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Recent advances in pancreatic endocrine and exocrine secretion

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Abstract

Purpose of review—This review presents recent advancements in the mechanisms by which integrated signaling mechanisms elicit and regulate pancreatic endocrine and exocrine secretion.

Recent findings—Cholecystokinin (CCK) can stimulate exocrine secretion by acting directly on neurons located in the dorsal motor of the vagus or indirectly by acting on pancreatic stellate cells. The importance of small GTPases such as RhoA and Rac1 in CCK-induced pancreatic secretion is also described. Ghrelin attenuates insulin secretion through the AMP-activated protein kinase–uncoupling protein 2 pathway. An exciting new report describes that leptin can influence insulin release by osteoclastin, a hormone produced by osteoblasts. This finding adds a new layer of complexity in the regulation of insulin secretion with implications for glucose and energy homeostasis. In addition, leptin also mediates insulin secretion through the sympathetic system and via pro-opiomelanocortin neurons, which could serve as the cross-road for leptin and melanocortin signaling pathways. Recent reports on the action of numerous other regulators such as atrial natriuretic peptide, neurotensin, and orexin B are also discussed.

Summary—The pancreas is an extremely complex gland. Elucidation of the secretory and regulatory pathways that control pancreatic secretion will aid in the development of treatment for diseases such as pancreatitis, diabetes, and obesity.

Keywords

endocrine; exocrine; pancreas; regulation; secretion

Introduction

Pancreatic secretions play an essential role in digestion and glucose homeostasis. These secretions are controlled by a host of neuronal and hormonal signaling pathways which modulate not only secretion, but also the cellular integrity of the gland.

The dorsal vagal complex in the brainstem is comprised of the nucleus of the solitary tract and the dorsal motor nucleus of the vagus (DMV) and exerts parasympathetic control on pancreatic secretion. Information relayed by sensory vagal afferent nerves in the pancreas is first processed in the nucleus of the solitary tract which then projects onto the preganglionic motor neurons of the DMV. The preganglionic vagal efferent fibers activate postganglionic nerves which innervate the pancreas. The DMV also receives inputs from other regions of the brain, such as the hypothalamus, and from numerous hormones and peptides.

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Both endocrine and exocrine pancreatic secretions are also mediated by the actions of numerous cell surface receptors. Receptor–ligand interaction leads to the activation of numerous downstream signaling pathways such as opening or closing of ion channels, increase of intracellular calcium, activation of kinases, and regulation of gene expression.

Here, we discuss the recent findings on the modulation of pancreatic secretion by neural and hormonal pathways.

Effect of cholecystokinin on pancreatic secretion

Cholecystokinin (CCK) is known to induce pancreatic exocrine secretion by the activation of CCK1 receptor-mediated signaling pathways. The action of CCK can be direct, through receptors expressed on pancreatic acinar cells, or indirect by receptors expressed on vagal afferents, which when depolarized, relay the final signal through efferent nerves present in the pancreas. Within the last year, two new paradigms have emerged, which propose that CCK can act directly on the neurons located in the DMV [1•] as well as on pancreatic stellate cells to stimulate exocrine secretion [2••]. In addition, we summarize the latest information on the downstream signaling pathways that lead to CCK-mediated pancreatic stimulation.

Preganglionic neurons of the DMV innervate the pancreas, and activation of these neurons (by CCK) elicits pancreatic secretion [3]. In order to determine the effects of these neurons on pancreatic secretion *in vivo*, deeply anesthetized rats were systemically injected with sulfated CCK-8 and the firing rate of the neurons in three areas of the DMV was recorded [1•]. The authors discovered that neurons of the DMV complex behave differently, depending on their spatial location; neurons in the caudal region were activated, those in the rostral region were unaffected, whereas those located in the intermediate region were inhibited. These effects occurred within seconds of drug injection suggesting that this CCK action was direct and differed from the mechanism mediated by Fos expression in the nucleus of the solitary tract and DMV as reported by earlier studies.

An intriguing new study proposed a novel mechanism for CCK action on the pancreas. Phillips *et al*. [2••] showed that pancreatic stellate cells from rats and humans express CCK1 and CCK2 receptors and also contain the cellular machinery to synthesize and release acetylcholine. Through a series of elegant experiments, the authors demonstrated that in co-cultures of stellate and acinar cells, CCK-8 stimulated the release of acetylcholine from stellate cells which in turn caused the release of amylase from acinar cells. Furthermore, blockade of muscarinic receptors on acinar cells prevented the release of amylase in the co-cultures. These results provide evidence for another distinct mechanism for CCK-stimulated pancreatic secretion.

It was recently reported that CCK-8 and CCK-58 peptides directly stimulated human pancreatic acinar cells with elevation of intracellular Ca^{2+} followed by exocytosis [4]. Criddle *et al*. [5] compared the effects of CCK-8 and CCK-58 on mouse acinar cells and showed that contrary to the results obtained in rats, these two peptides have similar effects in mice. They each elicited Ca^{2+} oscillations at physiological concentrations (1–10 pM) with a sustained elevation of Ca^{2+} at supra-physiological concentration (5 nM). CCK-induced exocytosis was similar as well, suggesting that differences in bioactivity observed previously were not because of peptide–receptor interactions, but resulted from either the stability of the peptides in circulation or because of yet unknown mechanisms.

CCK binds to CCK1 receptors that are expressed on pancreatic acinar cells. These receptors are coupled to heterotrimeric G proteins such as $G\alpha_q$ and $G\alpha_{12/13}$ [6], which activate downstream signal transduction pathways mediated by phospholipase C and small GTPases,

respectively [7]. RhoA and Rac1 are two small GTP-binding proteins that play a role in actin cytoskeleton reorganization and have been implicated in CCK stimulated enzyme secretion from pancreatic acinar cells [8]. Sabbatini *et al.* [9•] further characterized the molecules involved in this pathway and showed that CCK stimulation of acinar cells led to the activation of RhoA by $G\alpha_{13}$ and of Rac1 by $G\alpha_{13}$ and $G\alpha_q$. $G\alpha_{13}$ and $G\alpha_q$ both play a role in acinar secretion and actin cytoskeleton reorganization, whereas only $G\alpha_q$ is required for bleb formation associated with actin–myosin II cytoskeletal reorganization during secretion. As expected for members of the $G\alpha_{12/13}$ family, downstream events mediated by $G\alpha_{13}$ were Ca^{2+} independent and Rac1 activation was not dependent on signaling via the phospholipase C pathway.

Ethanol has been shown to impair amylase release [10]. Iwata *et al.* [11•] provided evidence that CCK stimulated interaction between $G\alpha_{13}$, Vav-2 (guanine nucleotide exchange factors that activate Rho GTPases) and RhoA, was attenuated by treatment of acini with 20 mM ethanol. Upon CCK stimulation, RhoA translocated to the subapical area around the lumen in pancreatic acini [8]. Ethanol caused a reduction in the translocation of RhoA to the membrane and loss of E-cadherin and p120 catenin from the acinar cell membranes. It had previously been shown that under conditions that destabilized cell junctions, p120 catenin could migrate from its cadherin bound membrane state to a cytoplasmic fraction where it interacted with Vav-2 and decreased Rho activity [12]. These changes in membrane structure and signaling molecules could impact pancreatic secretion as well as play a role in the development of alcohol induced pancreatitis.

Previous studies have shown that an isoform of protein kinase C (PKC), PKCδ, played a role in amylase release from acinar cells; overexpression of PKCδ led to an increase in CCK-stimulated amylase secretion, whereas expression of a dominant negative decreased secretion [13]. These effects were re-examined by Thrower *et al.* [14] using acinar cells from PKCδ knockout mice, as well as PKCδ inhibitors. CCK stimulated amylase release in PKCδ knockout mice was similar to wild-type mice and a broad spectrum PKC inhibitor failed to inhibit CCK-stimulated acinar secretion, suggesting that PKCδ does not play a significant role in exocrine secretion. It is possible that the physiology of mouse and rat acinar cells accounts for the differences observed between the two studies.

It has now been shown that CCK can exert a protective effect on β cells and islets of *ob/ob* mice. Lavine *et al.* [15•] showed that islets of *ob/ob* mice expressed large amounts of CCK compared to lean mice and helped modulate insulin expression by preventing cell death from stress-mediated pathways. The new data suggest that the secretory and homeostatic role of CCK in the pancreas is complex and remains to be fully elucidated.

Effect of ghrelin on pancreatic endocrine secretion

Ghrelin is a 28-amino acid orexigenic peptide that is secreted by X/A cells in the gastric mucosa. Small amounts of ghrelin are also secreted by other tissues such as the pancreas. Ghrelin levels increase at meal time and then plummet rapidly with food intake. In addition to regulating food intake, ghrelin has been shown to modulate glucose homoeostasis. Several investigators have studied the effect of acyl ghrelin, desacyl ghrelin, and obestatin on insulin secretion in mice, rats, and humans. An excellent review on this topic has been published by Granata *et al.* [16••]. A recent study by Tong *et al.* [17•] measured the acute insulin response in humans when intravenous infusions of acyl ghrelin at physiologic (0.3 nmol/kg per h), supraphysiologic (0.9 nmol/kg per h), or pharmacologic (1.5 nmol/kg/h) doses were given. Insulin secretion was attenuated upon injection of a bolus of glucose at all doses of ghrelin. Along with plasma insulin, C-peptide levels were also reduced, suggesting that ghrelin caused a decrease in insulin secretion, rather than clearance.

The mechanism of ghrelin-induced reduction in insulin secretion is still poorly understood. Wang *et al.* [18•] presented evidence that ghrelin inhibited insulin secretion from MIN6 cells (murine β cells transformed by SV40 large T antigen) through an AMP-activated protein kinase (AMPK)–uncoupling protein 2 (UCP2) pathway. This pathway is involved in fatty-acid oxidation and mediates ghrelin action on NPY/AgRP neurons to increase food intake [19]. In the presence of high glucose, addition of acyl ghrelin to MIN6 cells resulted in upregulation of UCP-2 mRNA, and overexpression of UCP-2 attenuated glucose stimulated insulin release by approximately 40%. Agonist-induced activation of AMPK also led to the upregulation of UCP-2 mRNA and a decrease in glucose-stimulated (but not basal) insulin secretion However, Chmielewska *et al.* [20•] showed that UCP-2 mRNA was downregulated by ghrelin in the presence of high glucose in the INS-1 cells (rat pancreatic cell line) and that glucose stimulated insulin release. Similar conflicting results have previously been reported on the effect of ghrelin on insulin release from pancreatic islets [16••].

Pancreatic polypeptide is released in response to food intake and suppresses appetite by slowing gastric emptying. Kumar *et al.* [21•] studied the effects of acyl ghrelin, desacyl ghrelin, and obestatin on the secretion of pancreatic polypeptide from isolated mouse islets. They discovered that obestatin and acyl ghrelin inhibited the secretion of pancreatic polypeptide in a concentration-dependent manner, whereas desacyl ghrelin had no effect. In addition, desacyl ghrelin blocked the effects of acyl ghrelin on pancreatic polypeptide secretion, but did not have any effect on obestatin-mediated inhibition, suggesting that obestatin and acyl ghrelin affect pancreatic polypeptide secretion via separate receptors. The physiological significance of this observation is not completely understood.

Effects of leptin and melanocortin on insulin secretion

Leptin is a hormone that is produced primarily by adipocytes and plays a role in energy homeostasis by reducing food intake while increasing energy expenditure. It has been shown to act on the long form of the leptin receptor expressed in pancreatic β cells and inhibits insulin secretion via the JNK/STAT pathway. Hinoi *et al.* [22] compared two mouse models, *ob/ob* and adipocyte-deficient (both with impaired leptin signaling), to identify novel leptin-dependent pathways that control insulin secretion. Through the use of numerous knockout mouse models as well as in-vitro experiments, these authors discovered that although leptin acts directly on β cells, it also regulates insulin secretion through a second pathway that involves neuronal signaling and hormone secretion by osteoblasts. Briefly, leptin acts on the sympathetic neurons in the ventromedial hypothalamus to release sympathetic hormones. These hormones act on β2 adrenergic receptors located on osteoblasts to increase the expression of *Esp* via the transcription factor ATF4. *Esp* in turn regulated the carboxylation of osteocalcin (a hormone secreted by osteoblasts), and carboxylation of osteocalcin decreased insulin secretion in isolated islets.

Park *et al.* [23•] also showed that leptin modulated insulin secretion via the sympathetic system. Intracerebro-ventricular leptin was administered to pancreatectomized rats exhibiting mild type 2 diabetes. This led to a decrease in insulin levels in sham but not sympathectomized rats, suggesting that sympathectomy led to a loss in leptin action on the pancreas. However, unlike *ob/ob* mice, pancreatic β cell mass and area were not significantly affected, as leptin could exert its effects at the pancreatic level.

Leptin and melanocortin pathways are linked through anorexigenic pro-opiomelanocortin (POMC) neurons. Leptin increases the expression of POMC in these neurons which is then proteolyzed to generate α-melanocyte stimulating hormone (α-MSH). α-MSH acts on melanocortin 3 receptors and melanocortin 4 receptors (MC4R) in the hypothalamus to decrease appetite [24].

In order to examine the role of the melatonin pathway in insulin secretion, Mansour *et al.* [25•] examined the expression of MC4R and α-MSH in the hypothalamus and pancreas of Zucker lean (control) and Zucker diabetic fatty (ZDF, leptin receptor mutation) rats. These investigators found that infusion of NDP-MSH (MC4R agonist) in the brain increased c-Fos and MC4R mRNA in the pancreas of lean and ZDF rats. In addition, the amount of MC4R protein and α-MSH also increased after 10 days of NDP-MSH treatment in the hypothalamus and pancreas. This increase of MC4R was concomitant with a two-fold to four-fold decrease of circulating insulin in ZDF and lean rats, respectively, suggesting that the melanocortin pathway can play a role in insulin regulation.

Additional regulators of pancreatic secretion

Atrial natriuretic peptide

A study by Ropero *et al.* [26••] showed that atrial natriuretic peptide (ANP) increased insulin secretion through guanylyl cyclase-A receptor coupled with cGMP second-messenger signaling. Although the concentration at which ANP elicited this response was supraphysiologic, there is significant evidence to support the involvement of natriuretic peptides in energy homeostasis through guanylyl cyclase-A receptor-mediated signaling pathways [27].

Orexin B

Orexins are expressed mainly in hypothalamic neurons and have been implicated in sleep and energy homeostasis. They are upregulated during fasting and in insulin-mediated hypoglycemia. Adeghate and Hameed [28•] demonstrated that in the pancreas, orexin B expressing nerves surround blood vessels. Orexin B was also present in many β cells (but not α cells) and the number of orexin B positive cells decreased with the onset of diabetes. Orexin B stimulated the insulin release by a β-adrenergic receptor-mediated pathway in normal and diabetic islet cells but had no effect on glucagon secretion in diabetic rats.

Per-arnt-sim protein kinase

Per-arnt-sim protein kinase (PASK) plays a role in insulin regulation [29]. In an elegant study, Da Silva Xavier *et al.* [30•] showed that PASK is expressed in α and β cells of mouse and human islets and inhibited glucose-stimulated glucagon release by regulation of preglucagon and AMPK alpha2 gene expression.

Glucose

The direct effects of glucose on the secretion of glucagon have been somewhat controversial. Le Marchand and Piston [31••] compared the effects of glucose on a pure population of α cells versus the intact islet. At low and high concentrations of glucose (1 or 12 mmol/l, respectively), there was an increase in the amount of glucagon released from α cells compared to intact islets, suggesting that the inhibitory action of glucose on glucagon release was lost upon α-cell dispersion. They also demonstrated that cellular metabolism of glucose led to an increase in intracellular Ca^{2+} and inhibitory effects of glucose were mediated by mechanisms downstream of Ca^{2+} signaling. The authors postulated that glucose does not directly mediate glucagon release but that paracrine factors are likely at play.

In addition to the above agents, ADP [32], neurotensin [33], GABA-A receptor [34], Zn^{2+}-coupled GPR39 [35], and β-arrestin-1 [36] have also been shown to play a role in pancreatic secretion.

Conclusion

This review provides insights into the complex physiology and biology of the pancreas. Numerous neural, paracrine, and endocrine pathways regulate pancreatic secretion and it will be important to understand how these signals are integrated and controlled in the body under normal and diseased conditions. This knowledge will enhance the development of drugs for treatment of pancreatic diseases such as diabetes, which now affects almost 300 million people worldwide and incurs over US$ 400 billion in healthcare-related costs per year.

Acknowledgments

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Key points

- Cholecystokinin (CCK) exerts a protective effect on β cells and can modulate acinar cell secretion by activation of neurons located in the dorsal motor nucleus of the vagus, as well as receptors on pancreatic stellate cells.
- Although the function of ghrelin in insulin secretion remains to be fully elucidated, it appears to decrease secretion, possibly through the AMPK–UCP2 pathway.
- The sympathetic system plays an essential role in leptin-mediated insulin secretion.
- α-MSH, ANF, orexin B, neurotensin, ADP, glucose, PASK, β-arrestin-1, GABA-A receptors, and GPR39 receptors are important in regulating pancreatic secretion.