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The Physiological Function of Store-operated Calcium Entry

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Abstract

Store-operated Ca^{2+} entry is a process whereby the depletion of intracellular Ca^{2+} stores signals the opening of plasma membrane Ca^{2+} channels. It has long been thought that the main function of store-operated Ca^{2+} entry was the replenishment of intracellular Ca^{2+} stores following their discharge during intracellular Ca^{2+} signaling. Recent results, however, suggest that the primary function of these channels may be to provide direct Ca^{2+} signals to recipients localized to spatially restricted areas close to the sites of Ca^{2+} entry in order to initiate specific signaling pathways.

Keywords

Calcium channels; Store-operated channels; Calcium signaling; Ion channels; Orai; STIM; Calcium oscillations

I am honored to contribute this review to this special issue, recognizing the multitude of accomplishments of Professor Katsuhiko Mikoshiba. The past 30 or more years of my scientific life have been focused primarily on understanding mechanisms of calcium entry into cells across the plasma membrane. But the calcium channels that I study receive their activation signal from depleted intracellular calcium stores, and the primary mechanism by which this depletion occurs is by release of calcium through the ubiquitous inositol trisphosphate receptor (IP_3R)—calcium channel. Through the years, I have continued to be impressed, inspired and sometimes awe-struck by the body of work assembled by Professor Mikoshiba, and by how this knowledge has shaped our current understanding of the function of this important intracellular release channel, from the level of the molecule to the whole organism.

One very important consequence of calcium release through the IP_3R is the subsequent activation of plasma membrane store-operated calcium channels. In this review I will briefly describe the historical development of this concept and our current understanding of its molecular basis, and will address some new ideas on how these channels function in cell signaling pathways.

The Concept of Store-Operated Calcium Entry

On the basis of work during the mid to late twentieth century, a generalization about cellular calcium signaling developed: commonly, cytoplasmic calcium signals could arise from the release of intracellular stores, or from influx across the plasma membrane, and often by a combination of the two [1,2]. In 1977, on the basis of a series of experiments examining the refilling of intracellular calcium pools following their discharge by receptor-activating

ligands, I concluded that (a) the refilling of intracellular stores involved influx of calcium through channels in the plasma membrane, and (b) the channels involved in refilling the stores were the same ones responsible for sustained calcium signaling during receptor activation, and thus (c) the processes of intracellular calcium release and plasma membrane calcium influx were functionally linked [3]. In a subsequent study the following year, a student in my laboratory at the time, Ralph Parod, demonstrated that the process of refilling stores occurred independently of receptor activation [4]. A few years later, a similar finding was reported by Casteels and Droogmans for smooth muscle [5]. In the latter report, the authors speculated that calcium did not enter the cytoplasm directly through channels, but rather entered the sarcoplasmic reticulum directly by an unspecified mechanism, from which it could subsequently be discharged. Following the discovery of the messenger function of IP_3 in 1983 [6,7], much attention was focused on this signaling molecule and its likely role in generating cytoplasmic calcium signals. Indeed, injection of IP_3 into cells results in both intracellular release as well as increased calcium influx [8] (and subsequently, see [9]); however, in a study utilizing membrane fractions, IP_3 could release calcium from endoplasmic reticulum vesicles, but not from plasma membrane vesicles [10]. On the basis of these observations, I concluded that although IP_3 was responsible for increasing plasma membrane calcium influx, this did not appear to be a direct effect. And reflecting on all of the work summarized above on mechanisms for refilling stores, I concluded that it was the emptiness of the store *per se* that provided the signal to activate influx [11]. My thinking on how this was accomplished was somewhat similar to the earlier idea put forth by Casteels and Droogmans. However, I believed that the calcium entered the cytoplasm through plasma membrane channels, but closely apposed calcium pumps would then accumulate it, and it would not enter the bulk of the cytoplasm until released through the IP_3 receptor. I saw this arrangement as analogous to the arrangement of resistor (channel) and capacitor (calcium store) in electrical circuitry, and coined the term “capacitative calcium entry” [11,12].

Store-Operated Calcium Entry: 1986–2005

Over the next 15–20 years, work in a number of laboratories, including my own, focused on characterizing capacitative or store-operated calcium entry with the ultimate goal of understanding the molecular nature of the signaling and the store-operated channels. During this period, there were a number of important findings. First, two publications provided a more direct proof for the concept of a store-operated calcium influx mechanism. The first of these demonstrated for the first time, by use of a fluorescent Ca^{2+} indicator, that an accelerated influx of Ca^{2+} occurred after removal of the phospholipase C-activating agonist [12]. This was the first direct demonstration of Ca^{2+} entry occurring independently of receptor activation. The second publication appearing in the same year described the action of a relatively unknown (at that time) plant toxin, thapsigargin [13]. At the time, the exact mechanism of action of thapsigargin was not known, but it was clear that it (a) released the same pool of Ca^{2+} as did agonists or IP_3 , and (b) it did this without itself activating phospholipase C and liberating IP_3 [14]. When applied to parotid acinar cells, thapsigargin caused a sustained increase in Ca^{2+} influx that was quantitatively similar to that produced by a phospholipase C-linked agonist, and was not additive with the agonist-induced influx [15]. This provided solid evidence that it was indeed the filling status of the intracellular Ca^{2+} pool, and not other consequences of receptor activation, that was responsible for Ca^{2+} influx. Subsequently, it was demonstrated that thapsigargin depletes Ca^{2+} stores by virtue of its ability to block the sarcoplasmic-endoplasmic reticulum Ca^{2+} -ATPase (SERCA) that is responsible for accumulating Ca^{2+} in the endoplasmic reticulum [16]. Thapsigargin continues to be the most commonly used pharmacological tool for maximally activating the store-operated pathway.

The ability of thapsigargin to activate Ca^{2+} influx to the same extent as IP_3 , despite the fact that thapsigargin did not enhance endoplasmic reticulum permeability, demonstrated that store-operated Ca^{2+} influx must occur across the plasma membrane directly to the cytoplasm rather than in a cycle of release and reuptake by the endoplasmic reticulum as suggested by Casteels and Droogmans [5]. This and a number of other arguments against the direct plasma membrane-endoplasmic reticulum connection were summarized in a review in 1990 [17].

If store-operated Ca^{2+} entry involves direct entry to the cytoplasm through Ca^{2+} permeable channels then there should be an electrical current associated with this process. A seminal contribution to our understanding came from the first identification of a store-operated plasma membrane Ca^{2+} current by Marcus Hoth and Reinhold Penner [18]. Interestingly, it is likely that this was the same current reported earlier for agonist activation of T-cells by Lewis and Cahalan [19] although these authors did not recognize it as such. In the Hoth and Penner publication, the authors clearly demonstrated the activation of a small inward current in mast cells in response to a number of different Ca^{2+} store depletion strategies. The current was strongly inwardly rectifying with a positive reversal potential as expected for a highly Ca^{2+} selective current. However, large Na^+ currents could be observed in the absence of divalent cations, indicating that, as for other Ca^{2+} selective channels, the selectivity results from Ca^{2+} blocking the channels while penetrating. Hoth and Penner could not detect single channel activity associated with this current, and concluded that it was likely too small to measure. This was subsequently confirmed by a noise analysis approach by Zweifach and Lewis [20]. Hoth and Penner called the store-operated current I_{crac} , for calcium-release-activated calcium current [18].

To date, I_{crac} is by far the most extensively studied and best characterized store-operated current. It is still too early to say whether it represents the only such current, however. A number of publications have described what appear to be store-operated currents with electrophysiological properties somewhat different from I_{crac} (summarized in [21]). For the most part, these non- I_{crac} -like currents have not been reproduced in multiple laboratories, as is certainly the case for I_{crac} . A particular class of channels worth mentioning in this regard is the TRP channels, specifically the subgroup known as TRPCs. TRP, which stands for transient receptor potential, was first described as a light-activated Ca^{2+} -permeable relatively non-selective cation channel in *Drosophila* photoreceptors [22,23]. In invertebrates, light-activated signaling in photoreceptor cells is initiated by phospholipase C. Since store-operated Ca^{2+} entry is similarly downstream of phospholipase C, in the early 90's Hardie and Minke [24] put forth the reasonable suggestion that TRP channels might be the long sought store-operated Ca^{2+} channels. Shortly thereafter mammalian homologs of TRP were cloned [25,26]. Eventually 7 such mammalian genes were found and designated TRPC1–7, for canonical TRP to distinguish them from other more distantly related TRP homologs (TRPV and TRPM for example) [27].

Electrophysiological characterization of TRPC channels revealed that, like the original *Drosophila* version, these channels are relatively non-selectively cation permeable [28]. Thus, it was soon realized that these channels were not likely the basis for I_{crac} . Nonetheless, a number of publications appeared presenting evidence that TRPCs can form store-operated channels with properties differing from I_{crac} ([29–34], others cited in [21]). However, there have been few instances in which these findings have been reproduced in different laboratories, and a few instances in which decidedly different results were obtained (compare [29–35;36,37;38–40]). In only a few instances have explanations for these discrepancies been forthcoming (for example see [37] which explains earlier results in [34]).

In contrast, many laboratories have confirmed that TRPCs can readily be activated through the phospholipase C pathway independently of store depletion [41,42]. As is the case for the founding *Drosophila* TRP [43], this appears to involve phospholipase C-mediated changes in plasma membrane lipid composition [44–46]. An exception may be TRPC1 which does not readily show non-store-operated activity [37,47] unless co-expressed with TRPC4 or TRPC5 [48]. However, overexpression of TRPC1 does appear capable of increasing Ca^{2+} influx following Ca^{2+} store depletion, and this effect depends upon the CRAC channel subunit Orai1 (discussed below) [49]. Thus the possibility remains open that TRPC1 may interact with, or depend in some manner on store-operated CRAC channels.

Store-Operated Calcium Entry: 2005 to the Present, STIM and Orai

In 2005 the modern era of research on store-operated calcium channels began with the first unequivocal discovery of a key molecular component of the pathway, the endoplasmic reticulum Ca^{2+} sensor. Within weeks of one another, two laboratories independently published the results of screens of limited siRNA libraries, both revealing the essential role of STIM proteins in store operated Ca^{2+} entry [50,51]. STIM1, or stromal interacting molecule-1, had been known for some time as a plasma membrane and endoplasmic reticulum single spanning transmembrane protein [52]. Vertebrates make two STIMs, designated STIM1 and STIM2 while invertebrates have only one. Most attention has been focused on STIM1, and the function of STIM2 is less clear (but discussed below). STIM1, but probably not STIM2, is found in both plasma membrane and endoplasmic reticulum. Its function in the plasma membrane is unclear [53]. Both STIM1 and 2 have a calcium-binding EF-hand motif in the N-terminus which faces the lumen of the endoplasmic reticulum. It is apparently this EF-hand which imparts a Ca^{2+} sensing function to STIM. Dissociation of Ca^{2+} from STIM1 results in its self-association and relocation within the endoplasmic reticulum to near plasma membrane sites [51,53–56]. In imaging studies, this results in the gathering of STIM1 molecules in discrete structures that are referred to as puncta. Mutations in the EF-hand of STIM1 results in constitutive formation of puncta and constitutive activation of Ca^{2+} entry [50,51,53].

Approximately a year after the discovery of the Ca^{2+} -sensing function of STIM, three laboratories, using whole genome siRNA screens in *Drosophila* cells, reported another gene essential for store-operated Ca^{2+} entry [57–59]. The first group to publish dubbed the gene *Orai*, a name given to mythological gate-keepers [57], probably because the exact function of the protein was not initially known. Another group publishing shortly thereafter called it *CRACM* for “CRAC modulator,” again implying that its actual function was not known. Most have now adopted the Orai nomenclature because this was the first group to publish, if only by a matter of weeks, and because it is now clear that this is not a “modulator” but rather a component of the CRAC channel itself. That Orai is a pore-forming component of the CRAC channel was not appreciated initially because the sequence of the protein encoded by the gene did not bear structural homology to any known ion channel. This is perhaps not too surprising given the distinct biophysical properties of the CRAC channel in comparison to other ion channels [21,60].

In invertebrates, including *Drosophila* which was used for the initial screens, there is a single *Orai* gene. In mammals there are three, encoding similar proteins, Orai1, 2 and 3. The evidence is now quite strong that all three proteins can function as pore forming subunits of CRAC or CRAC-like channels. First, when Orai1 is overexpressed with STIM1, the resulting I_{CRAC} can be 10–50 fold increased [53,59,61,62]. This suggests that these two proteins can fully reconstitute both the signaling and channel functions of I_{CRAC} . Second, mutations of specific residues in Orai1 result in channels with altered ion selectivity [63–65].

In the ensuing years, a number of important domains with the STIM and Orai molecules have been delineated, giving insight into how the signaling between these two molecules is regulated. OraIs are tetraspanning membrane proteins with both N and C termini directed to the cytoplasm. There is good evidence that both the N and C termini contain domains important for channel activation by STIM [66–68]. Within STIM1 there is a C-terminal domain lying within a larger coiled-coil domain that is sufficient to gate Orai channels [69–72]. This domain was termed SOAR by Yuan et al. for Stim-Orai Activating Region [69]. Park et al. [70] demonstrated that this domain can interact directly with homomeric Orai1 channel structures. Just downstream of the SOAR is a short acidic stretch that appears necessary for the process of Ca^{2+} -dependent fast inactivation of I_{crac} [73], and beyond that a domain that contains multiple sites that are phosphorylated during cell division causing STIM1 to be inactive [74].

Physiological Functions of Store-Operated Ca^{2+} Entry

A number of studies have demonstrated the role of store-operated Ca^{2+} entry in a variety of important biological processes, including breast cancer cell migration and metastasis [75], endothelial proliferation [76], skeletal muscle contractility [77], and smooth muscle migration and proliferation [78,79]. However, the physiological relevance of store-operated Ca^{2+} entry is perhaps best illustrated by patients with inherited defects in this pathway [80–82]. To date, the genetic basis for these defects has been attributed to mutations in the genes encoding either Orai1 or STIM1. The most striking phenotype in all cases is compromised immune function, due primarily to an almost complete lack of T-cells and T-cell activation [81,83]. Indeed, it was a specific mutation of an arginine to a tryptophan at position 91 in Orai1 that was instrumental in the initial discovery of Orai1 [57]. However, patients are also characterized by myotonia and ectodermal dysplasia [82]. There are currently three mouse models for investigating the function of store-operated Ca^{2+} channels. Two are global knockouts of Orai1, and one is a conditional knockout of STIM1. The global knockouts of Orai1 as well as the conditional knockout of STIM1, when crossed into the appropriate background for elimination of STIM1 in hematopoietic cells, all show strong immune system phenotypes.

When Ca^{2+} is released from intracellular stores, the rise in cytoplasmic Ca^{2+} activates plasma membrane Ca^{2+} ATPase such that a portion of the released Ca^{2+} is extruded to the extracellular space. Store-operated Ca^{2+} entry was originally identified as a mechanism for assuring the refilling of intracellular stores following release, usually by IP_3 [3–5,11,12]. Indeed, some early versions of this mechanism proposed that Ca^{2+} entered the endoplasmic reticulum through a mysterious direct route without traversing the cytoplasm [5,84]. However, as discussed above, this idea was soon disproved and it became clear that store-operated Ca^{2+} entry occurred through bona fide plasma membrane channels [60]. Nonetheless, the idea has to some degree persisted that the primary cytoplasmic Ca^{2+} signal comes from the intracellular release component of the response while store-operated entry is necessary for maintaining the stores. Some recent studies suggest an alternative function for store-operated channels, one in which the Ca^{2+} entering through the channels is more directly linked to the activation of downstream signals.

To appreciate the possible functions of store-operated channels, one must first consider the complexities of cellular Ca^{2+} signals when cells are activated with low physiological concentrations of agonists. With low agonist concentrations, one does not usually observe sustained elevations of Ca^{2+} but rather discrete episodic release events called Ca^{2+} oscillations [85]. The nature of the primary oscillator responsible for this pattern is still not entirely clear, the most popular ideas being either oscillatory activity of phospholipase C producing oscillations in IP_3 concentration, or oscillatory release of Ca^{2+} at a constant IP_3

concentration, due to complex regulatory mechanisms of the IP₃ receptor by Ca²⁺ [86,87]. Nonetheless, two general properties of Ca²⁺ oscillations are: (a) each Ca²⁺ spike or oscillation is due almost entirely to intracellular release, but (b) in the absence of extracellular Ca²⁺, the oscillations rapidly run down, indicating a need for Ca²⁺ influx to maintain them [87,88]. Although there has not been complete agreement on this point (for example see [89] which advocates a role for arachidonic acid-activated channels), considerable evidence suggests that this Ca²⁺ influx usually occurs through store-operated channels [88,90,91].

One of the most extensively investigated physiological systems in which store-operated channels play a significant role is the immune system [92]. Activation of key surface signaling receptors, for example the T-cell receptor, initiates a typical pattern of Ca²⁺ oscillations that appears to be essential for the activation of NFAT and other key downstream signaling pathways [93]. These oscillations depend upon a complex interrelationship between intracellular Ca²⁺ release and plasma membrane store-operated Ca²⁺ channels [94]. Heritable defects in store-operated entry lead to severe immunodeficiency [81,95] and this has generally been presumed to result from a failure to maintain intracellular Ca²⁺ oscillations. However, in some instances, store-operated channels have been shown to preferentially activate downstream signals independently of changes in global cytoplasmic Ca²⁺ [96–99]. Presumably this results from the establishment of microdomains of Ca²⁺ signaling very close to the intracellular openings of the store-operated channels [100]. One way in which to distinguish the contributions of Ca²⁺ entry from those of global Ca²⁺ signaling is through a technique termed “lanthanide insulation” [88,101,102]. Relatively high (mM range) concentrations of trivalent lanthanides (La³⁺, Gd³⁺) block both the entry of Ca²⁺ as well as its extrusion by exchangers and pumps [103]. Since the most commonly used Ca²⁺ indicators (Fura-2, for example) bind lanthanides with high affinity and are excited by them in the same way as by Ca²⁺, the failure to detect fluorescence signals in cells treated with lanthanides indicates that little if any of these cations penetrate into cells [101]. While it is always possible that the lanthanides might produce unexpected or toxic effects on cells, there is to date no evidence for such effects; remarkably, cells appear capable of carrying out their normal receptor-mediated internal signaling in the presence of mM lanthanides. Thus, by use of high lanthanide concentrations, it is possible to induce sustained intracellular Ca²⁺ oscillations even in the absence of extracellular Ca²⁺ [88,102]. With this technique, Di Capite et al. [104] examined the activation of expression of the early gene, *c-fos*, in a mast cell line showing Ca²⁺ oscillations in response to leukotriene C4. Leukotriene C4 activated *c-fos* expression in the presence of Ca²⁺, when sustained oscillations were produced, but not in the absence of Ca²⁺, when oscillations quickly ran down. However, in the presence of 1 mM La³⁺, oscillations were sustained yet *c-fos* was not activated [104]. Thus, in this instance it is clearly Ca²⁺ entering through the store-operated channels and not oscillations in global Ca²⁺ that are coupled to downstream signaling to *c-fos*.

A general consensus among investigators interested in Ca²⁺ oscillations is that they provide the advantages of a digital signaling system [87,105–107]. Digital signaling can assure high signal-to-noise if the downstream steps in the signaling pathway respond to, and integrate Ca²⁺ changes that exceed a certain unambiguous threshold. How then does this advantage come into play when the primary signal comes from Ca²⁺ entering through store-operated channels? The answer to this question may come from an analysis of the roles of the two Ca²⁺ sensors found in vertebrate cells, STIM1 and STIM2. Both STIM1 and STIM2 are known to sense endoplasmic reticulum Ca²⁺, and both can activate plasma membrane Orai channels, at least under conditions in which they are transfected into cell lines [108–110]. However, it appears that the two STIM proteins respond to, and regulate endoplasmic reticulum Ca²⁺ levels within different concentration ranges. STIM2 behaves as if its affinity

for Ca^{2+} is somewhat lower than STIM1 such that it seems to be partially active under resting endoplasmic reticulum Ca^{2+} loads [90,111]. STIM1 on the other hand appears to require a significant degree of endoplasmic reticulum depletion before it is capable of translocating to near plasma membrane puncta and activating Orai channels [90,111]. Since the Ca^{2+} influx occurring during Ca^{2+} oscillations is very small, one might then envision that STIM2 would play the predominant role in such situations of low agonist activation. However, surprisingly, precisely the opposite appears to be the case. When muscarinic receptor activation triggers Ca^{2+} oscillations in the kidney cell line, HEK293, the Ca^{2+} oscillations are inhibited by strategies that knock down STIM1 expression, but not those which knock down STIM2 expression [90]. Experiments utilizing TIRF microscopy to examine movements of STIM1 near the plasma membrane showed that in oscillating cells, STIM1 does in fact move to near membrane loci, often in an episodic manner just following each Ca^{2+} oscillation [90]. Given the fact that STIM1 requires a significant extent of Ca^{2+} depletion to become activated, then it must be that the Ca^{2+} oscillations, by virtue of their brief but extensive localized discharge of Ca^{2+} , reduce endoplasmic Ca^{2+} to this necessary level. Thus, it is the rather modest sensitivity of STIM1 to endoplasmic reticulum Ca^{2+} changes that provides the unambiguous threshold response to the Ca^{2+} oscillations. That is, it is the threshold of endoplasmic reticulum depletion, rather than the threshold of cytoplasmic Ca^{2+} elevation, that drives signaling in this case.

But why then does STIM2 not at least contribute to this process, given its higher sensitivity to Ca^{2+} depletion? This is probably because STIM2 driven Ca^{2+} influx is very small in comparison to that due to STIM1. In fact, this is what one would expect if STIM2 is partially active under resting conditions. In support of this idea, overexpression of STIM2 actually reduces store-operated Ca^{2+} influx [112]. Also, while EF hand mutants of STIM1 produce constitutive Ca^{2+} influx, EF hand mutants of STIM2 do not [90].

Conclusions

In this review, I have tried to build a model that ties together three main concepts: (a) store-operated Ca^{2+} entry can serve as the primary source of Ca^{2+} for signaling to downstream response effectors (a concept previously developed by Anant Parekh's laboratory [100]); (b) STIM1 and STIM2 play very different roles in Ca^{2+} entry, STIM1 being capable of strong activation of Orai channels providing sufficient Ca^{2+} to activate signaling and to maintain intracellular stores during oscillations, while STIM2 is capable of only weak activation of Orai channels and likely functions in the maintenance of stores under basal conditions; and (c) STIM1, because of its relatively low sensitivity for changes in store content, is ideally suited for exploiting the digital nature of Ca^{2+} oscillations for coupling them to store-operated channels and downstream signaling. In the context of this model, the interrelationship between store-operated Ca^{2+} entry and Ca^{2+} oscillations is seen in a new way. Formerly, it was thought that the Ca^{2+} entry served the function of maintaining stores so that oscillatory discharges of cytoplasmic Ca^{2+} can activate downstream effectors, leading to gene expression and other appropriate responses. There is support of this scenario; it is very clear that certain important cellular processes are indeed closely coupled to Ca^{2+} released from IP_3 receptors. The clearest example is perhaps the signaling pathway initiated in mitochondria involving regulation of carbohydrate metabolism, mitochondrial energetics or apoptosis [113,114]. The alternative idea put forth here is that, at least in some instances, the function of Ca^{2+} oscillations is to precipitously drop endoplasmic reticulum Ca^{2+} to the level needed for STIM1 activation which in turn activates Orai channels providing Ca^{2+} for downstream signaling. However, at present the number of specific examples of this latter model is limited. Additional research is needed to determine how extensive each of these alternative models is, and whether there are additional modes of

Ca²⁺ signaling involving interaction between store-operated channels and intracellular Ca²⁺ oscillations.

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