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Stimulus-secretion coupling in the pancreatic B-cell: concluding remarks

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The pancreatic B-cell may be viewed as a fuel-sensor organ. Thus, its secretory activity is mainly but not exclusively regulated by the level of circulating nutrients, and its main secretory product, insulin, regulates the uptake or release of nutrients in extrapancreatic tissues. The influence of non-nutrient secretagogues, e.g. catecholamines, cholinergic agents or gastrointestinal hormones, upon insulin release in vivo does not detract from such a schematic view. Indeed, the immediate effect of hormones and neurotransmitters upon the pancreatic B-cell allows modulation of nutrient-regulated insulin release at times when the supply or consumption of nutrients are dramatically modified, e.g. during muscular exercise or after food intake.

The functional organization of the B-cell can also be conceived of within the framework of this fuel concept. Thus, changes in the concentration of circulating nutrients are sensed by the B-cell through changes in the rate of nutrients oxidation. Increasing attention should be paid, therefore, to the regulation of metabolic events in islet cells exposed to the heterogenous constellation of circulating nutrients at their physiological concentration[1].

Several coupling factors may be generated by the metabolism of nutrients and affect distal events in the secretory sequence. For instance, changes in redox state, intracellular pH and ATP availability may influence the movements of ions in the islet cells or other cellular events involved in the stimulation of insulin release[2].

It is obvious that glucose and other insulin secretagogues dramatically affect ionic fluxes in the islet cells, this being associated with induction of bioelectrical activity. The precise determinism of the changes in membrane potential and their relevance to the exocytosis of secretory granules remain, however, to be fully elucidated[3].

The use of the fluorescent calcium-indicator quin-2 has recently allowed to validate the concept, already advanced almost 20 years ago, that the stimulation of insulin release usually coincides with in increase in cytosolic Ca^{2+} activity. The regulation of cytosolic Ca^{2+} concentration depends not solely on the net balance between Ca^{2+} influx and efflux across the plasma membrane but also on the sequestration or release of Ca^{2+} by such organelles as the endoplasmic reticulum and mitochondria[4].

The response to a rise in cytosolic Ca^{2+} concentration may be mediated, in part at least, by the Ca^{2+}-binding regulatory protein, calmodulin. Calmodulin as well as calmodulin-binding proteins are present in islet cells and Ca-calmodulin affects the activity of a number of enzymes in islet homogenates or subcellular fractions. However, further studies are required to define the precise role played by calmodulin in the secretory sequence[5].

The other classical second messenger, cyclic AMP, may also participate in the stimulus-secretion coupling process. It is obvious that an increase in cyclic AMP availability represents an efficient modality to enhance the secretory response of the B-cell to a number of secretagogues. However, it is less easy to define to which extent endogenously formed cyclic AMP participates in the normal process of glucose-induced insulin release[6]. Both Ca-calmodulin and cyclic AMP may act in the B-cell by activating suitable protein kinases. The participation of distinct kinases in the secretory sequence could conceivably help to distinguish between a Ca-calmodulin-dependent phosphorylation of proteins, which would be central to initiation of insulin release, whilst modulation of this process could be mediated by cyclic AMP-responsive kinases and the phospholipid-dependent and Ca^{2+}-sensitive protein kinase C, which is activated by diacylglycerol[7].

The process of stimulus-secretion coupling in the pancreatic B-cell apparently also involves enhanced metabolism of phospholipids, especially in the so-called phosphatidylinositol cycle. This may result, inter alia, in altered calcium permeability of the plasma membrane, mobilization of calcium from intracellular stores, and activation of protein kinase C by diacylglycerol[8]. Thus, an array of distinct translation systems may participate in the sequence of events eventually leading to exocytosis of secretory granules.

The secretory product of the pancreatic B-cell is stored in membrane-limited vesicles. In addition to proinsulin, insulin and C-peptide, some 150 other proteins may be visualized by electrophoresis of material derived from these secretory granules. Some of these peptides may be tailored for specific functions within the B-cell, e.g. the proteolytic conversion of proinsulin to insulin as catalyzed by suitable proteinases[9].

The B-cell microtubular-microfilamentous system is thought to play an essential role in controlling the motility of secretory granules and their access to sites of exocytosis at the plasma membrane, where fusion and fission of membranes takes place. The biochemical aspects of these mechanical events are now actively investigated[10].

The dynamics of insulin secretion including the release of both preformed and newly synthesized hormone, clearly indicate that secretory granules are not mobilized at random from a single and homogenous pool. It remains a challenge to understand how the intrinsic properties of secretory granules and their handling by the effector system may account for such a functional compartmentation[11].

Although the stimulation of insulin release obviously involves a large number of interconnected cytophysiological events, it may not be quite adequate to conceive of these events only in terms of a single cellular secretory unit. It indeed appears that the function of each pancreatic B-cell may be influenced, directly or indirectly, by the behavior of adjacent cells within the same islet[12].

With such a sophisticated knowledge at hand, it is rather amazing if not amusing, that we still poorly understand the mode of action of the major therapeutic agents currently used to modify the secretory activity of the B-cell, namely hypoglycemic and hyperglycemic sulfonylureas. These drugs obviously affect Ca^{2+} handling by the pancreatic B-cell, but the molecular determinant(s) of such a cationic response remain(s) to be elucidated[13].

In introducing this series of reports, I had underlined its several limitations. I now feel confident that, despite its restricted scope, the present review duly illustrates at least two points. First, the process of stimulus-secretion coupling in the pancreatic B-cell is not quite a narrow topic. Second, the knowledge so far gained on such a process represents a stimulus for further research in this fascinating field.

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