entry, as seen during fertilization in sea urchins, fish and frogs [1,2]. However, more commonly in eggs from different phyla, the sperm triggers a conspicuous series of cytoplasmic Ca^{2+} oscillations [1]. In all mammals studied to date, the sperm has been shown to cause a prolonged series of low frequency oscillations in intracellular Ca^{2+} [1–3]. An example of a recording of intracellular Ca^{2+} changes in a fertilizing mouse egg is shown in Fig. 1a. The first Ca^{2+} increase in fertilizing mouse eggs occurs about a minute after sperm–egg membrane fusion, and consists of a rise in Ca^{2+} concentrations that lasts one or several minutes and that exceeds 1 μM Ca^{2+} [4,5]. The initial Ca^{2+} transient in mouse eggs usually has two stages (Fig. 1b), the first being rather slow and taking several seconds whereas subsequent Ca^{2+} transients show a more rapid rate of rise [4]. However, hamster eggs show a monotonic rise in the first and all subsequent Ca^{2+} rises [6]. In both mouse and hamster eggs there is then a series of further oscillations that last for several hours, occurring at an interval of about 10 min [2,4,5]. The Ca^{2+} oscillations at fertilization in other mammals are broadly similar, although the frequency of oscillations tends to be lower in larger eggs (one transient every 30 min), such as those from human, cow and pig [7–9]. In mouse and hamster eggs, the initial Ca^{2+} increase has been shown to spread across the egg with a wave-like profile that takes about 5 s and is initiated from the region of sperm–egg fusion [4,6]. As more oscillations occur, the Ca^{2+} waves speed up so that they cross the egg in less than 1 s, and the starting point of each wave arises from variable regions of the egg cortex. This phenomenon is best observed with rapid imaging, but the change in Ca^{2+} wave speed is also reflected by the change in the rate of rise of Ca^{2+} transients measured from the whole cell [4]. The initial Ca^{2+} change at fertilization of a mouse egg lasts ~10 s during the first rising phase, whereas the later Ca^{2+} transients have a more rapid rising phase of ~1 s or less (Fig. 1b–d). The change in wave profiles and rate of rise of Ca^{2+} transients is apparently due to a transition from 'non-excitable' to an 'excitable' egg cytoplasm upon fertilization. For example, the injection of Ca^{2+} into unfertilized hamster or mouse eggs does not generate much Ca^{2+} release but, after fertilization, very small injections of Ca^{2+} into the egg triggers substantial further Ca^{2+} release [10,11]. Explaining this change in excitability is a key part of understanding how the sperm trigger Ca^{2+} oscillations.

The oscillations in Ca^{2+} at fertilization as a whole are known to be essential for egg activation since preventing them by injecting a Ca^{2+} chelator results in blockade of all the events of egg activation [12]. Mammalian eggs can be activated by a single large Ca^{2+} rise, as seen with application of Ca^{2+} ionophore, but this is not as efficient

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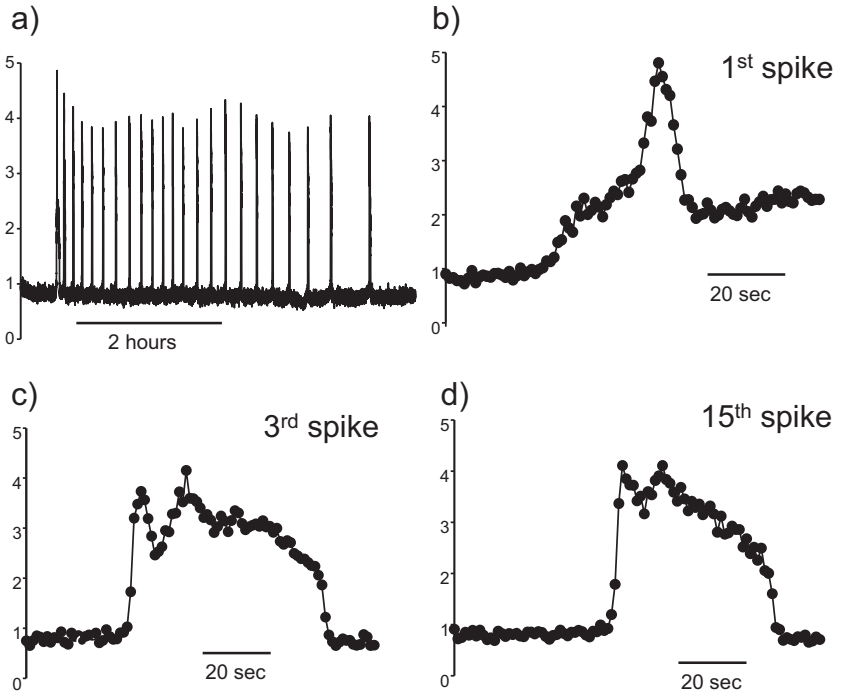

Fig. 1. Ca^{2+} oscillations at fertilization. The cytoplasmic Ca^{2+} oscillations occurring within a mouse egg at fertilization were monitored with a Ca^{2+}-sensitive fluorescent dye, Rhod-dextran, using a continuous fluorescence excitation and light collection with a photon counting camera (see [16] and [32] for methods). Each Y-axis represents a fluorescence ratio taken as the fluorescence at each point divided by the fluorescence at the start of the recording. In (a) is shown a recording of the entire series of Ca^{2+} oscillations for an egg that eventually formed 2 pronuclei. In (b), (c) and (d) are shown examples of the 1st, 3rd and 15th Ca^{2+} transient from the same recording but on an expanded timescale with each dot representing 1 s of integrated fluorescence. The 3rd and 15th Ca^{2+} transients occurred at 13 and 126 min, respectively, after the initial rise in Ca^{2+} at fertilization.

a stimulus as Ca^{2+} oscillations [3]. Some chemicals such as protein kinase inhibitors, or protein synthesis inhibitors can activate mammalian eggs without causing any Ca^{2+} increase [3,13], but these are non-physiological. The most reliable way to activate development is *via* Ca^{2+} oscillations, or at least *via* some form of repetitive Ca^{2+} increase. For example, in the mouse egg activation is effectively achieved by Ca^{2+} oscillations that can be induced by incubating eggs in Str^{2+} containing media [12]. In other non-rodent species, repetitive electrical pulses can activate eggs through the ability to cause repeated Ca^{2+} influx and Ca^{2+} transients [14].

Considerable progress has been made in understanding how these Ca^{2+} oscillations are generated and terminated, particularly in rodent eggs. The mechanism for generating Ca^{2+} release in fertilizing mouse eggs involves the $InsP_3$ receptor ($InsP_3R$) which also contains the Ca^{2+} channel responsible for Ca^{2+} release from intracellular stores. Injection of functional inhibitory antibodies to the $InsP_3R$ can block all Ca^{2+} oscillations at fertilization in hamster eggs [2]. In mouse eggs, the $InsP_3R$ has been shown to be down-regulated at fertilization, and since this only occurs when $InsP_3$ levels are increased it is clear that the sperm causes an increase in $InsP_3$ levels in the egg [15]. Furthermore, the $InsP_3R$ can be down-regulated prior to fertilization by injection of the potent $InsP_3R$ agonist, adenophostin, into an immature oocyte. When this is done, and the oocyte is allowed to develop into a mature egg, the Ca^{2+} oscillations and events of egg activation at fertilization are blocked [15]. These data suggest that the $InsP_3$ pathway is essential for sperm-induced Ca^{2+} oscillations, and they reconfirm that Ca^{2+} oscillations are the physiological pathway for egg activation. There are no consistent indications that other Ca^{2+} releasing messengers such as cyclic ADP ribose or NAADP cause physiological Ca^{2+} release in mouse eggs. The essential question for understanding signalling during egg activation is how the sperm generates the $InsP_3$ to stimulate release *via* the $InsP_3R$. This review describes what we know, and need to know, about how PLCζ generates $InsP_3$ and Ca^{2+} oscillations at fertilization in mammalian eggs [16]. We do not cover all aspects of PLCζ as other reviews are available for more in depth discussion of the structure of PLCζ or its role in human fertility [17,18].

2. PLCζ as the soluble sperm factor that triggers Ca^{2+} oscillations in eggs

The early models of $InsP_3$ production and Ca^{2+} release at fertilization suggested that the sperm acted upon egg surface membrane receptors that would then stimulate a PLC of the β or γ class to hydrolyse $PI(4,5)P_2$ in the plasma membrane [3]. In the mouse, it has been shown that sperm–egg fusion occurs before Ca^{2+} release by many seconds, and that fusion is a prerequisite for initiating Ca^{2+} oscillations [19,20]. So there is no need for a hormone-like trans-membrane signalling event. Measurements of Ca^{2+} level in the sperm and egg just after membrane fusion show the sperm has a low Ca^{2+} concentration, just like that of the unfertilized eggs [20]. Consequently, the idea that the sperm itself introduces Ca^{2+} to help trigger further Ca^{2+} oscillations in the egg, *via* the well-known Ca^{2+} induced Ca^{2+} release phenomenon, lacks support. The simplest idea to explain sperm-induced Ca^{2+} release is that the sperm introduces a protein factor into the egg cytoplasm after membrane fusion. Microinjection of sperm extracts has been shown to cause Ca^{2+} oscillations very similar to those at fertilization in hamster, mouse, pig and cow eggs [21,22]. The factor is not species-specific as sperm extracts from a wide range of species can trigger Ca^{2+} oscillations in mouse eggs, which appear to represent one of the most sensitive species of eggs to the Ca^{2+} releasing effect of sperm extracts. The sperm factor was shown to be a heat-sensitive protein that is sperm-specific [21,22]. The existence of such a sperm factor was also suggested by the clinical use of intra-cytoplasmic sperm injection (ICSI), where a sperm is injected into an egg to overcome cases of male factor infertility. ICSI in mouse and human eggs has

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