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The specificity of Ca^{2+} signalling

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A calcium signal is a sudden increase in the concentration of calcium ions (Ca^{2+}) in the cytosol. Such signals are crucial for the control of many important functions of the body. In the brain, for example, Ca^{2+} signals are responsible for memory, in muscle cells they switch on contraction, whereas in gland cells they are responsible for regulation of secretion. In many cases Ca^{2+} signals can control several different processes in the same cell.

As an example, we shall deal with one particular cell type, namely the pancreatic acinar cell, which is responsible for the secretion of the enzymes essential for the digestion of food. In this cell, Ca^{2+} signals do not only control the normal enzyme secretion, but also regulate growth (cell division) and programmed cell death (apoptosis).

Until recently, it was a mystery how the same type of signal could regulate such diverse functions in one and the same cell. Recent technical advances have shown that different patterns of Ca^{2+} signals can be created, in space and time, which allow specific cellular responses to be elicited.

Keywords: calcium signals, pancreatic acinar cell, pancreatitis, secretion, cell growth, apoptosis

Coordination of the many bodily functions occurs by means of the nervous and hormonal systems. These systems create chemical signals (messages in the form of neurotransmitters and hormones), which are received and read by specific receptor proteins in the surface cell membranes. When a hormone or a neurotransmitter binds to a specific receptor site on the outside of a cell membrane, a transduction process (often a complex cascade of chemical reactions) occurs and the result is the creation of an intracellular signal (intracellular messenger) (3). In many cases the signal is a rise in the

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ionized calcium (Ca^{2+}) concentration in the intracellular fluid (cytosol) that surrounds cellular organelles such as the endoplasmic reticulum (ER), the mitochondria and the nucleus (2, 23). One of the perhaps most remarkable features of Ca^{2+} signalling is the ability, in the same cell, to regulate entirely different processes. In this short article, we shall first present briefly the general features of cellular Ca^{2+} handling and thereafter consider a specific example, namely the pancreatic acinar cell, in which Ca^{2+} signals regulate enzyme and fluid secretion. However, Ca^{2+} signals can also elicit cell division or programmed cell death (apoptosis) and initiate the process of intracellular trypsin activation that leads to autodigestion, which is a central feature of the human disease acute pancreatitis. Our aim is to demonstrate how different Ca^{2+} signalling patterns can elicit very specific effects.

How do cells handle Ca^{2+}?

Ca^{2+} has probably been selected as a signalling molecule in evolution because of its ability to bind to many proteins and thereby change the shape (conformation) of these complex molecules. Life evolved in the sea, but the presence of Ca^{2+} in seawater was a problem. Ca^{2+} can form insoluble complexes with phosphates, can cause fatty acids to aggregate into soapy globules and can activate enzymes breaking down proteins (proteases). Mechanisms for essentially keeping Ca^{2+} out of the water inside cells therefore had to evolve.

Very powerful mechanisms have evolved to exclude Ca^{2+} from the normal intracellular environment. The most important mechanism is the chemical machinery that transports Ca^{2+} from inside the cell to the exterior, known as the plasma membrane Ca^{2+} pump (**P**lasma **M**embrane **C**a^{2+}-activated **A**TPase – PMCA). This pump catalyses the process of moving Ca^{2+} from a low to a high concentration (6). Since there is an electrical potential difference (about –50 to –90 mV) across all cell membranes, Ca^{2+} also has to be moved against an electrical force. In some cell types there is an additional Ca^{2+} extrusion mechanism that exchanges Ca^{2+} for Na^{+}. The Ca^{2+} extrusion process can only work if the cell membrane is relatively tight for Ca^{2+}; i.e. the membrane must have a low Ca^{2+} permeability. The importance of this can be appreciated when one considers that the normal Ca^{2+} concentration in the extracellular fluid is about 1 mM. This is four orders of magnitude higher than the normal Ca^{2+} concentration in the intracellular fluid, which is about 0.1 μM. This means that, even disregarding the electrical potential difference across the membrane, Ca^{2+} is 10^4 (10000) times more likely to move into than out of the cells.

The expulsion (extrusion) of Ca^{2+} from the cell interior is therefore a formidable task for the cells, but this problem has been solved in the evolutionary process, so that

cells are able to survive by having a very low intracellular Ca^{2+} concentration. It turns out that this system is also ideal for signalling purposes. Sudden addition of a very small amount of Ca^{2+} to the cell interior creates a relatively large rise in the intracellular Ca^{2+} concentration. The simplest way to produce such a Ca^{2+} signal is to open pores (channels) in the cell membrane that allow movement of Ca^{2+}. Since the Ca^{2+} concentration outside the cell is so much higher than inside and since the electrical potential across the cell membrane is such that the interior is negative with respect to the outside, opening of gates to Ca^{2+}-permeable channels results in movement (flow) of Ca^{2+} into the cell. This is indeed one of the important mechanisms for Ca^{2+} signal generation and there are many types of Ca^{2+} channels, which can be regulated by voltage and/or by external or internal messengers (13, 25, 31).

In general, channels can transport many more ions per unit time than pumps. It is therefore relatively easy to produce quickly large intracellular Ca^{2+} signals, but not so easy to remove quickly the excess Ca^{2+} from the intracellular solution. In order to create sharp and short-lasting Ca^{2+} signals, there are important Ca^{2+} transport mechanisms in the membranes surrounding various intracellular organelles. One of the most important organelles in this respect is the ER, which is a huge system of connected cisterns inside cells that is essential for the production and processing of proteins. In the present context, the most important property of this system is the ability to accumulate Ca^{2+} in the internal space (lumen) of the reticulum. This is due to the existence in the organelle membrane of a Ca^{2+} pump (**S**arco-**E**ndoplasmic **R**eticulum **C**a^{2+}-activated **A**TPase – SERCA), which is similar, but not identical to that in the surface cell membrane (3, 27). The result is a substantial reservoir of Ca^{2+}, held inside the ER. The Ca^{2+} concentration in this compartment is typically about 100–500 μM (1, 15, 32), which is about 1000–5000 times higher than in the surrounding cytosol.

The ER could in principle diminish cytosolic Ca^{2+} signals, created by the opening of Ca^{2+} channels in the surface cell membrane, by absorbing some of the Ca^{2+} entering the cell. In the short term this could be more effective than Ca^{2+} extrusion across the surface cell membrane, since the surface area of the ER is much larger (at least by a factor of 10) than the surface area of the cell membrane. On the other hand, the ER can also be used as a source of Ca^{2+} to primarily create intracellular Ca^{2+} signals that do not depend on entry of Ca^{2+} from the outside. Special Ca^{2+} channels in the ER membrane accomplish this. There are several types of such Ca^{2+} channels, which can be regulated by various chemicals produced inside cells in response to neurotransmitter or hormone actions on the outside of the cell (3). The most important channels in non-muscle cells are activated by inositol 1,4,5-trisphosphate (IP_3) (IP_3 receptors), whereas the most important Ca^{2+} release channels in muscle cells are activated by a rise in the cytosolic Ca^{2+} concentration (ryanodine receptors). However, many cell types contain both IP_3 and ryanodine receptors. The IP_3 receptors are also controlled by changes in the

cytosolic Ca^{2+} concentration and some subtypes of ryanodine receptors are controlled by the cytosolic messenger cyclic ADP-ribose (cADPR) (24). The Ca^{2+} sensitivity of the ER Ca^{2+} release channels allows for the interesting phenomenon of Ca^{2+}-induced Ca^{2+} release, originally described by Endo and his collaborators (8) in skinned muscle fibres. Very recently this phenomenon has been demonstrated directly and elegantly, by simultaneous measurements of the Ca^{2+} concentrations in the cytosol and in the ER, in intact voltage-clamped sensory neurones (32). The Ca^{2+}-induced Ca^{2+} release phenomenon is crucial for the generation of repetitive Ca^{2+} spiking (22).

Finally the role of another important organelle, with respect to cellular Ca^{2+} handling, should be mentioned. The mitochondria are the cellular power generators. The chemical energy is produced in the form of adenosine triphosphate (ATP), which is used to drive very many cellular processes including contraction and secretion. It turns out that three dehydrogenases in the Krebs cycle are modulated by the intramitochondrial Ca^{2+} concentration in the μM range (7). Furthermore, it has now become clear that cytosolic Ca^{2+} signals result in uptake of Ca^{2+} into the inner mitochondrial space via a special Ca^{2+} transporter in the inner mitochondrial membrane known as the Ca^{2+} uniporter (28). When an external signal activates a cell, for example to secrete, by creating a cytosolic Ca^{2+} signal, this results in mitochondrial Ca^{2+} uptake, which subsequently stimulates mitochondrial Ca^{2+}-dependent dehydrogenases and leads to ATP production (7, 11, 29, 33). Ca^{2+} signalling in this way controls both the physiological end product, namely in this case secretion, but also the necessary energy production. We can use the terms ‘stimulus-secretion coupling’ and ‘stimulus-metabolism coupling’ as headings under which to discuss these events. Mitochondria also need to have an exit pathway for Ca^{2+}; this is a so-called ion exchanger, which takes up Na^{+} in return for Ca^{2+}.

The pancreatic acinar cell

The pancreas is an organ in the abdominal cavity, which mainly consists of exocrine cells involved in producing the pancreatic juice, which is secreted into the gut. The pancreatic juice contains many different enzymes, which break down the food products. The pancreas of course also contains a much smaller number of vitally important endocrine cells contained in the islets of Langerhans, which secrete insulin and several other peptides involved in the control of sugar metabolism. Here we are only concerned with the dominant exocrine cell type, the acinar cell, which manufactures and secretes the digestive enzymes.

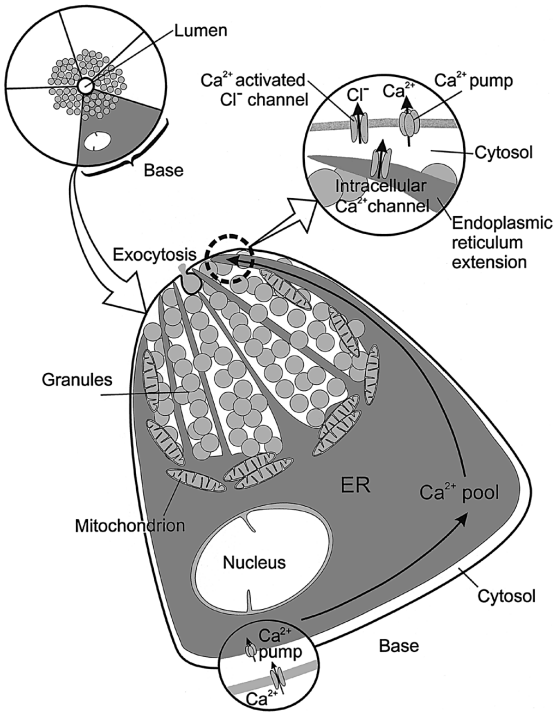

Fig. 1. Schematic drawing of a pancreatic acinar cell. The inset in the upper left corner shows a schematic representation of an acinar unit. Five cells are shown surrounding a small lumen. The secretory material is delivered into this lumen, which in a three-dimensional model would have been seen to be connected to a small duct. Several ducts would converge and finally the secretory material would be delivered into the gut, where the digestion of the food would occur. The main part of the figure shows the organization of an individual acinar cell. The so-called apical pole, near the lumen, is tightly packed with granules containing the digestive enzymes. A single exocytotic event is shown, whereby a granule has fused with the luminal cell membrane and at the point of fusion an opening has been created through which the secretory material can escape into the lumen. The nucleus in the basal part of the cell is surrounded by the very densely packaged endoplasmic reticulum (ER). The ER basically takes up all the space outside the nucleus and the granular pole. Importantly, there are also ER strands penetrating into the granular pole all the way to the luminal membrane. Although the major part of the ER Ca^{2+} pool is in the basal part of the cell, extensions of this Ca^{2+} pool therefore also get very close to the luminal membrane, where the secretion process takes place. This is important, since the Ca^{2+} release channels in the ER membrane are clustered in these extensions into the granular area (14, 34). Opening of such Ca^{2+} channels, as shown in detail in the inset in the upper right corner creates the physiologically important Ca^{2+} signals, eliciting secretion. Secretion depends not only on exocytosis, but also on fluid movement. The crucial event initiating fluid secretion is the opening of Cl^- channels specifically in the luminal membrane (21). These channels are also activated by the Ca^{2+} signals in the apical pole (inset in upper right corner). Ca^{2+} moves into the cell through Ca^{2+} channels in the basal surface cell membrane and is then immediately taken up into the ER by powerful Ca^{2+} pumps (bottom inset) (14). The whole of the ER is fully functionally connected, so that Ca^{2+} can move without difficulty throughout this organelle (19). The mitochondria are placed as a belt around the granular pole. They can take up Ca^{2+} and therefore function as a barrier to free Ca^{2+} diffusion in the cytosol (35). The Ca^{2+} signals that are produced in the apical pole are therefore normally confined to this part of the cell

Figure 1 illustrates the basic structure of the pancreatic acinar cell. The cell is highly polarized. The apical pole is tightly packed with vesicles, normally referred to as secretory or zymogen granules. They contain the digestive (pro)enzymes. The basal part of the cell contains the nucleus surrounded by the very densely packed ER which, as already explained, contains the major mobilisable internal Ca^{2+} store. There are functionally important extensions of the ER into the granular pole. The mitochondria are principally located on the border between the granular apical pole and the basal part of the cell (23, 26).

There are two important stimulants of pancreatic enzyme secretion. The neurotransmitter acetylcholine (ACh) is secreted from nerve endings belonging to the parasympathetic part of the autonomous nerve system and interacts with specific (muscarinic [M3]) receptor sites on the acinar cell membrane. The other physiologically important secretory stimulant is the circulating hormone cholecystokinin (CCK). There are specific high, as well as low, affinity binding sites for CCK on the basal membrane of the acinar cell. It is well established that both CCK and ACh evoke enzyme secretion in a Ca^{2+}-dependent manner and that both these stimulants elicit primarily release of Ca^{2+} from the ER (23).

The normal calcium signals

Both ACh and CCK elicit Ca^{2+} signals in the pancreatic acinar cell. At the lowest concentrations of the stimulants, the signal consists of repetitive short-lasting rises in the Ca^{2+} concentration, which are confined to the granular apical pole (local spiking). These signals are due to repetitive and co-ordinated openings of Ca^{2+} release channels located in the ER extensions in the granular pole (Fig. 1). These local Ca^{2+} signals in the apical granular pole are fully sufficient to elicit the secretory response (12, 21). The confinement of the physiological Ca^{2+} signals to the apical granular pole is essentially due to two factors: the concentration of the Ca^{2+} release channels in the granular ER extensions (5, 26, 34) and the perigranular mitochondrial Ca^{2+} buffer barrier (20, 35).

The rise in the local cytosolic Ca^{2+} concentration in the apical pole evokes secretion by exocytosis. This is a process by which a granule fuses with the plasma membrane and at the point of fusion produces an opening through which secretory material from the granule interior is exported to the solution outside the cell. Exocytosis requires energy in the form of ATP, which is produced locally from neighbouring mitochondria, stimulated by the local Ca^{2+} signals (20, 36). It has been demonstrated that a single shortlasting Ca^{2+} spike in the granular apical pole is able to elicit such an exocytotic response (12). In addition to the secretion of enzymes there is also a need for fluid to be secreted, so that the enzymes can be washed into the duct system and from

there into the gut. Fluid secretion is principally activated by opening of channels permeable to Cl^- in the luminal plasma membrane. It has recently been demonstrated directly that a local elevation of the cytosolic Ca^{2+} concentration in the apical granular pole elicits opening of the Cl^- channels in the luminal plasma membrane (21) (Fig. 1).

ACh and CCK both elicit the same type of secretory response but CCK, in addition to the local Ca^{2+} signals, also occasionally induces the appearance of global and much longer lasting Ca^{2+} elevations. The global Ca^{2+} signals, which also involve the nucleus, can elicit mitosis (cell division) and it is known that CCK evokes substantial growth of the pancreas (22).

Toxic calcium signalling and human disease

When high, and unphysiological, concentrations of ACh or CCK are used, it is possible to elicit prolonged (sustained) global elevations of the cytosolic Ca^{2+} concentration. Whereas the initial rise in the cytosolic Ca^{2+} concentration induced by such toxic stimulation is due to release of Ca^{2+} from the endoplasmic reticulum, the subsequent sustained phase is entirely dependent on entry of Ca^{2+} from outside the cell through special channels in the surface cell membrane (Fig. 2). For further details concerning the oscillation mechanism and the activation of the sustained phase, see the legend to Figure 2.

What is the consequence of such a sustained Ca^{2+} elevation? The pancreatic acinar cell contains, as already mentioned, high concentrations of very powerful digestive enzymes capable of breaking down all ingested food products including proteins. These enzymes could of course also digest the pancreatic acinar cells themselves, as well as other cells in the pancreas and indeed other organs. This is what happens in the human disease acute pancreatitis. This is a disease, which often has a fatal outcome, in which the pancreas digests itself. In the UK alone, more than 10000 people develop pancreatitis every year and currently there is no known cure. Life-threatening complications occur in about a quarter of cases and the mortality rate is about one in ten. Recent work has shown that a toxic CCK concentration (10 nM as compared to the physiological range of 1–10 pM), activates the protein degrading enzyme trypsin inside the granules in the pancreatic acinar cell. This never happens when physiological stimulation is applied. Furthermore the toxic CCK concentration also elicits structural changes in the cell (secretory granules are replaced by vacuoles), which are similar to those encountered in the disease acute pancreatitis (30).

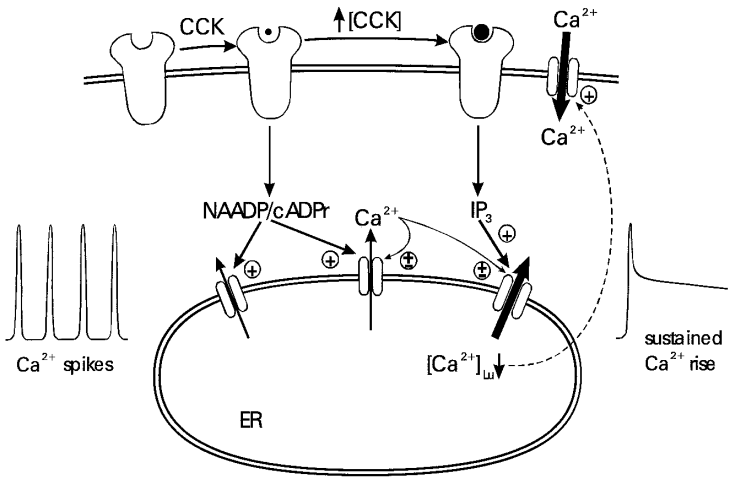

Fig. 2. Schematic diagram illustrating the difference between the cytosolic Ca^{2+} signal created by a low physiological level of the hormone cholecystokinin (CCK) and a high toxic concentration, which inappropriately activates the digestive enzymes inside the cell. At the low CCK concentration (left part of the diagram), CCK interaction with its specific high affinity receptor results in the formation of the intracellular messengers nicotinic acid adenine dinucleotide phosphate (NAADP) and cyclic adenosine diphosphate-ribose (cADPr). These messengers activate Ca^{2+} release channels in the ER membrane, which through complicated (both positive and negative) Ca^{2+} feedback regulations result in repetitive cytosolic Ca^{2+} spiking (4). The amounts of Ca^{2+} released from the ER store are quite small and do not in the short term result in any major reduction in the Ca^{2+} concentration inside the store (19). At much higher CCK concentrations (interacting with low affinity CCK receptors) (right part of the diagram), the messenger inositol trisphosphate (IP_3) is generated. This opens up other specific channels in the ER membrane resulting in a major Ca^{2+} release (5), which causes a marked reduction in the concentration of Ca^{2+} inside the store ($[Ca^{2+}]_{Lu}$) (19). This, in a manner not yet understood, activates a Ca^{2+} channel in the surface cell membrane through which substantial amounts of Ca^{2+} enter the cytosol. The result is a sustained elevation of the cytosolic Ca^{2+} concentration, which is toxic for the cell. [This figure is a modified version of Figure 1 in Parekh (18)]

Hyperstimulation with CCK may therefore provide a useful animal model system for the human disease. The most interesting aspect of these recent studies is that the dangerous enzyme activation inside the pancreatic acinar cell can be prevented simply by removal of external Ca^{2+} (30). These and other findings indicate that the inappropriate enzyme activation in the granular pole is dependent on entry of Ca^{2+} from the solution outside the pancreatic acinar cell (18, 30). A specific blocker of the store-operated Ca^{2+} channel in the acinar cell membrane could therefore be effective in preventing the inappropriate enzyme activation (Fig. 2).

Although CCK hyperstimulation is effective in producing a condition that resembles acute pancreatitis, this disease is not caused by excessive CCK stimulation. One of the classical causes of acute pancreatitis is reflux of bile into the pancreas (17). Very recently we have been able to show that several bile acids, applied in pathophysiologically relevant concentrations, induce prolonged cytosolic Ca^{2+} signals (37). Since prolonged cytosolic Ca^{2+} signals generated pharmacologically by blocking the SERCA pumps with thapsigargin induce intracellular trypsin activation and vacuole formation in a Ca^{2+}-dependent manner, it is likely that the bile acids would do the same. Further investigations are needed, but probably the ability of bile acids to induce acute pancreatitis (16) is due to excessive and prolonged cytosolic Ca^{2+} signals.

Calcium as a death signal

Apoptosis, or programmed cell death, is currently the subject of intense investigations around the world. Ca^{2+} signals play a role in the regulation of this phenomenon (9) and one of the widely used methods for inducing apoptosis experimentally is to apply the compound thapsigargin, which is a very specific inhibitor of the SERCA pump in the ER. Thapsigargin therefore releases Ca^{2+} from the major internal store into the cytosol. However, in the pancreatic acinar cells, it is difficult to elicit apoptosis by thapsigargin itself. Normal physiological or even toxic stimulation with CCK also fails to elicit programmed cell death. Our recent work indicates that Ca^{2+} signals can elicit apoptosis in the acinar cells only if there is a simultaneous reduction in the electrical potential difference across the inner mitochondrial membrane (mitochondrial depolarisation). This can occur by opening a special channel known as the permeability transition pore (10).

The control of apoptosis is very complex and a detailed account is outside the scope of this article, but one important event is the release of the protein cytochrome c from the mitochondria which, via various steps, leads to activation of enzymes known as caspases. Caspases are the ‘executioners’ of apoptosis (9).

In general, various oxidants can induce inappropriate programmed cell death. In pancreatic acinar cells, it has been established that the oxidant menadione is able in a consistent and reproducible manner to elicit apoptosis. Menadione elicits global Ca^{2+} signals and also depolarises the mitochondrial membrane by opening the permeability transition pore. Our recent work shows that both global Ca^{2+} signals and opening of permeability transition pores in mitochondria are absolutely required for induction of apoptosis in the pancreatic cells. This is best explained by a twin-track model, in which Ca^{2+} signal generation and co-operative oxidant and Ca^{2+} actions on the mitochondria induce the apoptotic signal (10).

Conclusion

Figure 3 summarizes the different types of Ca^{2+} signals and their functions. We have focussed attention on one particular cell type, which has been investigated in some detail. It seems remarkable that one signal, a rise in the concentration of Ca^{2+} in the fluid inside these cells, is capable of such very different actions ranging from normal secretion of fluid and enzymes to execution of cell death. The explanation lies in the complex patterns, both in time and space, of the Ca^{2+} signals, which allow different parts of the cell to be involved at different times. There are still very many details, concerning the specific regulation of the various types of Ca^{2+} release channels, to be worked out, but it is likely that further studies will enable us to modify pathological Ca^{2+} signals by interfering with specific molecules governing the extent and distribution of these signals. This might provide therapies effective against diseases caused by abnormal Ca^{2+} signalling.

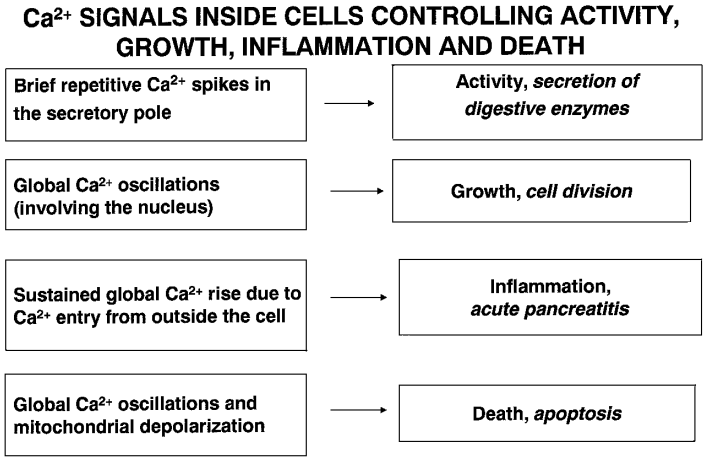

Fig. 3. Summary of the actions, in the pancreatic acinar cell, of different kinds of Ca^{2+} signals

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