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Neural and Hormonal Regulation of Pancreatic Secretion

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Abstract

Purpose of review—The biology of the pancreas is exquisitely complex and involves both endocrine and exocrine functions that are regulated by an integrated array of neural and hormonal processes. This review discusses recent developments in the regulation of both endocrine and exocrine secretion from the pancreas.

Recent Findings—New data suggest that cholecystokinin can stimulate neurons located in the dorsal motor nucleus of the vagus. Addressing a controversial topic, recent evidence suggests a direct secretory action of CCK on human acinar cells. An emerging concept is that some hormones and peptides such as melatonin, ghrelin, obestatin and leptin perform dual functions in the pancreas by regulating secretion and maintaining metabolic homeostasis. The regulation of pancreatic secretion by several appetite-controlling neuropeptides such as ghrelin, orexin A, NPY, is also discussed. Recent data highlight findings that mechanisms of hormone action may be different between species possibly due to a divergence in signaling pathways during evolution.

Summary—The regulation of the secretory function of the pancreas by numerous hormones suggests that there are multiple and perhaps redundant signals governing the control of this important organ. Understanding these diverse pathways is essential to the treatment of pancreatitis, diabetes and obesity.

Keywords

pancreas; exocrine; endocrine; secretion; regulation

Introduction

The pancreas performs both exocrine and endocrine functions. Acinar cells comprise 75-90% of the glandular mass, and release digestive enzymes into ducts which empty into the duodenum. Pancreatic duct cells secrete fluid and bicarbonate ions, which neutralize the acidity of gastric contents that enter the duodenum. Endocrine cells of pancreas are assembled in islets that are scattered throughout the gland. Islets are comprised primarily of alpha cells which produce glucagon, beta cells which secrete insulin, delta cells which release somatostatin and PP cells which produce pancreatic polypeptide. The endocrine pancreas has a dense network of capillaries, so that hormones can be quickly released into the blood stream.

The pancreas is innervated by sympathetic and parasympathetic nerves. The parasympathetic efferent fibers originate from the dorsal motor nucleus of the vagus (DMV) nerve (located in

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the brain stem) and synapse with intrapancreatic ganglionic cells, and activate post-ganglionic neurons. Neurotransmitters such as acetylcholine and peptide hormones modulate pancreatic secretion via changes in parasympathetic activity.

Regulation of Pancreatic Secretion

The secretions of the exocrine and endocrine pancreas are regulated by neurotransmitters as well as numerous hormones. Here, we describe the developments that have occurred in this field primarily in the last year.

Effects of CCK on exocrine secretion

Cholecystokinin (CCK) is released from neuroendocrine cells located in the mucosa of the upper small intestine. Food molecules, primarily proteins and fats, stimulate these cells and CCK is released into the blood stream(1,2). CCK stimulates pancreatic secretion by two possible mechanisms. First, CCK binds CCK-1 receptors on pancreatic acinar cells and stimulates release of enzymes. A second mechanism is indirect whereby CCK binds CCK-1 receptors on capsaicin-sensitive C-type vagal afferent fibers. Stimulation of vagal afferent nerves generates a signal that is sent to the medial nucleus tractus solitarius (NTS) located in the brain stem and eventually transmitted via cholinergic postganglionic vagal efferent fibers to the pancreas and other target organs. Acetylcholine released from the efferent nerve endings, binds M3 muscarinic receptors on the pancreatic acinar cells and causes release of pancreatic enzymes (3).

Two recent papers (4,5) provided data suggesting that at least a portion of the neural modulation of pancreatic secretion by CCK is via non-paracrine mechanisms. Viard et al., (4) showed that in chemically and surgically deafferented rats, microinjection of CCK-8 in the dorsal vagal complex stimulated pancreatic secretion. Wan et al., (5) used a very different approach to study this mechanism. A tracer dye DiI, when applied to the pancreas, labeled pancreas-projecting dorsal motor nucleus of the vagus (DMV) motoneurons by retrograde transport. Whole cell patch clamp recordings showed that 60% of these neurons depolarized following application of CCK-8. The depolarization was dependent on potassium channels and sensitive to inhibition by lorglumide (a CCK-1 receptor antagonist) and pancreatic polypeptide. It is not entirely clear from these experiments whether activation of vagal fibers in the physiological state would be caused by CCK released from the brain or periphery.

The action of CCK on pancreatic acinar cells is somewhat controversial and perhaps species specific. Release of exocrine secretions by CCK has been well characterized in mouse, rat and dog acinar cells whereas human acinar cells have been thought to lack this activity, due to the low abundance or absence of CCK-1 receptors. A recent paper, however, showed that application of physiological amounts of synthetic CCK-8 or CCK-58 to human acinar cells caused apical to basolateral Ca^{2+} oscillations, along with an increase in mitochondrial NADH and release of amylase from zymogen granules (6**). This cascade occurred when neural signaling was blocked by atropine and tetrodotoxin, suggesting that functional CCK-1 receptors are present on human acinar cells. It will be interesting to determine the level of CCK-1 receptor mRNA in these cells and whether selective CCK-1 receptor antagonists block CCK-stimulated secretion from human acini.

Effects of serotonin on exocrine secretion

Serotonin secreting cells are present throughout the gastrointestinal tract and release serotonin in response to wide range of stimuli. Serotonin receptor-type specific agonists and antagonists have been employed to determine the function of this neurotransmitter in pancreatic secretion.

It has been shown that 5-HT_{1P} receptor agonists inhibit amylase secretion (7) while 5-HT_3 agonists stimulate exocrine stimulation via vagal afferent fibers (8).

In support of earlier studies, Mussa et al., (9**) demonstrated that increased pancreatic afferent discharge in response to the 5-HT_3 agonist phenylbiguanide was blocked by the 5-HT_3 antagonists granisetron and MDL72222. Using CCK-1 antagonists in combination with phenylbiguanide, they also showed that phenylbiguanide can increase pancreatic vagal afferent discharge by interacting with CCK-1 receptors, but that the ability of CCK to stimulate pancreatic vagal discharge did not depend upon 5-HT_3 receptor activation.

Effects of melatonin on exocrine secretion

The hormone melatonin plays a central role in the maintenance of circadian rhythm. Melatonin is produced by the pineal gland and by endocrine cells in the gastrointestinal tract. The synthesis of melatonin by cells of the gastrointestinal tract increases during day time. Melatonin receptors are present on cells in the exocrine and endocrine pancreas (10) and its release is stimulated by CCK and acetylcholine.

Melatonin is known to stimulate enzyme release from pancreas although the physiological significance of this function is unclear. Two recent studies showed that melatonin plays a homeostatic role in pancreas by maintaining Ca^{2+} stores and limiting the severity of oxidative damage. Treatment of aged mice with melatonin for three months restored the intracellular Ca^{2+} oscillations and amylase secretion from aged acinar cells to levels obtained from younger adult cells (11*). Amylase secretion was dependent on CCK release and stimulation of vagal afferents since inhibition of either signal was accompanied by a loss in amylase release. In a second study, intraperitoneal injection of melatonin reduced the severity of caerulein-induced pancreatitis (12), possibly by reducing cytokine production and activating other pathways that reduce inflammation (e.g., scavenging reactive reactive oxygen species).

Role of C-natriuretic peptide in pancreatic secretion

C-natriuretic peptide (CNP) is a 22 amino acid peptide that is structurally similar to atrial natriuretic peptide (ANP). CNP is abundant in the central nervous system and gastrointestinal tract. When injected intravenously, CNP has been shown to stimulate pancreatic exocrine secretion. The CNP receptor is a member of the G protein coupled receptor family and has been localized on both acinar and duct cells (13) of the pancreas. Sabbatini et al., (14) recently showed that CNP increased pancreatic protein, chloride and fluid secretion without affecting bicarbonate output suggesting that its main effects were through actions on acinar cells rather than ductal cells. The secretion of chloride was attenuated in rats following truncal vagotomy and perivagal application of capsaicin or hexamethonium, suggesting that this function of CNP is modulated by the parasympathetic nervous system. However, protein secretion was not affected, implying that CNP modulates exocrine pancreatic secretion both at the level of acinar cells and vagus nerve.

Effects of cannabinoids on endocrine and exocrine function

Endocannabinoids such as anandamide and 2-arachydonylglycerol, are lipophilic ligands derived from arachidonic acid that modulate the activity of two G protein coupled receptors, cannabinoid receptors 1 and 2 (CB1 and CB2). CB1 receptors are present in the brain, adipose tissue, muscle, and in neurons of the enteric system. Plasma levels of endocannabinoids are elevated in obese patients raising the possibility that they play a role in energy balance and food intake. CB1 antagonists such as rimonabant and taranabant have been shown to induce weight loss and improve insulin resistance.

Several recent studies have shown that CB1 and CB2 receptors are present in the pancreas and play a role in regulating exocrine and endocrine function in rat, mouse and humans. In rats, activation of cannabinoid receptors inhibited amylase release from lobules of exocrine pancreas, possibly via inhibition of neural inputs by acetylcholine (15*). In mouse islets, CB1 agonists decreased Ca^{2+} oscillations as well as insulin release (16*). However, species differences may be important, since in contrast to the above studies, a report on tissue harvested from human pancreas showed lack of CB1 receptor expression in the exocrine pancreas and stimulation (instead of inhibition) of insulin release from islet cells in response to CB1 agonists (17*). The function of the cannabinoid system in the pancreas and during pancreatitis (18) remains to be elucidated due to conflicting data obtained from the three species (19).

Effects of ghrelin and obestatin on exocrine and endocrine pancreas

Ghrelin is an orexigenic peptide secreted by endocrine cells located in the gastric mucosa (20). In the last 10 years, numerous studies have examined the effects of ghrelin on exocrine and endocrine secretion. Lai et al., (21) reported that ghrelin and its receptor are expressed in rat acinar cells and the receptor is downregulated during acute pancreatitis. The physiological effects of ghrelin were analyzed by Nawrot-Porąbka et al., (22) who showed that intraduodenal infusion of ghrelin stimulated amylase secretion possibly through a neural pathway involving release of CCK. Bilateral vagotomy, deactivation of C-afferent fibers and application of lorglumide blocked ghrelin-dependent amylase release.

A recent study (23) compared the effects of physiological levels of acyl ghrelin with two other proghrelin-derived peptides, desacyl ghrelin and obestatin. Obestatin was first discovered in 2005 (24) and is known to induce anorexia. However, the role of obestatin in satiety is still controversial. Qader et al., (23*) showed that obestatin and acyl ghrelin both stimulated glucagon release but inhibited insulin, pancreatic polypeptide and somatostatin release from mouse and rat pancreas. Obestatin was a more potent inhibitor of insulin release than acyl ghrelin. In contrast, however, another study (25**) showed that obestatin stimulated insulin release from human islet cells. These authors also showed that obestatin induced proliferation and reduced apoptosis of cultured beta cells. It is possible that, similar to cannabinoids, the effects of obestatin are species dependent and further work is needed to elucidate its effects on pancreatic secretion.

Effects of hypothalamic neuropeptides on endocrine secretion

The hypothalamus plays a critical role in regulating food intake and energy balance. Two recent studies examined the effects of orexin and vasopressin/corticotrophin releasing hormone on pancreatic endocrine secretion.

Like the ghrelin peptides, orexin A and B are neuropeptides that are processed from the same precursor molecule (prepro-orexin) and increase food intake. Both peptides are also expressed in the endocrine pancreas and orexin A has been shown to stimulate release of pancreatic fluid and enzymes (26). New evidence from Göncz et al., (27**) suggested that orexin A attenuates glucagon release by inhibiting the expression of proglucagon through a pathway mediated by Ca^{2+}, CREB phosphorylation and Foxo-1 transcription factor. Orexin-1 receptors were localized on alpha cells suggesting that this was a direct effect that may be physiologically relevant.

The hypothalamic peptides, arginine vasopressin (AVP) and corticotropin releasing hormone (CRH) stimulate adrenocorticotropin (ACTH) secretion under conditions of stress. ACTH in turn stimulates the release of cortisol, a glucocorticoid that increases blood glucose levels. Receptors for AVP and CRH are located on islet cells. A recent study (28**) showed that similar to AVP's potentiation of CRH-induced ACTH release, AVP also enhanced CRH-

mediated insulin release. This action was dependent on the presence of AVPR1b receptors on beta islet cells, and required intracellular Ca^{2+} and activation of protein kinase C. AVP enhanced insulin release was not observed in AVPR1b knockout mice. These findings are significant for two reasons: First, under conditions where glucocorticoid levels are raised by the actions of CRH and AVP, a concomitant increase in insulin release could help reduce elevated glucose levels. Second, this is another example of a highly integrated neuroendocrine system in which brain peptides exert important peripheral metabolic regulatory actions.

Effects of NPY on pancreatic secretion

Neuropeptide Y (NPY) is a member of the gastrointestinal polypeptide family that includes peptide YY (PYY) and pancreatic polypeptide (PP). PYY is a satiety signal that is released when food reaches the distal small intestine and is known to reduce enzyme secretion from the pancreas (29). PP is also a satiety-inducing hormone and inhibits pancreatic exocrine secretion (30).

NPY is an abundant neuropeptide in the brain and is the most potent orexigenic peptide in the central nervous system. NPY is also present in pancreatic islets where it decreases insulin secretion. A recent study (31) examining the effects of NPY gene deletion on islet function found that NPY deletion caused a modest increase in basal and glucose-stimulated insulin secretion associated with islet hypertrophy. An interesting finding of this study was the reduction of NPY and Y_1 receptor mRNAs in three models of obese mice, suggesting that NPY signaling could potentially be downregulated in pancreatic islets as they cope with increasing demands of insulin secretion during obese and diabetic conditions.

Effects of GLP-1 on endocrine secretion

Glucagon-like peptide-1 (GLP-1) is a glucose-dependent insulinotropic hormone that is produced postprandially by gut neuroendocrine cells. GLP-1 stimulates insulin release from beta cells, modulates glucagon secretion from alpha cells and increases somatostatin from delta cells of the pancreas. GLP-1 mimetics have been developed for the treatment of type 2 diabetes (32).

Recent studies have helped to elucidate the role of GLP-1 in the modulation of pancreatic endocrine secretion. Using retrograde dye uptake, Wan et al., (33) showed that GLP-1 (which can cross the blood brain barrier) depolarized the DMV neurons in the brain stem. These neurons were not depolarized by pancreatic polypeptide (which regulates pancreatic exocrine secretion), suggesting that they excite the endocrine areas of the pancreas and that GLP-1, like CCK, can regulate endocrine secretion via indirect neural input. Perfusion of pancreas with GLP-1 inhibited glucagon secretion under low glucose concentrations (34**) and the inhibitory effects were mediated by the somatostatin receptor type 2 (SSRT2). It is postulated that GLP-1 binds to GLP-1 receptors on delta cells, stimulating somatostatin release which in turn binds to SSRT2 receptors on alpha cells, inhibiting glucagon secretion. GLP-1 also interacts with receptors on insulin-producing beta cells leading to activation of adenylyl cyclase and generation of cAMP ultimately causing insulin secretion (35). Importantly, it has been shown that GLP-1 partially suppressed destructive NO signaling in islet cells of a diabetic model of rat and restored glucose-dependent insulin release (36**). These results are poised to have a significant impact in the clinical treatment of type 2 diabetes.

Effects of leptin on endocrine secretion

Leptin is a 16 kDa orexigenic peptide that is secreted by adipocytes and regulates energy homeostasis (37). Levels of circulating leptin reflect body fat stores and rise as obesity develops. Leptin receptors are present in the hypothalamus and in peripheral tissues and several

C-terminally spliced isoforms are known. Morioka et al., (38) made a pancreas-specific conditional knockout for the long form of leptin receptor that is expressed in regions of the hypothalamus and pancreatic beta cells. They showed that knockout mice fed on normal chow, had normal body weight, but a two-fold higher fasting insulin level and better glucose tolerance than wild type mice. In addition, they had increased islet mass, due to an increase in beta cell size. However, when fed a high fat diet, knockout mice developed impaired glucose tolerance accompanied with reduction in islet mass, suggesting that leptin plays a homeostatic role in the function of the endocrine pancreas under normal as well as stressful conditions.

Conclusion

The pancreas is controlled by numerous hormones, regulatory peptides and neurotransmitters, several of which are not included in this review. In addition to regulating secretory functions, these agents can also stimulate growth of the pancreas. Initial research focused primarily on elucidating the role of individual hormones and transmitters on either exocrine or endocrine secretion. As this work progressed, many secretagogues were found to have multiple actions and affected not only both exocrine and endocrine secretion but diverse metabolic functions as well. We expect that future work will illustrate the interplay between various hormones and transmitters that regulate pancreatic signaling, secretion, and growth. Given the global obesity and diabetes pandemic, a better understanding of the regulation and homeostasis of the endocrine and exocrine pancreas is essential for the treatment of these disorders.

Acknowledgments

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