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Regulation of Acinar Cell Function in The Pancreas

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Abstract

Purpose of Review—This review identifies and puts into context the recent articles which have advanced understanding of the functions of pancreatic acinar cells and the mechanisms by which these functions are regulated.

Recent Findings—Receptors present on acinar cells, particularly those for cholecystokinin and secretin, have been better characterized as to the molecular nature of the ligand-receptor interaction. Other reports have described the potential regulation of acinar cells by GLP-1 and cannabinoids. Intracellular Ca^{2+} signaling remains at the center of stimulus secretion coupling and its regulation has been further defined. Recent studies have identified specific channels mediating Ca^{2+} release from intracellular stores and influx across the plasma membrane. Work downstream of intracellular mediators has focused on molecular mechanisms of exocytosis particularly involving small G proteins, SNARE proteins and chaperone molecules. In addition to secretion, recent studies have further defined the regulation of pancreatic growth both in adaptive regulation to diet and hormones in the regeneration that occurs after pancreatic damage. Lineage tracing has been used to show the contribution of different cell types. The importance of specific amino acids as signaling molecules to activate the mTOR pathway is being elucidated.

Summary—Understanding the mechanisms that regulate pancreatic acinar cell function is contributing to knowledge of normal pancreatic function and alterations in disease.

Keywords

Receptors; Calcium Signaling; Exocytosis; Secretion; Growth

Introduction

Pancreatic acinar cells synthesize and secrete almost all the digestive enzymes active in the lumen of the small intestine which are necessary for nutrient digestion. Both synthesis and secretion are highly regulated over both short and long time frames to insure an appropriate supply of digestive enzymes. While the intake of food classically has been believed to act via neural pathways and the release of hormones, there is increasing evidence for a direct regulatory role of some nutrients. This review focuses on the receptors and intracellular regulatory signal transduction pathways activated by neurotransmitters, hormones and nutrients to insure an adequate supply of digestive enzymes. The primary information to be covered is that published since the last reviews of the subject in this journal [1,2].

Receptors

The primary secretagogues for acinar secretion are acetylcholine released from vagal postganglionic neurons and CCK released from intestinal endocrine cells. Secretin is the primary secretagogue for ductal secretion but also has actions on acinar cells. A number of other hormones, neurotransmitters and growth factors have receptors on acinar cells and may affect secretion as well as other cellular functions. CCK is known to activate CCK receptors on vagal afferent endings in a paracrine mechanism but also enters the blood to bind to receptors and regulate gallbladder contraction and gastric emptying as well as binding to receptors on pancreatic acinar cells. The presence of CCK receptors on human acinar cells remains controversial [2] but the CCK receptors on rodent acinar cells continue to be used as a model to study CCK action. CCK in plasma is known to exist in longer molecular forms with CCK-58 being prominent in many species. Recently the better availability of natural purified and synthetic CCK-58 has allowed more detailed studies of its receptor binding. Using purified rat CCK-58 this form of CCK was shown to be a full receptor agonist on CCK1 receptors but with a five fold lower affinity than synthetic CCK-8 [3]. In another study using synthetic human CCK-58 and CCK-8 to stimulate mouse acinar cells, both peptides induced similar effects on Ca^{2+} signaling, mitochondrial function and digestive enzyme secretion [4].

An area of continuing interest is the molecular nature of the ligand-receptor interaction as this may inform the generation of specific agonists and antagonists especially for the CCK receptor [5]. Harikumar et al used multidimensional FRET to establish distances between three amino acid residues in the active region of CCK and four residues in the extracellular domain of the CCK receptor [6]. The distance between fluorescence donors and acceptor were determined and then applied to modeling of the ligand receptor interaction. In a latter study by the same research group, two new photolabile CCK analogs were developed with the active group at positions 28 and 32 (CCK-33 nomenclature) and the site of attachment to the receptor determined [7]. These were located in the second and first extracellular loop. The receptor was modeled using recent crystal structure of the Beta2 adrenergic receptor and prior distance constraints such as discussed above. The CCK binding pocket was defined by the top of TM segment 2, extracellular loops 2 and 3, and TM segment 7. This model accommodates longer forms of CCK whose amino terminal can extend out of the receptor. Similar studies for the secretin ligand- receptor interaction have been reported by the group of LJ Miller. The secretin receptor is a Class II or Family B (alternate nomenclature) receptor and therefore has a somewhat different structure. In one recent study the secretin receptor was shown to associate with RAMP3 a member of the receptor activity-modifying proteins [8]. No effect of RAMP3 on affinity or signaling by the secretin receptor was observed but RAMP assisted the membrane targeting of a mutant receptor.

The effects of other regulatory peptides on acinar cell function have also been studied. GLP-1, a incretin hormone secreted by the distal small intestine has been studied with regard to its actions on islets but its potential actions on the exocrine pancreas has assumed importance with the reported cases of clinical pancreatitis in patients receiving exenatide-4 (Ex-4) [9]. Ex-4 is based on a scorpion venom peptide which is a GLP-1R agonist. Koehler et al [10*] carried out an extensive study of Ex-4 and related peptides on gene expression in acinar cells. Acute Ex-4 administration increased expression of early response genes *egr-1* and *c-fos*. When Ex-4 was given twice daily for a week, the pancreas increased in mass and this was accompanied by expression of mRNA for anti-inflammatory molecules including pancreatitis associated protein. In both acute and chronic studies there was no determination of whether Ex-4 was acting directly or indirectly on the exocrine pancreas. When pancreatic fragments were stimulated with forskolin a 10 fold increase in cAMP was seen but there was no change in cAMP in response to Ex-4 [10*]. Although Ex4 had been reported to increase

cAMP in guinea pig acini it did not increase amylase release similar to secretin or VIP in that species [11]. Thus it is not clear whether a GLP-1 receptor exists on mouse acini and whether GLP-1 directly regulates acinar cell function or acts indirectly through the vagus nerve since GLP-1 activated vagal motorneurons in the brain [12].

Other work has appeared evaluating the role of two other novel receptors on pancreatic exocrine secretion. In the first study, cannabinoid CB-1 and CB-2 receptors were found in rat acinar cells by Western blotting and immunohistochemistry [13]. However, a receptor agonist WIN 55,212, although it inhibited pancreatic synaptic acetylcholine release, had no effect on amylase release by isolated acini. The second work involves the actions of natriuretic peptides in GI secretion especially the pancreas and provides a comprehensive review of this area [14].

Intracellular Ca^{2+} Signaling

An increase in intracellular free Ca^{2+} is the primary driver of digestive enzymes by pancreatic acinar cells. The current paradigm for Ca^{2+} signaling includes the receptors for CCK, ACh and bombesin acting through heterotrimeric G proteins to produce messengers that act to release intracellular Ca^{2+} (For a review see [15]). While inositol trisphosphate (IP_3) produced by phospholipase C is the best studied of these messengers, other messengers include nicotinic acid adenine dinucleotide (NAADP) and cyclic ADP ribose (cADPR) [1]. IP_3 acts on IP_3 receptors in the endoplasmic reticulum while NAADP acts on an acidic lysosomal/endosomal compartment [16]. The decrease of the Ca^{2+} concentration in the lumen of the ER then enhances Ca^{2+} influx through membrane channels referred to as store operated channels (SOCs) with this influx necessary to maintain Ca^{2+} signaling.

Recently, there have been significant advances in two areas that provide molecular definition at key points of the above model of Ca^{2+} signaling. The first is the identification of two-pore channels (TPCs) and their role in releasing Ca^{2+} in response to NAADP [17]. TPC proteins have twelve transmembrane domains with six forming a channel. TPC2 was shown to be localized on lysosomes and mediate NAADP binding and Ca^{2+} release [18]. The TPC mediated Ca^{2+} release was local but triggered a larger release of Ca^{2+} from the ER via the IP_3 receptor. Pancreatic beta cells from a Tpc2 knockout mouse were shown to be NAADP insensitive [18]. A similar role for TPC1 was demonstrated which included showing that mutation of a residue in the pore forming region abolished Ca^{2+} release by NAADP [19]. Although this has not yet been studied in acinar cells, further studies are expected soon.

The other area of progress is in defining the mechanism of store operated or capacitative Ca^{2+} entry [20]. In 2005 two research groups using RNAi screens, identified Stim proteins as ER membrane proteins necessary for Ca^{2+} influx when thapsigargin was used to deplete Ca^{2+} stores (For a review see [21]). Shortly thereafter Orai proteins were discovered by another RNAi screen and shown to be able to duplicate the properties of the Ca^{2+} current in lymphocytes that is activated by depleting intracellular Ca^{2+} stores. A model has emerged in which the luminal domain of Stim forms oligomers, moves to the plasma membrane and accumulates in clusters termed “puncta” associated with Orai molecules which are activated to conduct Ca^{2+} . Forms of Stim and Orai are present in acinar cells and when a YFP labeled Stim was expressed in mouse acinar cells it was diffusely located but formed puncta just under the basolateral membrane following depletion of ER calcium by thapsigargin or stimulation by CCK or acetylcholine [22*]. Morphologically, ribosome free terminals of ER were observed only 12–13 nm from the plasma membrane. Accumulated evidence had also indicated that transient receptor potential (Trp) family of channels could also mediate store operated Ca^{2+} entry. TrpC channels have been shown to also be gated by Stim although by a

mechanism different than for Orai [23]. TrpC3 and TrpC6 are present in acinar cells and carbachol stimulates the translocation of TrpC3 to the plasma membrane [24]. Recently TrpC3 knockout mice were used to show that TrpC3 mediates both receptor mediated and store regulated calcium influx [25*]. Reducing Ca^{2+} influx shifted the amylase secretion dose-response curve, reduced high dose inhibition of amylase secretion and reduced cellular damage in caerulein-induced pancreatitis in mice.

The matching of Ca^{2+} release from intracellular stores with Ca^{2+} influx in acinar cells is also regulated by ATP levels. Depleting ATP by either chemical inhibitors or expression of luciferase was shown to inhibit Ca^{2+} influx as well as extrusion thereby preventing a toxic build up of intracellular Ca^{2+} [26]. Depleting ATP also inhibited Ca^{2+} oscillations; however, it did not block the effects of bile acids to overload the cell with Ca^{2+} .

Mechanisms of Exocytosis

Understanding of how intracellular signaling in acinar cells leads to secretion of digestive enzymes by exocytosis has been a continuing area of study that is highly relevant both to understanding of normal acinar function and the mechanism of pancreatitis. This has been approached both through understanding of signaling which includes Ca^{2+} and other molecules but also by understanding the structural machinery that forms secretory granules, moves them to the apical membrane and brings about fusion and release of granule contents.

Small G proteins have been identified as playing a role at multiple steps in the secretory process. One group are the Rho family G proteins that are believed to regulate the remodeling of the actin cytoskeleton. Recent work by Sabbatini et al [27*] evaluated how Rho and Rac are activated by secretagogues. Activation of RhoA was mediated by the heterotrimeric G protein, $\text{G}_{\alpha 13}$ which binds and activates a RhoGEF containing a RGS like domain. Using an isolated RGS like domain from p115RhoGEF they showed that it would block RhoA activation, cytoskeletal reorganization and reduce amylase secretion without an effect on Ca^{2+} mobilization or cAMP formation. In contrast, activation of Rac1 was mediated by $\text{G}_{\alpha q}$ in a phospholipase C independent manner [27*].

The other main small G protein family involved in digestive enzyme secretion are the Rab proteins. A number of Rabs have been identified on zymogen granules and Rab3D and Rab27B are believed to be involved in acinar cell secretion. A comprehensive review of Rabs and other small G proteins including Rap1 involved in secretion appeared in the last year [28]. One protein involved in Rab cycling that has not previously been studied in acini is RabGDI. GDIs play a role in extracting GDP liganded small G proteins from membranes and in maintaining them as a cytosolic pool. Raffaniello et al [29] studied RabGDI in acinar derived AR42J cells and found that both known isoforms, GDI-1 and GDI-2 were present and that GDI-1 existed in a complex with Hsp90. Amylase release stimulated by CCK was partially inhibited by the Hsp90 inhibitor, geldanamycin [29]. It would be interesting to know if secretagogues cause a release of any Rabs from GDI and where they go in the cell, as most Rab3D and Rab27B is already on secretory granules. Such a model could also apply to Rho family members where most cellular Rho or Rac exists in a complex with RhoGDI. Because differences exist between AR42J cells and acinar cells studies of Rab GDI needs to be carried out using acinar cells.

Another intracellular control system involved in secretion is protein kinase C (PKC). Both activating PKC with phorbol esters and inhibiting PKC by down regulation or use of a general PKC inhibitor supports a role for PKC in secretion [15]. Because PKC has multiple isoforms it seems likely that different isoforms mediate different functions. PKC- δ has been suggested to be involved in secretion in rat acinar cells based on the overexpression of dominant negative isoforms [30]. Thrower et al [31] recently reported studies of amylase

secretion by acini from mice with deletion of the PKC- δ gene and found no change in secretion although zymogen activation and NF- κ B activation were reduced. They did not test other PKC isoforms and in fact did not observe inhibition by the broad spectrum PKC inhibitor GF109203X. Further work is need to evaluate the role of PKC in mouse pancreatic acinar secretion. In a study more related to pancreatitis, Ramnath et al [32] showed that Substance P activated PKC δ in mouse acinar cells and that this activation led to chemokine synthesis.

Continued interest exists in defining the role of proteins on the external surface of the zymogen granule [2]. Weng et al [33] studied the role of cysteine string protein (CSP α) and its amino terminal J domain which acts as a co-chaperone to regulate Hsc70/Hsp70 family members. They found CSP α to associate with VAMP8 and that when the isolated J domain was introduced into permeabilized cells it enhanced secretion.

The role of myosin II in the control of secretion was studied by Bhat and Thorn [34*]. They found that myosin IIA was localized in the apical pole of the cells along with F-actin and that its phosphorylation was enhanced by secretagogue stimulation. Using confocal microscopy to visualize secretion and myosin inhibitors they found that myosin was not necessary for granule fusion but rather maintained the fusion pore open allowing content to be released. Another potential regulator of actin is Src family kinases. Although primarily focused on supramaximal secretagogue effects, Singh and McNiven [35] showed that the Src family member Yes could phosphorylate the actin binding protein cortactin on tyrosine residues and this specific phosphorylation was necessary for redistribution of actin. Thus Src joins Rho, Rac, and FAK as regulators of the actin cytoskeleton.

An alternative pathway for secretion involving lysosomal related vesicles is raised by the finding that the protein CRHSP-28 (Calcium Regulated Heat Stable Protein of 28 kDa, also known as D52) promotes translocation of a lysosomal marker to the plasma membrane in cultured cells when phosphorylated on Ser136 by a calcium dependent kinase [36]. CRHSP-28 previously had been shown to promote Ca²⁺-stimulated secretion of amylase in permeabilized rat acinar cells and localize to an early apical endosomal compartment [37].

Regulation of Pancreatic Growth and Regeneration

Pancreatic growth and regeneration often recapitulates some of the events in pancreatic development. There has been continued interest both in regulatory factors and intracellular signaling but also in the cell types that serve to divide and regenerate. This has been stimulated by interest in plasticity whereby one cell type in the pancreas might serve as a source for others, especially insulin producing beta cells.

While preexisting acinar cells can divide and this underlies adaptive growth in rodent pancreas [1] the presence of a pancreatic progenitor has remained controversial. Sangiorgi and Capecchi [38] used lineage tracing of cells expressing Bmi1, a marker of hematopoietic and neural stem cells to show that a subset of differentiated acinar cells possessed the ability to proliferate to maintain organ homeostasis. Inada et al, [39] used lineage tracing of pancreatic ductal cells that were marked using the carbonic anhydrase promoter to drive Cre expression and showed differentiation into adult acinar and beta cells in the neonatal period. In adult mice this differentiation occurred at a low rate but was enhanced after ductal ligation.

In an important study using a different approach, Rovira et al [40**] developed a method to isolate centroacinar/terminal duct cells based on expression and enzymatic activity of ALDH1 (Aldehyde Dehydrogenase). Using a fluorescent substrate, these cells were purified by cell sorting and were shown to express transcripts associated with progenitor populations.

They showed that these cells could form “pancreatospheres” in culture that could differentiate into both exocrine and endocrine cells. They concluded that CA/TD cells were capable of progenitor function and might contribute to tissue homeostasis in adult mouse pancreas [40**].

Pancreatic plasticity has been studied both in vivo and in vitro. Glucocorticoid administration to rats for 25 days was shown to induce a small fraction of acinar cells to assume a hepatocyte phenotype and express the cytochrome P450, CYP2E1, albumin and glutamine synthetase [41]. This could also be modeled using the AR42J B-13 cell line. Several earlier studies have shown acinar to ductal or acinar to islet transformation. In a recent paper, Rapoport et al [42] showed that human acini could be cultured in plastic dishes, and after 3 days cells grew out without division and became dedifferentiated. These cells could then be trypsinized and afterward could proliferate and give rise to multiple cell types expressing markers for mesoderm and endoderm in culture but without expression of amylase or insulin.

A number of gene deletion studies in mice have led to failures in pancreatic differentiation with some being unexpected. A recent study [43] showed pancreatic insufficiency in mice without LXR β (Liver X receptor), a nuclear oxysterol receptor. The size of the pancreas was not reported but serum amylase and total fecal protease were reduced. The pancreas also showed decreased aquaporin 1 expression and this was suggested, but not proven experimentally, to mediate pancreatic insufficiency.

Pancreatic insufficiency is also known to accompany dietary protein deficiency in humans even with adequate calories with the syndrome termed Kwashiorkor. Crozier et al [44*] modeled this condition in mice by feeding a protein free diet for 4 days. Acinar cells showed hypoplasia, reduced protein but normal DNA and blockage of the mTOR pathway which was reversed by refeeding protein in a manner independent of CCK. The lack of dietary protein also led to a reversible reduction of pancreatic secretion in vivo. These studies show that dietary protein can modulate pancreatic growth via CCK-independent activation of the mTOR pathway.

Adaptive pancreatic growth involves CCK and is mediated in part by early response genes [1]. In a recent paper, Fedirko et al [45] reviewed the evidence for calcium signaling in the nucleus and presented new data showing that early response gene expression is regulated by the extracellular Ca²⁺ concentration.

Other Signaling Pathways

Akt protein kinases regulate a number of biological functions including protein synthesis, cell growth, apoptosis and cell survival. Growth factors and G protein coupled receptors are known to activate Akt in acinar cells. The mechanism of this activation is not clear with both PI3K α and γ potentially involved. Berna et al. [46] showed that five of seven growth factors with receptors on rat acinar cells could activate (phosphorylate) Akt through the p85 subunit of PI3K α which is tyrosine phosphorylated by growth factor receptor tyrosine kinase. CCK at low concentrations increased Akt phosphorylation through Src mediated phosphorylation of p85. High concentrations of CCK inhibited both basal and growth factor stimulated Akt phosphorylation through activation of a tyrosine phosphatase. These results show the potential for interaction between G-protein coupled and growth factor receptors on acini.

Hydrogen sulfide (H₂S) is a potential new signaling molecule in acinar cells. It is produced from L-cysteine and normally is present in serum at 20–40 μ M concentrations. It has been most studied as a potential mediator of inflammation and is upregulated in caerulein-induced

pancreatitis and in acini stimulated with high concentrations of caerulein [47]. Treatment of pancreatic acini with a H_2S induces apoptosis by activation of caspase cascades [48]. In a recent study, Tamizhselvi et al [49] showed that low concentrations of H_2S activated PI3K and Akt phosphorylation and thereby down regulated the production of TNF α . Further studies are necessary to determine the complete effects of H_2S on acinar cells and acute pancreatitis.

The effects of intracellular metabolism on acinar function were studied using streptozotocin-induced diabetic mice as a model [50]. Isolated acini from diabetic mice had depressed glucose utilization, oxidation, and ATP levels were only half of control. Changes in amylase secretion observed appear secondary to a reduced amylase content although the reduction in content was less than usually seen in rats. The authors concluded that metabolic alterations might underlie the pancreatic insufficiency seen in diabetes. How this relates to previously described effects of diabetes on Ca^{2+} and Mg^{2+} handling remains to be determined.

Conclusion

Continued progress is being made in understanding the full complement of regulatory molecules affecting pancreatic acinar cells. For the major secretagogues progress is being made in understanding the physical nature of the ligand-receptor interaction and signal transduction mechanisms activated by the receptor. The molecular machinery underlying secretory granule formation, movement to the apical membrane and exocytosis continues to be an area of active investigation. Small G proteins, SNARE proteins and chaperones play important roles in these events. Other mechanisms regulate pancreatic protein synthesis, growth, and regeneration. The importance of amino acids as signals as well as the building blocks for proteins is becoming clearer. Understanding of the interaction of a variety of signaling pathways continues to be an evolving field.

Acknowledgments

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