Published in final edited form as:

Int J Biochem Cell Biol. 2010 November ; 42(11): 1757–1761. doi:10.1016/j.biocel.2010.07.007.

Pancreatic Acinar Cells: Molecular insight from studies of signal-transduction using transgenic animals

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Abstract

Pancreatic acinar cells are classical exocrine gland cells. The apical regions of clusters of coupled acinar cells collectively form a lumen which constitutes the blind end of a tube created by ductal cells—a structure reminiscent of a “bunch of grapes”. When activated by neural or hormonal secretagogues, pancreatic acinar cells are stimulated to secrete a variety of proteins. These proteins are predominately inactive digestive enzyme precursors called “zymogens”. Acinar cell secretion is absolutely dependent on secretagogue-induced increases in intracellular free Ca^{2+} . The increase in $[\text{Ca}^{2+}]_i$ has precise temporal and spatial characteristics as a result of the exquisite regulation of the proteins responsible for Ca^{2+} release, Ca^{2+} influx and Ca^{2+} clearance in the acinar cell. This brief review discusses recent studies in which transgenic animal models have been utilized to define in molecular detail the components of the Ca^{2+} signaling machinery which contribute to these characteristics.

Keywords

pancreatic acinar cell; Ca^{2+} Signaling; exocytosis; Inositol 1,4,5-trisphosphate receptor

1. Introduction

The pancreas is a mixed exocrine and endocrine tissue, physically situated as an accessory organ connected to the gut tube at the level of the duodenum. The exocrine pancreas primarily consists of two major cell types; acinar and ductal cells. Together these cells are responsible for the production of a HCO^- rich solution containing a plethora of proteins which are responsible for the efficient assimilation of nutrients. While the ductal cells account for the production of the vast majority of alkaline fluid, pancreatic acinar cells are classical polarized epithelial cells and are morphologically and functionally specialized for the exocrine secretion of protein containing vesicles across the apical membrane (Figure 1).

The exocytosis of secretory granules is absolutely dependent on secretagogue induced elevations in cytosolic free Ca^{2+} ($[\text{Ca}^{2+}]_i$) (Futatsugi et al., 2005). The important event leading to the increase in $[\text{Ca}^{2+}]_i$ following binding of the neurotransmitter acetylcholine or gastrointestinal hormone cholecystikinin on the basolateral aspects of the acini (Figure 1) is the $\text{G}\alpha_q$ -stimulated increase in activity of phospholipase C, leading to the generation of the

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second-messenger inositol 1,4,5 trisphosphate (InsP₃) (Williams & Yule, 2006). Binding of InsP₃ to its receptors (InsP₃R), which are calcium permeable channels localized in the endoplasmic reticulum (ER) results in Ca²⁺ release into the cytoplasm (Streb et al., 1983). Secretagogue stimulation also triggers Ca²⁺ influx from the extracellular space across the plasma membrane (PM). Contributions from both Ca²⁺ release and Ca²⁺ influx are necessary for continued, sustained exocytosis of granules (Tsunoda et al., 1990). Activation of this machinery results in intracellular calcium signals with complex spatial and temporal characteristics. For example, although production of InsP₃ occurs predominately at the lateral and basal membranes, Ca²⁺ release invariably is initiated in the extreme apical pole of the acinus where the vast majority of InsP₃R are located (Figure 2) (Kasai & Augustine, 1990; Thorn et al., 1993; Nathanson et al., 1994; Yule et al., 1997). At threshold levels of stimulus, Ca²⁺ signals can be confined to this domain, allowing standing gradients of [Ca²⁺]_i to be established (Kasai et al., 1993; Thorn et al., 1993). It is thought that Ca²⁺ uptake by a peri-granular belt of mitochondria function as a “fire-wall” to confine signals to the apical domain (Tinel et al., 1999; Straub et al., 2000). Physiological levels of agonist result in the propagation of a Ca²⁺ wave traveling from the initiation sites in the so called apical “trigger zone” towards the basal region of the cell (Kasai et al., 1993; Thorn et al., 1993) (Figure 2A). The Ca²⁺ wave relies on Ca²⁺-induced Ca²⁺ release via InsP₃R and ryanodine receptors distributed on ER throughout the cytoplasm (Straub et al., 2000). In the continued presence of secretagogue, extrusion of Ca²⁺ across the PM and sequestration into mitochondria and the ER serves to reduce [Ca²⁺]_i prior to the initiation of a further apical to basal Ca²⁺ wave (Figure 2B) (Lee et al., 1997a; Tinel et al., 1999; Straub et al., 2000). These spatial characteristics result temporally in the generation of Ca²⁺ spikes or oscillations (Yule & Gallacher, 1988; Yule et al., 1991). Together these stereotyped features of the Ca²⁺ signals are thought to be fundamentally important in the appropriate activation of effectors necessary for secretion (Maruyama et al., 1993).

These remarkable spatial and temporal characteristics are attributed to the dynamic interplay between the proteins responsible for Ca²⁺ release, influx and clearance from the cytoplasm (Figure 2B). While the general class, or in some cases, the gene family of the proteins responsible has been indicated, it is common that multiple individual members of gene families are expressed. With little discriminating conventional pharmacology available, the particular proteins which are responsible for a specific attribute of the Ca²⁺ signal has been difficult to establish. Additionally, whether expression of multiple protein family members represents redundancy or a means of permitting subtype specific regulation is not clearly established. Recently, studies utilizing transgenic gene targeting of particular signaling proteins have begun to address these gaps in our knowledge. In this review, selected studies will be highlighted which have provided insight into the particular proteins contributing to Ca²⁺ homeostasis in pancreatic acinar cells in both physiological and pathological conditions.

2. Cellular Origins

In mice at embryonic day 9.5, the pancreas begins to develop from buds that form as the endodermal gut tube invaginates into the overlying mesenchyme (Gittes, 2009). The bud elongates and undergoes extensive branching morphogenesis in response to complex signals to the epithelial cells from the surrounding mesenchyme and matrix. At around E14 cellular differentiation and lineage selection is initiated. A major amplification in the numbers of both endocrine cells expressing insulin and concurrent activation of acinar cell specific gene programs occurs. The latter event results in cells with substantial rough endoplasmic reticulum and zymogen granules. An increase in the zymogen content and the size of the granules in the acinar cells occurs until birth.

3. Functional significance of the expression of multiple InsP₃R family members in acinar cells

All three members of the InsP₃R gene family are expressed in acinar cells with largely the same sub-cellular distribution, albeit with differing relative abundances (Wojcikiewicz, 1995; Lee et al., 1997b; Yule et al., 1997). The majority, ~90% of the InsP₃R complement comprises roughly equal numbers of InsP₃R-2 and InsP₃R-3 with the remainder InsP₃R-1 (Wojcikiewicz, 1995). This raises the question as to whether this is reflective of redundancy or do particular sub-types make specific contribution to the signals? Transgenic knock-out of individual or a combination of InsP₃R genes has provided significant insight into these issues. Futatsugi and colleagues (Futatsugi et al., 2005) reported that targeted ablation of either the type-2 or type-3 InsP₃R individually, had no significant effects on muscarinic-receptor stimulated digestive enzyme secretion and these animals had no overt phenotype. Consistent with these observations, the peak secretagogue-stimulated increases in $[Ca^{2+}]_i$ were not altered (Futatsugi et al., 2005) by the removal of InsP₃R-3 and only modestly impacted by the loss of the InsP₃R-2 (Futatsugi et al., 2005; Park et al., 2008). In InsP₃R-2 *null* acini, marked changes were only seen at low secretagogue or InsP₃ concentrations (Park et al., 2008). In both cases the spatial aspects of the signals were largely unaffected. Taken together these data indicate that the complement of InsP₃R-2 or InsP₃R-3 in isolation, or perhaps in combination with InsP₃R-1, is sufficient to maintain signaling and preservation of stimulated exocytosis.

Analysis of the compound InsP₃R-2/InsP₃R-3 *null* animal revealed a much more striking phenotype resulting from the widespread general disruption of exocrine function (Futatsugi et al., 2005). Although animals were born normally, they failed to survive past weaning, largely due to a failure to ingest and subsequently assimilate food. Even when fed wet mash food to overcome the salivary deficit, the animals failed to thrive as a result of diminished pancreatic secretory function. The immediate cause being, somewhat surprisingly, the complete absence of any measurable secretagogue-induced Ca^{2+} signal-even at supramaximal concentrations of agonist (Futatsugi et al., 2005). The conclusion from these data is that while the residual expression of InsP₃R-1 is not sufficient to mount a Ca^{2+} signal, either the InsP₃R-2 or InsP₃R-3 in isolation will suffice.

InsP₃R are subject to diverse regulatory input which is thought to markedly influence the properties of the Ca^{2+} signal (Patel et al., 1999). As a result of considerable diversity in the primary sequence of the family members, modulation often occurs in a subtype specific manner. Given the previous data, the important modes of regulation of Ca^{2+} release in acinar cells would be predicted to occur predominately through either modulation of InsP₃R-2 and InsP₃R-3. It is however difficult to predict if one particular receptor's properties would dominate over the other. Ca^{2+} release via InsP₃R is markedly influenced by the levels of cellular ATP, potentially linking the extent of Ca^{2+} release to the metabolic status of the cell. In acini, ATP (~K_d 40 μ M) markedly enhances Ca^{2+} release at low levels of stimulation but appears not to influence release at high InsP₃ levels (Park et al., 2008). In contrast in InsP₃R-2 knock out animals, presumably dominated by InsP₃R-3, ATP was shown to modulate release at all InsP₃ levels, however the K_d for this effect was 10 fold higher (~450 μ M). Interestingly, the properties of the wild-type animal are essentially identical to those shown for the InsP₃R-2 in isolation, while the InsP₃R-2 KO mirror those of the InsP₃R-3 (Betzenhauser et al., 2008). These data indicate that while for Ca^{2+} release *per se*, InsP₃R-2 and InsP₃R-3 are interchangeable, in terms of the fine regulation of Ca^{2+} release, the individual InsP₃R are not redundant. Further, when expressed together the properties of InsP₃R-2 dominate over InsP₃R-3. Moreover, the high ATP sensitivity of InsP₃R-2 would be consistent with acinar cells being relatively resistant to the deleterious effects of ATP depletion.

4. The molecular basis of Ca²⁺ influx in pancreatic acinar cells

Secretagogue stimulated Ca²⁺ influx from the extracellular space is absolutely required for sustained exocytosis (Tsunoda et al., 1990). In acinar cells, like other exocrine cells, voltage-operated Ca²⁺ channels, common to nerves and muscles, are not expressed. Instead, following the InsP₃-mediated depletion of Ca²⁺ pools, so called “store-operated channels” (SOCs) are activated (Kim et al., 2009). In addition, at lower concentrations of secretagogues, a pathway dependent on the arachidonic- acid activation of a Ca²⁺ selective channel is engaged (Mignen et al., 2005). In other cells, recent studies have indicated that the channels constituting the depletion-operated pathway are from either the Orai or TRPC family (Feske et al., 2006; Liu et al., 2007). In both cases, an additional protein, STIM-1, functions as the luminal ER Ca²⁺ sensor responsible for relaying the state of store depletion to the actual channel protein (Roos et al., 2005). Pancreatic acinar cells express TRPC1, 3 and 6. Using a TRPC3 *null* animal, Kim and colleagues demonstrated that the magnitude of Ca²⁺ influx initiated by high-concentrations of agonist was significantly reduced. In addition, the frequency of Ca²⁺ oscillations stimulated by physiological concentrations of secretagogues was also markedly reduced. These data suggest that TRPC3 is a constituent of the native SOC in pancreatic acinar cells (Kim et al., 2009). Pancreas also express Orai 1 (Gwack et al., 2007) and this is consistent with the presence of an additional SOC, Calcium-Release Activated Current (I_{CRAC}) and the Arachidonate-Activated Current (I_{ARC}) both of which have Orai-1 as a component of their native channel (Feske et al., 2006; Mignen et al., 2008).

5. Dysregulated Ca²⁺ signaling is associated with pancreatitis

To safeguard the organ from auto-digestion, digestive enzymes are largely secreted as inactive precursors termed zymogens and under physiological conditions only become activated when they reach the duodenum. The inappropriate activation of zymogens occurs as an early event in the pathogenesis of acute pancreatitis- a serious and often life threatening malady which can result in a wide-spread immune response and severe necrosis of the pancreas (Pandol et al., 2007). Disruption of physiological Ca²⁺ signaling and premature, intracellular activation of proteases has been strongly implicated in the etiology of acute experimental pancreatitis in animal models (Petersen & Sutton, 2006). Aberrant Ca²⁺ release and Ca²⁺ influx have both been reported to contribute to this phenomenon. For example, exposure of isolated acini to pancreatic toxins such as bile acids or ethanol metabolites results in Ca²⁺ release from InsP₃-sensitive stores (Gerasimenko et al., 2009). In turn, this results in intracellular trypsin activation and the cellular hallmarks of pancreatitis. It has been reported that this occurs at least in part through activation of InsP₃R directly. Consistent with the dominant expression of InsP₃R-2 and InsP₃R-3, toxin-induced Ca²⁺ release and trypsin activation are markedly attenuated in either the InsP₃R-2 or InsP₃R-3 *null* animal, unaffected in the InsP₃R-1 animal, and absent in the compound double knock-out (Gerasimenko et al., 2009). A question arises as to why Ca²⁺ release *via* InsP₃R stimulated by toxins is detrimental to the acinar cell, while physiologically InsP₃-induced release is essential for normal exocytosis? The answer may be related to the identity of the store as both bile acids and ethanol metabolites appear to activate insP₃R in a compartment defined as an “acidic store” distinct from the ER (Gerasimenko et al., 2009). Prolonged Ca²⁺ entry through SOCs has also been demonstrated to contribute to experimental pancreatitis. Consistent with the role of TRPC-3 as a component of native SOC, the severity of experimental pancreatitis is markedly reduced in TRPC-3 *null* animals (Kim et al., 2009).

6. Concluding Remarks

Analysis of Ca^{2+} signaling in transgenic animal models has provided a wealth of information regarding stimulus-secretion coupling in pancreatic acini in both physiological and pathological situations. The availability of additional animal models, particularly pancreas-specific knock-downs of other signaling proteins will similarly be insightful in the future. Obvious potential targets for investigation include other Ca^{2+} release channels such as ryanodine receptors and Two-Pore Channels (TPC); Ca^{2+} influx channels including the Orai channels and clearance proteins such as Ca^{2+} ATPases and mitochondrial Ca^{2+} transport proteins.

Acknowledgments

The Author is supported by grants RO1-DK05458 and RO1-DE014756 from the National Institutes of Health. The Author would like to thank Jill Thompson for thorough proof reading of the manuscript and Dr. Guy Groblewski and Diana Thomas for providing the electron micrograph in figure 1.

References

- Betzenhauser MJ, Wagner LE 2nd, Iwai M, Michikawa T, Mikoshiba K, Yule DI. ATP modulation of Ca^{2+} release by type-2 and type-3 inositol (1, 4, 5)-triphosphate receptors. Differing ATP sensitivities and molecular determinants of action. *J Biol Chem.* 2008; 283:21579–21587. 2008. [PubMed: 18505727]
- Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, Hogan PG, Lewis RS, Daly M, Rao A. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature.* 2006; 441:179–185. 2006. [PubMed: 16582901]
- Futatsugi A, Nakamura T, Yamada MK, Ebisui E, Nakamura K, Uchida K, Kitaguchi T, Takahashi-Iwanaga H, Aruga J, Mikoshiba K. IP3 receptor types 2 and 3 mediate exocrine secretion underlying energy metabolism. *Science.* 2005; 309:2232–2234. 2005. [PubMed: 16195467]
- Gerasimenko JV, Lur G, Sherwood MW, Ebisui E, Tepikin AV, Mikoshiba K, Gerasimenko OV, Petersen OH. Pancreatic protease activation by alcohol metabolite depends on Ca^{2+} release via acid store IP3 receptors. *Proc Natl Acad Sci U S A.* 2009; 106:10758–10763. 2009. [PubMed: 19528657]
- Gittes GK. Developmental biology of the pancreas: a comprehensive review. *Developmental biology.* 2009; 326:4–35. 2009. [PubMed: 19013144]
- Gwack Y, Srikanth S, Feske S, Cruz-Guilloty F, Oh-hora M, Neems DS, Hogan PG, Rao A. Biochemical and functional characterization of Orai proteins. *J Biol Chem.* 2007; 282:16232–16243. 2007. [PubMed: 17293345]
- Kasai H, Augustine GJ. Cytosolic Ca^{2+} gradients triggering unidirectional fluid secretion from exocrine pancreas. *Nature.* 1990; 348:735–738. 1990. [PubMed: 1701852]
- Kasai H, Li YX, Miyashita Y. Subcellular distribution of Ca^{2+} release channels underlying Ca^{2+} waves and oscillations in exocrine pancreas. *Cell.* 1993; 74:669–677. 1993. [PubMed: 8395348]
- Kim MS, Hong JH, Li Q, Shin DM, Abramowitz J, Birnbaumer L, Muallem S. Deletion of TRPC3 in mice reduces store-operated Ca^{2+} influx and the severity of acute pancreatitis. *Gastroenterology.* 2009; 137:1509–1517. 2009. [PubMed: 19622358]
- Lee MG, Xu X, Zeng W, Diaz J, Kuo TH, Wuytack F, Racymaekers L, Muallem S. Polarized expression of Ca^{2+} pumps in pancreatic and salivary gland cells. Role in initiation and propagation of $[\text{Ca}^{2+}]_i$ waves. *J Biol Chem.* 1997a; 272:15771–15776. 1997a. [PubMed: 9188473]
- Lee MG, Xu X, Zeng W, Diaz J, Wojcikiewicz RJ, Kuo TH, Wuytack F, Racymaekers L, Muallem S. Polarized expression of Ca^{2+} channels in pancreatic and salivary gland cells. Correlation with initiation and propagation of $[\text{Ca}^{2+}]_i$ waves. *J Biol Chem.* 1997b; 272:15765–15770. 1997b. [PubMed: 9188472]
- Liu X, Cheng KT, Bandyopadhyay BC, Pani B, Dietrich A, Paria BC, Swaim WD, Beech D, Yildirim E, Singh BB, Birnbaumer L, Ambudkar IS. Attenuation of store-operated Ca^{2+} current impairs

- salivary gland fluid secretion in TRPC1(−/−) mice. *Proc Natl Acad Sci U S A*. 2007; 104:17542–17547. 2007. [PubMed: 17956991]
- Maruyama Y, Inooka G, Li YX, Miyashita Y, Kasai H. Agonist-induced localized Ca²⁺ spikes directly triggering exocytotic secretion in exocrine pancreas. *Embo J*. 1993; 12:3017–3022. 1993. [PubMed: 8344243]
- Mignen O, Thompson JL, Shuttleworth TJ. Both Orai1 and Orai3 are essential components of the arachidonate-regulated Ca²⁺-selective (ARC) channels. *J Physiol*. 2008; 586:185–195. 2008. [PubMed: 17991693]
- Mignen O, Thompson JL, Yule DI, Shuttleworth TJ. Agonist activation of arachidonate-regulated Ca²⁺-selective (ARC) channels in murine parotid and pancreatic acinar cells. *J Physiol*. 2005; 564:791–801. 2005. [PubMed: 15760932]
- Nathanson MH, Fallon MB, Padfield PJ, Maranto AR. Localization of the type 3 inositol 1,4,5-trisphosphate receptor in the Ca²⁺ wave trigger zone of pancreatic acinar cells. *J Biol Chem*. 1994; 269:4693–4696. 1994. [PubMed: 7508924]
- Pandol SJ, Saluja AK, Imrie CW, Banks PA. Acute pancreatitis: bench to the bedside. *Gastroenterology*. 2007; 133:1056 e1051–1056 e1025. 2007.
- Park HS, Betzenhauser MJ, Won JH, Chen J, Yule DI. The type 2 inositol (1,4,5)-trisphosphate (InsP3) receptor determines the sensitivity of InsP3-induced Ca²⁺ release to ATP in pancreatic acinar cells. *J Biol Chem*. 2008; 283:26081–26088. 2008. [PubMed: 18658132]
- Patel S, Joseph SK, Thomas AP. Molecular properties of inositol 1,4,5-trisphosphate receptors. *Cell Calcium*. 1999; 25:247–264. 1999. [PubMed: 10378086]
- Petersen OH, Sutton R. Ca²⁺ signalling and pancreatitis: effects of alcohol, bile and coffee. *Trends in pharmacological sciences*. 2006; 27:113–120. 2006. [PubMed: 16406087]
- Roos J, DiGregorio PJ, Yeromin AV, Ohlsen K, Lioudyno M, Zhang S, Safrina O, Kozak JA, Wagner SL, Cahalan MD, Velicelebi G, Stauderman KA. STIM1, an essential and conserved component of store-operated Ca²⁺ channel function. *J Cell Biol*. 2005; 169:435–445. 2005. [PubMed: 15866891]
- Straub SV, Giovannucci DR, Yule DI. Calcium wave propagation in pancreatic acinar cells: functional interaction of inositol 1,4,5-trisphosphate receptors, ryanodine receptors, and mitochondria. *J Gen Physiol*. 2000; 116:547–560. 2000. [PubMed: 11004204]
- Streb H, Irvine RF, Berridge MJ, Schulz I. Release of Ca²⁺ from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. *Nature*. 1983; 306:67–69. 1983. [PubMed: 6605482]
- Thorn P, Lawrie AM, Smith PM, Gallacher DV, Petersen OH. Local and global cytosolic Ca²⁺ oscillations in exocrine cells evoked by agonists and inositol trisphosphate. *Cell*. 1993; 74:661–668. 1993. [PubMed: 8395347]
- Tinel H, Cancela JM, Mogami H, Gerasimenko JV, Gerasimenko OV, Tepikin AV, Petersen OH. Active mitochondria surrounding the pancreatic acinar granule region prevent spreading of inositol trisphosphate-evoked local cytosolic Ca(2+) signals. *Embo J*. 1999; 18:4999–5008. 1999. [PubMed: 10487752]
- Tsunoda Y, Stuenkel EL, Williams JA. Characterization of sustained [Ca²⁺]_i increase in pancreatic acinar cells and its relation to amylase secretion. *Am J Physiol*. 1990; 259:G792–G801. 1990. [PubMed: 1700626]
- Williams, JA.; Yule, DI. Stimulus-secretion coupling in pancreatic acinar cells. In: Johnson, ELR., editor. *Physiology of the Gastrointestinal Tract*. Academic Press; 2006. p. 1337-1369.
- Wojcikiewicz RJ. Type I, II, and III inositol 1,4,5-trisphosphate receptors are unequally susceptible to down-regulation and are expressed in markedly different proportions in different cell types. *J Biol Chem*. 1995; 270:11678–11683. 1995. [PubMed: 7744807]
- Yule DI, Ernst SA, Ohnishi H, Wojcikiewicz RJ. Evidence that zymogen granules are not a physiologically relevant calcium pool. Defining the distribution of inositol 1,4,5-trisphosphate receptors in pancreatic acinar cells. *J Biol Chem*. 1997; 272:9093–9098. 1997. [PubMed: 9083036]
- Yule DI, Gallacher DV. Oscillations of cytosolic calcium in single pancreatic acinar cells stimulated by acetylcholine. *FEBS Lett*. 1988; 239:358–362. 1988. [PubMed: 3141216]

Yule DI, Lawrie AM, Gallacher DV. Acetylcholine and cholecystokinin induce different patterns of oscillating calcium signals in pancreatic acinar cells. *Cell Calcium*. 1991; 12:145–151. 1991. [PubMed: 2059990]

Figure 1. Pancreatic acinar cell morphology

In A, a low magnification transmitted laser light image obtained using multi-photon microscopy of an isolated mouse pancreatic lobule. Red arrows indicate the apical, zymogen granule region and blue arrow heads highlight the basal aspects of the acinar cells in all images. In B, a DIC image of a small clump of mouse acinar cells isolated by enzyme digestion. In C, a transmitted electron microscopy image of the extreme apical aspects of an acinus is shown. The blue asterisks indicate zymogen granules and the black arrows point to ER strands. In D, a cartoon depicting a single polarized acinar cell. The nucleus is located towards the basal pole while ER strands extend into the zymogen granule region. Mitochondria are present surrounding the granular region.

Figure 2. Spatial characteristics of Ca^{2+} release in pancreatic acinar cells

In A, the Ca^{2+} signal evoked following global flash photolysis (activation) of chemical-caged (inert) InsP_3 is shown. The image series demonstrates that despite the uniform production of InsP_3 following the flash that the Ca^{2+} signal is initiated in the extreme apical region of the cell-mimicking precisely the spatial dynamics of secretagogue stimulation. The change in $[\text{Ca}^{2+}]_i$ measured in an apical region (red trace and box) and basal region (black trace and box) is shown in the top panel, illustrating the delay as the wave proceeds across the cell (Adapted from (Straub et al., 2000) with permission). In B, a cartoon illustrates the Ca^{2+} signaling machinery localized to the extreme apical pole. All InsP_3R family members are localized immediately below the apical PM and at much higher density than elsewhere in the cell and are responsible for initiating the Ca^{2+} signal (Yule et al., 1997). SERCA and PMCA Ca^{2+} pumps are expressed in this region on apical ER and PM respectively (Lee et al., 1997a). Mitochondria surround the apical granule containing region and are responsible for limiting the spread of Ca^{2+} waves (Tinel et al., 1999; Straub et al., 2000).