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Recent Advances in the Regulation of Pancreatic Secretion

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Abstract

Purpose of review—This review highlights recent progress made in the field of pancreatic secretion.

Significant findings—This review summarizes a number of recent studies demonstrating the intracellular pathways by which hormones and neural inputs regulate pancreatic exocrine and endocrine secretion. In particular, the effects of VIP and secretin on intra-acinar cell cAMP are explored. Considerable attention is paid to regulation of β-cell function and includes studies detailing the mechanisms of regulation of insulin by somatostatin, serotonin, and melanocortins. These studies emphasize the critical role that hormonal, paracrine, and neural factors play in glucose homeostasis.

Summary—Exocrine and endocrine pancreatic secretions are regulated by hormonal and neural mechanisms and understanding these pathways will enable the discovery and design of new and improved therapies for prevention and control of diabetes and perhaps exocrine insufficiency.

Keywords

Pancreas; exocrine; endocrine; neural; secretion

INTRODUCTION

The pancreas is a complex gland that performs both exocrine and endocrine functions. The exocrine pancreas is comprised of acinar and duct cells which secrete digestive enzymes and fluid into the small intestine. The endocrine function is performed by islets that are embedded within the exocrine pancreatic tissue and secrete hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide. The exocrine and endocrine functions of the pancreas are regulated by multiple hormonal and neural mechanisms. This regulation is complex given that numerous intracellular signaling pathways are coupled to inhibition or stimulation of secretory function. Recent findings describing the regulation of pancreatic secretion by hormonal and neural pathways are discussed in this review.

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Regulation of Exocrine Secretion

Membrane receptors expressed on pancreatic acinar and duct cells are coupled to second messenger signaling pathways, which transduce extracellular signals and regulate exocrine secretion. Interaction of receptors with certain secretagogues such as secretin or VIP causes elevation of cAMP and secretion of protein and fluids. Within cells, cAMP is generated from ATP by the action of adenylyl cyclases. Sabbatini et al., discovered that of the ten known isoforms of adenylyl cyclase, at least four are present in both acinar and duct cells (AC3, AC4, AC6, and AC9), while AC7 is present only in duct cells [1]. Acinar cells from AC6 knockout mice exhibited significantly reduced protein kinase A activation and cAMP elevation compared to wild type mice. Consequently, amylase and fluid release from acinar and duct cells was also reduced in AC6 knockout mice suggesting that AC6 is vital in mediating the secretory effects of secretin and VIP on exocrine pancreas.

Pancreatic ducts cells secrete bicarbonate ions that neutralize the acidity of gastric chyme in the small intestine. Secretion of bicarbonate ions is a complex event mediated by many transporters and ion channels [2]. Wang et al., evaluated the role of purinergic receptors in regulating fluid release from a human adenocarcinoma cell line (Capan-1) that retains many properties of pancreatic duct cells [3]. Incubation of cellular monolayers with ATP or UTP produced large changes in membrane potential, which were attenuated in the presence of a Ca^{2+} chelator, suggesting that intracellular Ca^{2+} stores were mobilized upon activation of purinergic receptors. Exposure of the apical surface to ATP or UTP activated Ca^{2+}-activated chloride channels and intermediate conductance K^{+} channels, which have previously been shown to regulate bicarbonate secretion [4, 5]. This study has important implications in the elucidation of mechanisms responsible for pancreatic insufficiency in cystic fibrosis, since the cystic fibrosis transmembrane regulator (CFTR) is expressed in pancreatic duct cells and is regulated by purinergic receptors.

Thus, recent findings demonstrate the importance of adenylyl cyclase AC6 isoform and purinergic receptors in acinar and duct cell function.

Regulation of Endocrine Secretion

Ghrelin is a 28 amino acid peptide hormone that is released from gastric oxyntic glands and possesses orexigenic properties. Recent studies have shown that ghrelin may be involved in glucose homeostasis raising the possibility that ghrelin may be expressed in the pancreas [6]. In order to identify ghrelin-expressing cells, Raghay et al., compared ghrelin expression in the human and rat pancreas and discovered marked differences between human and rat islets [7]. In humans, ghrelin was present in some glucagon-expressing α-cells, while in rats it was expressed mostly in insulin-expressing β-cells. These data contradict recent findings which suggest that ghrelin-expressing cells in human islets do not express glucagon [8].

Pancreatic polypeptide (PP) is a 36-residue peptide belonging to the peptide YY/ neuropeptide Y (NPY) family of polypeptides. Infusion of PP in humans caused loss of appetite and reduced food intake [9]. In the pancreas, PP containing cells have been localized mainly in the head of the pancreas [10]. Wang et al., systematically mapped the human pancreas and showed that PP cells are greatly enriched in the uncinate process, which

lies posterior to the superior mesenteric vein and medial to the head of the pancreas [11]. During development, physiological variations can occur in the positioning and size of the uncinate process, which probably made this correlation challenging in earlier studies. PP-rich and poor areas exist in the head of the pancreas although areas with high concentrations of PP cells had significantly reduced α- and β-cells. It will be important to determine if this spatial localization of PP cells is accompanied with specialized features that modulate the secretion of this peptide hormone.

Glucagon-like peptide (GLP-1) is secreted from L cells located in the intestinal mucosa and stimulates insulin release from islet β-cells. Nie et al., showed that downstream effects of GLP-1 on insulin release are mediated by SAD-A, a member of the AMP-activated protein kinase family [12]. SAD-A is expressed in the hypothalamus as well as in exocrine and endocrine pancreas. In islets, SAD-A protein expression appears to be regulated by glucose. Overexpression of SAD-A in islets by adenoviral infection greatly enhanced insulin release following stimulation with high glucose, exendin-4 (a GLP-1 analog), and KCl. Deletion of SAD-A in pancreas resulted in elevation of blood glucose and worsening of oral glucose tolerance in wild type mice. However, intraperitoneal glucose tolerance tests, which bypass the incretin effect, were similar between wild type and knockout mice, suggesting that SAD-A plays a critical role in GLP-1-mediated insulin release.

Similar to GLP-1, glucose-dependent insulinotropic polypeptide (GIP) is an incretin secreted by enteroendocrine cells distributed in the small intestine. It is released into circulation as food empties from the stomach into the small intestine and mediates glucose-stimulated insulin secretion (GSIS). Like GLP-1, GIP-1 is not released upon intraperitoneal or intravenous injection of glucose, and as a consequence, the amount of insulin secreted under these conditions is much smaller. Chowdhury et al., showed that the combination of GIP and xenin, produced by a subset of GIP cells, increased the secretion of PP in humans with normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes (T2D) [13]. The authors suggest that xenin acts on enteric cholinergic neurons to stimulate pancreatic islets, delineating another pathway by which nutritional information in the gut is transmitted to islets for maintenance of glucose homeostasis.

Endocannabinoids regulate food intake and metabolism, and are important mediators of energy homeostasis. It has previously been shown that cannabinoid receptors (CB1 and CB2) are expressed in islets and regulate insulin release [14]. In an attempt to identify mechanisms downstream of cannabinoid receptor activation, Malenczyk et al., studied the effects of 2-arachidonoylglycerol and anandamide on insulin secretion from INS-1E cells [15]. Treatment of cells with endocannabinoids resulted in internalization of CB1 receptors and augmentation of GSIS. These effects were specific to CB1 receptors and were not modulated by transient receptor potential cation channel subfamily V member 1 (TRPV1) or CB2 receptors which also interact with anandamide. Stimulation of INS-1E cells by endocannabinoids triggered intracellular Ca^{2+} release and activation of Akt and ERK1/2 kinases. This signaling cascade resulted in phosphorylation of focal adhesion kinase, which promoted cytoskeletal remodeling events central to exocytosis such as formation of actin stress fibers and vinculin-positive focal adhesion plaques. Thus endocannabinoids appear to

regulate insulin release from INS-1E cells and elevated levels of endocannabinoids may contribute to hyperinsulinemia in type 2 diabetes mellitus.

The renin-angiotensin system regulates blood pressure and fluid balance. Angiotensin type 1 (AT1) receptors have been identified in the pancreas and shown to regulate insulin secretion [16]. Pancreatic islets also express high levels of angiotensin type 2 receptor (AT2). Angiotensin II and AT2 receptor agonist significantly elevated serum insulin levels and this effect was abolished by AT2 but not AT1 antagonists [17]. Exposure of rat pancreatic islets to angiotensin II and AT2 agonist increased proinsulin mRNA levels which were decreased upon treatment with AT2 antagonist, suggesting that AT2 receptor activation can increase the synthesis of insulin in β-cells. These results were corroborated in INS-1E cells where stimulation of AT2 receptors with an agonist augmented intracellular Ca^{2+} levels and promoted insulin secretion. These experiments show that AT2 receptors can stimulate insulin release and improve glucose tolerance. Evaluation of AT2 receptor function in islets of diabetic mice will help elucidate the therapeutic potential of AT2 receptor agonists.

Somatostatin is an inhibitory peptide secreted by δ-cells located in the periphery of the islets. To elucidate whether somatostatin regulates glucagon secretion through somatostatin receptors (SSTR2) expressed on α-cells, Karimian et al., examined this effect in nondiabetic and a type 1 diabetic (T1D) rat model known as biobreeding diabetes prone (BBDP) [18]. BBDP rats are initially pre-diabetic but develop T1D after inflammation-induced β-cell death. In the non-diabetic state α-cells were located on the periphery of islets, but in T1D α-cells migrated towards the interior of the islets as islet reorganization occurred upon loss of β-mass. In diabetic rat pancreas, glucagon was released by very low concentrations of glucose (1 mM) and inhibited by 7 mM glucose. This suggested that somatostatin blocked glucagon release perhaps through SSTR2 located on α-cells. In humans, SSTR2 was localized on α- and β-cells, and unlike rodents, these cells were intermingled in the islets. Despite this organizational difference, the effect of SSTR2 inhibition in human pancreatic slices and isolated islets was similar to that observed in rodents. SSTR2 inhibition in the presence of 1 mM glucose increased glucagon, but not insulin secretion and was further enhanced by arginine. These results suggest that SSTR2 antagonists could be used to stimulate glucagon release and correct hypoglycemia by blocking the inhibitory actions of somatostatin on α-cells. .

Glucose entry in β-cells stimulates insulin release through the following series of events. Glucose elevates cellular ATP levels, which in turn close ATP-sensitive K^+ channels (K_{ATP}) leading to membrane depolarization, influx of Ca^{2+} through voltage-dependent Ca^{2+} channels, and eventually insulin release. However, mice lacking the pore subunit of the K_{ATP} channel (*Kir6.2* $^{-/-}$) have plasma insulin levels that are similar to wild type mice, suggesting that a K_{ATP}-independent mechanism is also involved in insulin secretion. Seino et al. discovered that when carbohydrates were instilled directly into the stomach of *Kir6.2* $^{-/-}$ mice, plasma insulin levels were lower than those observed in wild type mice, suggesting that the cephalic phase of insulin secretion was independent of K_{ATP} activity [19]. Stimulation of cholinergic nerves with carbachol significantly elevated plasma insulin levels in *Kir6.2* $^{-/-}$ mice, while treatment with atropine prior to feeding abolished insulin secretion. Thus insulin secretion in *Kir6.2* $^{-/-}$ mice is mediated by the ATP-independent

parasympathetic system. Since the cephalic component contributes ~25–50% of insulin secretion [20], the above data suggest that in the absence of functional K_{ATP} channels, the cephalic phase could have a much larger impact by serving as a compensatory mechanism in glucose homeostasis.

Together these studies further elucidate the mechanisms by which endocrine pancreas is regulated by hormones (xenin-25, GLP-1, GIP, somatostatin), receptors (CB1, AT2, SSTR2), intracellular signaling pathways (AMP-dependent protein kinase) and neurotransmitters (acetylcholine).

Neural Regulation of Pancreatic Secretion

The pancreas is innervated by parasympathetic nerve fibers, postganglionic sympathetic neurons, as well as a network of intrapancreatic nerves. Together these nerves regulate pancreatic exocrine function by releasing neural transmitters such as acetylcholine and numerous neuropeptides such as VIP, serotonin, NPY, etc.

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. Parasympathetic preganglionic efferent vagal nerves innervating the pancreas originate primarily from the DMV and terminate in pancreatic ganglion [21]. The melanocortin 4 receptors (MC4R) have a central role in food intake, glucose homeostasis and energy utilization. Using retrograde tracing techniques in transgenic mice that express green fluorescent protein (GFP) reporter under the control of MC4R promoter, Tsumori et al, showed almost half the pancreas-projecting neurons originated in the rostrocaudal area of the DMV [22]. These MC4R neurons innervated the periphery of the pancreas, pancreatic acini, as well as the periphery and interior of islets. The terminal boutons of these GFP-positive neurons resided in close proximity to VIP-positive postganglionic cells, suggesting synaptic connections to intrapancreatic neurons. In addition, MC4R expression in these cholinergic neurons regulated insulin secretion, as deletion of MC4R in cholinergic neurons resulted in significantly higher plasma insulin levels [23]. These studies provide further evidence of the role of pancreas-projecting vagal afferents in endocrine secretion.

Serotonin is mainly produced by enteroendocrine cells and neurons of the myenteric plexus and modulates intestinal motility and secretion. Serotonin and cholecystokinin (CCK) have previously been shown to stimulate vagal cholinergic pathways and mediate pancreatic exocrine secretion. Intraperitoneal or intraduodenal administration of L-tryptophan, serotonin, and melatonin stimulated amylase secretion from intact pancreas, but not from dissociated acini suggesting an indirect neuronal action on pancreatic secretion [24]. Serotonin receptor 2 and 3 antagonists and bilateral vagotomy completely blocked serotonin-mediated amylase release, suggesting that serotonin released from enteroendocrine cells acted on serotonin receptors on vagal afferents to stimulate pancreatic secretion. Activation of CCK1 receptors on vagal afferents can trigger a vago-vagal enteropancreatic reflex leading to pancreatic secretion. The CCK1 receptor antagonist, lorglumide, inhibited serotonin release suggesting that CCK may directly or indirectly affect serotonin cells and together CCK and serotonin may modulate some of the same nerve fibers. Capsaicin-mediated deactivation of sensory nerves also partially blocked serotonin-mediated amylase

release, providing further evidence for the involvement of this pathway in pancreatic exocrine stimulation.

These studies emphasize the importance of neuronal signaling in endocrine and exocrine secretion.

CONCLUSION

Recent progress in the field of pancreatic secretion is described in this review. Neurons from the brain stem or intestine transmit signals to specialized regions of the pancreas. Diverse membrane receptors and transporters present on endocrine and exocrine cells transmit hormone- or neurotransmitter-mediated signals inside the cells. Finally, intracellular signaling pathways powered by kinases and other enzymes regulate secretion by amplification of extracellular signals or reorganizing the cytoskeleton for hormone exocytosis. Thus pancreatic secretion is an intricate process involving the integration of numerous signals that affect both stimulatory and inhibitory pathways.

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KEY POINTS

1. Purinergic receptors are important in regulating bicarbonate secretion and may be responsible for pancreatic insufficiency observed in CFTR.
2. An AMP-activated protein kinase, SAD-A, plays an important role in GLP-1-mediated insulin release.
3. Angiotensin II stimulates angiotensin type 2 receptor to stimulate insulin release.
4. Somatostatin inhibits glucagon secretion by acting locally through somatostatin receptors located on α-cells.
5. MC4R-expressing cholinergic nerves synapse with intrapancreatic ganglia and inhibit insulin secretion, thereby influencing glucose homeostasis.