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The Functional Organisation of Calcium Signalling in Exocrine Acinar Cells

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Basic outline of Ca^{2+} signalling processes in acinar cells

The original evidence for agonist-induced release to the cytosol of Ca^{2+} stored inside cells came from studies of radioactive Ca^{2+} fluxes (1, 2). These experiments showed that agonists evoke Ca^{2+} signals by mobilisation of Ca^{2+} accumulated in intracellular stores. Further study led, ten years later, to the discovery of the intracellular second messenger inositol 1,4,5-trisphosphate (IP_3), which acts on Ca^{2+} channels in the endoplasmic reticulum (ER) to release Ca^{2+} stored in this organelle (3).

In the early 1980s, the concept of cytosolic Ca^{2+} signalling in pancreatic acinar cells was simple: acetylcholine (ACh) and cholecystokinin (CCK) bind to specific receptors on the surface of the acinar cell membrane activating phospholipase C, which results in generation of IP_3 (and diacyl glycerol). IP_3 is released into the cytosol and binds to a special type of Ca^{2+} release channel in the ER (the IP_3 receptor) and thereby opens these channels causing release of stored Ca^{2+} into the cytosol. This general concept was not wrong, but incomplete. Further work has revealed important additional elements.

The problem

Activation of exocytosis requires rather large local cytosolic Ca^{2+} signals (4). In the pancreatic acinar cells exocytosis occurs under normal physiological conditions exclusively through the apical (luminal) membrane and all the secretory (zymogen) granules (ZGs) are concentrated in the apical part of the cells. The substantial cytosolic Ca^{2+} signals needed to initiate exocytosis must therefore occur in the apical part of the cells. However, the apical pole is so tightly packed with ZGs that there is very little space for ER elements. In fact, ultrastructural studies show clearly that the ER is densely packed in the baso-lateral part of the acinar cells surrounding the nucleus with only tiny and very thin elements penetrating into the granular area. Nevertheless, low – and physiologically relevant – agonist concentrations do in fact evoke repetitive cytosolic Ca^{2+} spikes, which most of the time are entirely confined to the apical granule containing part of the cells (5, 6).

Key Words: *Calcium Tunnel; Granule; Pancreas; Acinar Cells; cADPR*

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The Ca^{2+} tunnel hypothesis

Ca^{2+} needed for stimulus-secretion coupling ultimately comes from the blood and is therefore first presented to the basal acinar cell membrane. Reloading empty intracellular Ca^{2+} stores by only allowing Ca^{2+} entry through a cell-attached patch pipette, placed in contact with the basal part of an isolated acinar cell, occurs without any measurable cytosolic Ca^{2+} rise in any part of the cell (7). Subsequently, ACh stimulation evokes a normal cytosolic Ca^{2+} rise, which takes place, as usual, in the apical pole (7). Ca^{2+} entering the cell at the base therefore traverses the cell, not through the cytosol, but through an intracellular tunnel and can in this way reach the release sites in the apical pole. Ca^{2+} reloading of the intracellular stores depends on thapsigargin-sensitive Ca^{2+} pumps (SERCA pumps). We have therefore proposed (7) that Ca^{2+} entering at the base via store-operated Ca^{2+} channels would immediately be taken up into the ER by SERCA pumps, diffuse through the luminally continuous ER and therefore also reach the fine ER terminals penetrating the granular area, where the Ca^{2+} release channels are concentrated.

Recent work supporting Ca^{2+} tunnel hypothesis

It is implicit in the Ca^{2+} tunnel hypothesis that Ca^{2+} can diffuse more easily in the lumen of the ER than in the cytosol. Mogami et al. (8) measured the Ca^{2+} binding capacity in the cytosol and in the lumen of the ER and came to the result that the efficiency of Ca^{2+} buffering in the cytosol was about 100 times larger than in the ER. This indicates that the mobility of Ca^{2+} inside the ER is considerably higher than in the cytosol.

Mogami et al. (7) proposed that Ca^{2+} liberated from the ER terminals in the granule area could be taken up by the ZGs for subsequent release, since it had previously been shown that IP_3 could stimulate Ca^{2+} outflow from isolated ZGs (9). More recently, the relationship between the Ca^{2+} reloading of the ER and the ZGs has been investigated. During stimulation, Ca^{2+} moving into the cell and then into the ER, was found to be conveyed toward the apical pole driven by proton gradients generated by vacuolar H^+ ATPases in the ZG membranes (10). These findings together with other recent evidence confirming that the granular Ca^{2+} pool can be mobilised (11) indicate a much more active role for the granules in stimulus-induced Ca^{2+} signalling than has hitherto been generally accepted.

The role of the mitochondria

Active mitochondria in living pancreatic acinar cells are mainly located in a ring surrounding the granular region (12). The ability of mitochondria to take up Ca^{2+} prevents spreading throughout the cytosol of IP_3-elicited local Ca^{2+} signals generated in the apical granular pole. When mitochondrial function is inhibited, the local IP_3-induced Ca^{2+} signals are transformed into a global cytosolic Ca^{2+} rise (12).

New messengers

Ca^{2+} release from intracellular stores does not exclusively occur through IP_3 receptors. Receptors for cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP) can also mediate Ca^{2+} release and functional IP_3, cADPR and NAADP receptors are all required for CCK-elicited intracellular Ca^{2+} release (13). NAADP receptors are likely to function as triggers, cADPR/ryanodine receptors as amplifiers and the IP_3 receptors as oscillators (13).

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