The islet-acinar axis of the pancreas: more than just insulin

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Barreto SG, Carati CJ, Toouli J, Saccone GT. The islet-acinar axis of the pancreas: more than just insulin. Am J Physiol Gastrointest Liver Physiol 299: G10–G22, 2010. First published April 15, 2010; doi:10.1152/ajpgi.00077.2010.—Although the role of the islets in the regulation of acinar cell function seemed a mystery to investigators who observed their dispersion among pancreatic acini, over time an appreciation for this intricate and unique structural arrangement has developed. The last three decades have witnessed a steadily growing understanding of the interrelationship of the endocrine and the exocrine pancreas. The islet innervation and vascular anatomy have been more fully characterized and provide an appropriate background for our current understanding. The interrelationship between the endocrine and exocrine pancreas is mediated by islet-derived hormones such as insulin and somatostatin, other humoral factors including pancreastatin and ghrelin, and also neurotransmitters (nitric oxide, peptide YY, substance P, and galanin) released by the nerves innervating the pancreas. Although considerable progress has been achieved, further work is required to fully delineate the complex interplay of the numerous mechanisms involved. This review aims to provide a comprehensive update of the current literature available, bringing together data gleaned from studies addressing the actions of individual hormones, humoral factors, and neurotransmitters on the regulation of amylase secretion from the acinar cell. This comprehensive view of the islet-acinar axis of the pancreas while acknowledging the dominant role played by insulin and somatostatin on exocrine secretion sheds light on the influence of the various neuropeptides on amylase secretion.

neuropeptides; amylase; galanin; somatostatin

IN 1969, HENDERSON (58) WROTE, “Why are the islets of Langerhans?,” stemming from his observation at that time that although all the endocrine organs in the body were organized as compact structures, only in the pancreas was the endocrine portion dispersed as islets within the predominantly exocrine gland. Since then there has been an increasing amount of activity focused on understanding all aspects of this unusual anatomical arrangement.

Streptozotocin-induced islet destruction in experimental animals resulted not only in anatomically recognized atrophy (9) but also in a functional reduction in the exocrine portion of the pancreas (154, 177). This phenomenon, i.e., exocrine insufficiency, implied some functional relationship between islet and acinar cells. Exocrine insufficiency is well appreciated clinically in insulin-dependent diabetic patients (46, 70, 96). Moreover, the islet’s hormones appear to play an important role in regulating the structure and function of the exocrine pancreas. The early findings by Williams and Goldfine (210) led them to propose the “insulin-acinar axis.” Early investigators (41, 199, 207) appreciated capillary-like microvascular connections between the endocrine and exocrine portions of the pancreas. More recently, the existence of an ultrastructural, interstitial matrix connection between the endocrine and exocrine pancreas has been observed (55).

Although the initial focus of many studies was on insulin alone, the involvement of somatostatin, glucagon, pancreatic polypeptide, and other humoral agents such as a group of neuropeptides found in the exocrine portion has been recognized. These findings have rendered the term “islet-acinar axis” as more appropriate to describe this complex endocrine-exocrine relationship. The present review aims to briefly recapitulate the early data that led to the description of the anatomical entity of the islet-acinar axis while providing an overview of our current understanding of the effects of the islet hormones and their associated humoral factors, primarily neuropeptides, in the regulation of pancreatic exocrine function. Descriptions of the islet innervation and vascular anatomy are included to provide an appropriate background.

Vascular and Neuroanatomy of the Islet-Acinar Axis

Ferner (41), Wharton (207), and Thiel (199), on the basis of experiments using conventional light microscopy of India ink-injected tissue samples, described a capillary-like microvascular connection between the endocrine and exocrine portions of the pancreas in various mammals. Fujita and colleagues (47, 48) using the electron microscopy to study vascular casts in horses and monkeys, were able to confirm the existence of this anatomical system, the “insulo-acinar portal...
system.” These findings have been subsequently confirmed in humans by other investigators (133, 143, 190).

**Vascular anatomy.** Although the islets constitute ~1–2% of the human pancreatic mass, the arterial blood supply to the pancreas predominantly flows first to the islets and via the islets to the exocrine portion of the gland (156). This has been shown in humans (133) and other mammals (45, 47, 134). However, arterioles may also form capillary networks that may proceed directly to the acini or the ductal system (133, 144). The distribution of blood flow is relevant to the potential physiological actions of islet-released humoral factors at both a local and systemic level.

Unlike the small to medium-sized arteries supplying the islets, the efferent vessels form three types of capillary arrangements (135, 140), designated as e1, e2, and e3 (Fig. 1A). The blood flow in type e1 proceeds from the border of the islet to the exocrine gland in a radial manner and can serve to uniformly perfuse the peri-insular region with islet secretions. Type e2 consists of one or two relatively large efferent capillaries that leave the islet and pursue a direct course toward the teleinsular region and anastomose with the exocrine capillary network formed by the e1-type efferent vessels, permitting islet-derived humoral factors to reach these regions. Type e3 constitutes vessels which empty directly into the portal system. Nakagawa et al. (136) eloquently demonstrated that islet secretions including insulin and somatostatin actually entered the exocrine interstitial space via some of the microvasculature running between the islet and acinar cells, providing yet another pathway by which islet hormones could regulate exocrine function.

The islet cell populations have a distinct distribution in rodents. The alpha (α) and delta (δ) cells are distributed in the mantle (periphery) with the vast majority of the islet core containing insulin-producing beta (β) cells (206). The specific location of the other subtypes of islet cells, viz., epsilon (ε) and the PP or F cells, within the islets has not been clearly described. This distribution, in combination with blood flow through the islets, may contribute to the regulatory actions of islet secretion. It is important to note though that in human islets Cabrera et al. (27), using confocal microscopy and multiple immuno-fluorescence labeling, did not find the clear anatomical subdivisions in the islet cell population as has been appreciated in rodents. Instead they found that α-, β-, and δ-cells were aligned along blood vessels with no particular order or arrangement. Wayland (206) summarized the three possible models of blood flow through the islets (Fig. 1B). In the first model (A1), blood flows initially to the mantle and then to the core; this was based on vascular cast studies and does not take into account the actual flow dynamics. In the second model (A2), blood flows through the islets initially to the core and then onto the α- and δ-cells. This model was based on the work by Stagner and Samols (185) in dogs. The third model (A3) involves blood flow from mantle to core returning to mantle, permitting regulatory interaction between glucagon, somatostatin, and insulin. This latter model is based on the work by Nishino et al. (140) and Liu et al. (110), using fluorescent microspheres or fluorescently labeled erythrocytes. In reality it appears that all three models may coexist under functionally appropriate conditions (206). The findings of Cabrera et al. indicate that islet microcirculation may have a more heterogeneous effect on paracrine interactions in humans. It is beyond the scope of this review to address the direct vascular effect of islet hormones and factors on pancreatic perfusion.

**Innervation.** The islets are densely innervated (158), as was initially appreciated by Langerhans (95). The innervation is complex, involving the central and autonomic nervous systems with afferent and efferent signaling (Fig. 2). The major regulatory pathway is the vagus nerve. In addition, enteropancreatic neurons between the pancreas and the gastrointestinal tract.
have been described and are believed to mediate enteropancreatic reflexes that are important for the intestinal phase of pancreatic exocrine secretion (79, 175, 176). The classical neurotransmitters acetylcholine and norepinephrine are the major transmitters, with numerous peptides including vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), substance P, and galanin as cotransmitters (Table 1). Cholecystokinin (CCK) has also been localized to islet nerves (161).

Pancreatic Hormones and Neuropeptides

The five main cell types that constitute the islets elaborate pancreatic hormones and factors, viz., the α-cells that produce glucagon, the β-cells that produce insulin and amylin, δ-cells that produce somatostatin, the PP or F cells that produce pancreatic polypeptide and adrenomedullin, and the ε-cells that produce ghrelin. In addition, the islets also contain other bioactive agents that have been shown to influence exocrine function by virtue of their modulatory effect on the hormone actions. These bioactive agents include neuropeptides associated with the nerve terminals, e.g., neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), and substance P, and agents like pancreastatin, a proteolytic cleavage product of chromogranin. Moreover, galanin has been shown to be localized with a subpopulation of islet cells (10). Consequently there are several peptides such as somatostatin and galanin that

Table 1. Agents involved in the regulation of the islet endocrine-exocrine axis

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Neurotransmitters</th>
<th>Cotransmitters/Neuropeptides</th>
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</thead>
<tbody>
<tr>
<td>Glucagon</td>
<td>Acetylcholine</td>
<td>Galanin</td>
</tr>
<tr>
<td>Insulin</td>
<td>Norepinephrine</td>
<td>Substance P</td>
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<tr>
<td>SST</td>
<td></td>
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<tr>
<td>PP</td>
<td></td>
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<tr>
<td>Ghrelin</td>
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<tr>
<td>Amylin</td>
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<tr>
<td>Pancreastatin</td>
<td></td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td></td>
<td>PACAP</td>
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<tr>
<td></td>
<td></td>
<td>Cholecystokinin</td>
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</tbody>
</table>

SST, somatostatin; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide; CGRP, calcitonin gene-related peptide; NPY, neuropeptide Y; PYY, peptide YY; PACAP, pituitary adenylate cyclase-activating peptide.
can act in several capacities viz., as neurotransmitters (when released from nerves) and paracrine agents and/or endocrine agents (if released from islets cells). Autocrine signaling by these agents may also occur.

The following section describes the action of the islet-derived bioactive agents on exocrine secretion, more specifically, on amylase secretion. In general terms, the action of these agents is usually dependent on the species, the experimental conditions (in vivo and in vitro), and the concentration used.

**Glucagon.** Glucagon’s effect on exocrine secretion is inconsistent. Early work using extracted glucagon applied to mouse, guinea pig, or rat pancreatic acinar cells reported a stimulatory influence (115, 149, 178, 179). However, subsequent studies using biologically active synthetic glucagon failed to confirm this finding (149). The previously reported stimulatory effects were attributed to unidentified biologically active peptides contaminating the preparation. Although some subsequent studies have confirmed the stimulatory effects (62, 72) of glucagon, others have reported an inhibitory effect (42, 204).

**Insulin.** Insulin is a major and one of the most well-characterized regulators of exocrine secretion. Insulin secreted by the islets serves two important roles, viz., systemically to aid glucose uptake in tissue, and locally on the exocrine pancreas influencing pancreatic growth and exocrine function. Insulin’s influence on amylase secretion was first appreciated when studies of insulin deficiency (diabetes mellitus) showed pancreatic exocrine tissue fibrosis and reduced response to hormonal stimulation (29, 202). Experiments conducted in vivo in diabetic rats and rats supplemented with insulin further supported these findings (13, 148). The effects of insulin on the production of amylase by acinar cells have been extensively studied. Table 2 provides a comprehensive description of these various studies that have addressed the effect of insulin on exocrine secretion in vivo and in vitro, by using exogenously supplied insulin or by stimulating endogenous insulin with known insulin stimulators (12, 14, 39, 52, 65, 77, 94, 99–102, 150, 153, 165). The conclusion drawn from the animal studies is that insulin affects basal amylase secretion and also potentiates secretagogue-stimulated secretion. In humans, however, the complexity of the experimental system precludes an accurate appreciation of the effects of insulin on pancreatic exocrine secretion. In the two studies published so far, the results have been contrary: potentiation and inhibition of pancreatic exocrine secretion (77, 94). Further investigations using normal human pancreas are required to resolve this discrepancy.

Insulin is believed to bind to its own receptor on the acinar cell (128, 168, 183, 211), leading to stimulation and potentiation of amylase secretion by various mechanisms including regulation of amylase gene transcription (90); stimulation of DNA, RNA, and acinar protein synthesis (89, 129, 145); and increase in glucose uptake (209).

**Somatostatin.** Somatostatin’s action on exocrine secretion is inhibitory. Boden et al. (18) were the first to show that somatostatin inhibited pancreatic exocrine secretion. Subsequently, Albinus et al. (5) noted differential effects of somatostatin on stimulated and basal amylase secretion and postulated a neurohumoral mechanism of action. Thereafter, studies using somatostatin or its analogs have confirmed its inhibitory effect (11, 44, 75, 83, 92, 106, 107, 118, 124, 130, 132, 142, 151, 152, 180, 212).

The mechanism underlying this inhibitory action has been debated since the 1990s. The fact that somatostatin acts as a neurotransmitter as well as a hormone (depending on the setting) has probably contributed to the uncertainty. One of the proposed mechanisms whereby somatostatin inhibits the CCK- and caerulein-stimulated amylase secretion includes inhibition of insulin release and thus a reduction in insulin’s stimulatory effect (100, 101, 111). Another mechanism is via somatostatin binding to its receptors on the acinar cell (166, 167) leading to a reduction in intracellular cyclic adenosine monophosphate (cAMP) (119, 142, 151), consequently reducing Ca$^{2+}$ signaling directly affecting the secretory response of the acinar cells (171).

Several neurally mediated mechanisms, both central and peripheral, have also been postulated. These include central effects on the vagal and sympathetic pathways (106, 118) or via somatostatin receptor 2 in the dorsal vagal complex (107). Peripheral effects include indirect actions through intrinsic peptidergic pancreatic neurons (132) or via an intrapancreatic cholinergic mechanism (92) whereby specific somatostatin receptors expressed on nerve terminals inhibit acetylcholine release (56).

**Pancreatic polypeptide.** Pancreatic polypeptide, irrespective of whether endogenously secreted or exogenously administered, is known to inhibit pancreatic exocrine secretion (87, 108, 173, 197). Endogenous pancreatic polypeptide, which is released in a biphasic manner following ingestion of a meal, plays an inhibitory role on pancreatic exocrine secretion in both the interdigestive and postprandial states (173). The initial response to endogenous pancreatic polypeptide is believed to be mediated by the vagus (169, 196). The mechanism of the latter response is yet to be determined with the possibility of a humoral mechanism being strongly considered (173).

Pancreatic polypeptide has been shown to inhibit CCK-stimulated amylase release in vivo (112). Pancreatic polypeptides’ action in vitro is, however, less clear owing to contradictory reports. Pancreatic polypeptide inhibits stimulated amylase release as well as the glucose and exogenous insulin potentiation of CCK-stimulated amylase release in isolated rat pancreas (150). However, pancreatic polypeptide did not affect CCK-stimulated amylase release from isolated rat (78, 150) and cat pancreas (78) or rat pancreatic acini and lobules (112). On the basis of these findings and the absence of binding of $^{125}$I-labeled bovine pancreatic polypeptide to rat pancreatic acini, it has been postulated that pancreatic polypeptide exerts its action on amylase secretion indirectly by inhibiting the effect on insulin secretion (112).

**Ghrelin.** Ghrelin, a peptide originally described in the stomach, was found to be produced in the pancreas (203). Wierup et al. (208) were able to demonstrate that ghrelin was secreted by a cell different from the a, b, d, and PP cells. This cell was characterized by Prado et al. (157) and named “the e-cell.” The presence of e-cells has been confirmed in fetal and adult human pancreas (8). Interestingly, Lai et al. (93) have demonstrated ghrelin protein and mRNA in rat acinar cells. The effect of ghrelin on insulin secretion is uncertain because of conflicting reports (1, 31, 37, 98). Similarly, ghrelin’s action on amylase secretion is unclear. In rats, intraduodenal infusion of ghrelin was shown to dose dependently enhance basal and stimulated amylase secretion, an effect that was accompanied by an increase in plasma CCK concentration (138). This effect was
Table 2. Experimental evidence of the action of insulin on pancreatic amylase secretion

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Preparation</th>
<th>Basal/Stimulated Amylase Secretion</th>
<th>Exogenous/Endogenous Insulin</th>
<th>Response</th>
<th>Postulated Mechanism of Action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al. (1980)</td>
<td>Isolated perfused rat pancreas</td>
<td>CCK-stimulated</td>
<td>Exogenous and endogenous (glucose stimulated)</td>
<td>Potentiation</td>
<td>Increase in intracellular Ca^{2+} mobilization, or the activity of a membrane Na^{+}-K^{+} transport pump, or the activity of a membrane Na^{+}-H^{+} transport pump</td>
<td>165</td>
</tr>
<tr>
<td>Garry et al. (1989)</td>
<td>Isolated perfused rat pancreas</td>
<td>CCK-stimulated</td>
<td>Exogenous and endogenous (glucose stimulated)</td>
<td>Potentiation SST inhibited insulin’s effect</td>
<td>SST may act directly via specific receptors on acinar cells to exert its inhibitory effect</td>
<td>52</td>
</tr>
<tr>
<td>Lee et al. (1990)</td>
<td>Conscious rats</td>
<td>Liquid meal and secretin/ CCK-8 stimulated</td>
<td>Endogenous (using rabbit anti-insulin serum)</td>
<td>Anti-insulin serum abolished stimulated amylase secretion</td>
<td>CCK and other secretagogues stimulate amylase release via their action on insulin</td>
<td>101</td>
</tr>
<tr>
<td>Lee et al. (1994)</td>
<td>Isolated intra-arterially perfused rat pancreas</td>
<td>Secretin/CCK-8 stimulated</td>
<td>Endogenous (using rabbit anti-insulin serum)</td>
<td>Anti-insulin serum abolished stimulated amylase secretion and increased SST levels, which were reversed by anti-SST serum</td>
<td>Action of insulin on exocrine pancreas—local/paracrine and involves SST</td>
<td>100</td>
</tr>
<tr>
<td>Lee et al. (1995)</td>
<td>Isolated intra-arterially perfused dog pancreas</td>
<td>Secretin/CCK-8 stimulated</td>
<td>Endogenous (using rabbit anti-insulin serum)</td>
<td>Anti-insulin serum abolished stimulated amylase secretion and increased SST and PP levels, which were reversed by anti-SST serum</td>
<td>Action of insulin on exocrine pancreas—local/paracrine and involves SST and PP</td>
<td>99</td>
</tr>
<tr>
<td>Berry et al. (1996)</td>
<td>Chronic pancreatic fistulae in dogs</td>
<td>IV CCK- and intra-duodenal meal stimulated</td>
<td>Exogenous (prior to stimulation)</td>
<td>No effect of insulin on amylase secretion</td>
<td>Hyperinsulinaemia does not alter pancreatic acinar cell secretion in the intact animal</td>
<td>14</td>
</tr>
<tr>
<td>Lee et al. (1996)</td>
<td>Isolated perfused rat pancreas</td>
<td>Secretin/CCK-8 stimulated</td>
<td>Exogenous and endogenous (glucose stimulated)</td>
<td>CCK/secretin—no effect in STZ treated animals except when exogenous insulin added; Insulin did not affect secretin actions alone but potentiated CCK effect</td>
<td>Insulin intensifies the combined actions of secretin and CCK by potentiating the CCK action. In the presence of insulin, secretin is able to potentiate the pancreatic enzyme secretion stimulated by CCK.</td>
<td>102</td>
</tr>
<tr>
<td>Iwabe et al. (2001)</td>
<td>Anesthetized rats</td>
<td>CCK/Intra-duodenal casein</td>
<td>Endogenous (glucose stimulated)</td>
<td>Insulin potentiates CCK and casein stimulated amylase release</td>
<td>Not specifically addressed</td>
<td>65</td>
</tr>
<tr>
<td>Park et al. (1993)</td>
<td>Isolated rat pancreas</td>
<td>Basal</td>
<td>Exogenous</td>
<td>Intra-arterial administered insulin stimulated amylase release</td>
<td>Not specifically addressed</td>
<td>150</td>
</tr>
<tr>
<td>Fan et al. (2006)</td>
<td>Anesthetised rats</td>
<td>Basal</td>
<td>Endogenous (glucose stimulated)</td>
<td>50% Glucose stimulated amylase release more than 30% glucose</td>
<td>Not specifically addressed</td>
<td>39</td>
</tr>
<tr>
<td>Barreto et al. (2009)</td>
<td>Mouse pancreatic lobules</td>
<td>Basal</td>
<td>Endogenous (glucose stimulated)</td>
<td>Glucose significantly stimulated amylase release above basal</td>
<td>Not specifically addressed</td>
<td>12</td>
</tr>
</tbody>
</table>

SST, somatostatin; PP, pancreatic polypeptide; IV, intravenous; CCK, cholecystokinin; STZ, streptozotocin; CCK-8, cholecystokinin octapeptide.
attributed to an indirect action of ghrelin which was dependent on the stimulation of CCK release and activation of an enteropancreatic vago-vagal reflex (67, 138). However, in other studies ghrelin significantly inhibited CCK-stimulated pancreatic exocrine secretion in vivo as well as in pancreatic lobule preparations but did not affect basal amylase release. On the basis of the lack of action of ghrelin on isolated acinar cells, it was concluded that ghrelin possibly exerts its inhibitory effect via intrapancreatic neurons (218).

**Amylin.** Amylin is cosecreted with insulin by the pancreatic β-cells in response to a nutrient stimulus (113). Although its secretion parallels that of insulin in response to various secretagogues, Ogawa et al. (141) found that doses of streptozotocin, which did not affect insulin secretion, significantly reduced amylin secretion. This suggested that the selective depletion of amylin may serve as an early manifestation of β-cell depletion or injury.

With regard to pancreatic exocrine secretion, contradictory effects of amylin have been reported. No effect of amylin on basal and stimulated amylase secretion from acinar cells has been reported (40, 76). Funakoshi et al. (50) observed a dose-independent stimulatory effect of amylin on pancreatic exocrine secretion in conscious rats, an effect attributed to inhibition of somatostatin secretion. In contrast, Young et al. (216) found that amylin did not affect basal amylase secretion in anesthetized rats but significantly inhibited CCK-stimulated amylase release. This inhibitory effect was not seen in acinar cell preparations or AR42J cells, indicating an indirect or possibly an extrapancreatic mechanism. Thus, although it is clear that amylin exerts an indirect effect on amylase secretion, the precise nature of the effect needs further clarification.

**Pancreastatin.** This 49-amino acid peptide originally isolated from the porcine pancreas was found to inhibit glucose-induced insulin secretion (193). Subsequent investigation (4, 36) confirmed this finding and also showed that arginine-induced insulin and somatostatin secretion were inhibited but that basal glucagon secretion in vivo (4) and arginine-stimulated glucagon secretion in isolated perfused pancreas were augmented by pancreastatin (36).

The application of pancreastatin in vitro has produced inconsistent effects. Basal amylase secretion from isolated guinea pig acinar cells was not affected but CCK-8 stimulated secretion was inhibited (64). In contrast, neither basal nor CCK-stimulated amylase secretion from isolated rat pancreatic acinar cells was affected by pancreastatin administration (49, 126). In vivo, pancreastatin has no effect on basal secretion but has been consistently shown to inhibit stimulated exocrine secretion irrespective of the stimulus used (49, 51, 60, 125). Pancreastatin’s mechanism(s) of action is believed to be via modulation of presynaptic acetylcholine release (60) and/or reduction of local pancreatic blood flow (123).

**Adrenomedullin.** The existence of adrenomedullin, was first suggested by Washimine et al. (205), but it was Martinez et al. (117) who established the presence of adrenomedullin and its colocalization with pancreatic polypeptide in the F (PP) cells. They also showed that adrenomedullin inhibited insulin secretion. Subsequent studies with isolated rat pancreatic acinar cells (201) demonstrated that adrenomedullin inhibited basal and Ca\(^{2+}\) ionophore-stimulated amylase secretion, acting by directly binding to acinar cells and reducing the Ca\(^{2+}\) sensitivity of the exocytotic machinery.

**Peptide YY.** Peptide YY is another 36-amino acid peptide originally isolated from the porcine intestine (194) and later demonstrated by immunochemical and/or immunocytochemical techniques to exist in mammalian pancreatic endocrine cells (19). It is structurally similar to pancreatic polypeptide and was found to significantly inhibit secretin- and CCK-stimulated pancreatic exocrine secretion in the anesthetized cat (191). Huang and Tsai (63) demonstrated binding of \(^{125}\)I-labeled peptide YY to guinea pig isolated pancreatic acinar cells. They concluded that these effects were mediated via Y2 and not Y1 receptors on acinar cells by using a series of experiments based on receptor antagonism using peptide YY, NPY, and [Leu\(^{31}\),Pro\(^{39}\)]NPY (a specific Y1 receptor agonist). They functionally correlated the binding with inhibition of amylase release stimulated by VIP and forskolin, but not CCK-8 or bombesin.

Bilski et al. (16) studied the effect of peptide YY in conscious dogs and rats and found that peptide YY inhibited basal as well as meal- and duodenal oleate-stimulated secretion. On the basis of further studies, peptide YY appears to act via intrapancreatic cholinergic nerves and independent of adrenergic nerves and pancreatic blood flow (22, 23, 32, 33). The contribution of pancreatic blood flow to the observed effects of peptide YY in the pancreas cannot be ruled out since Sheikh et al. (172), using a slide-mount autoradiographic technique on frozen sections of rat pancreas, were able to demonstrate autoradiographic Y1 receptor localization predominantly over vascular smooth muscle cells and not to acinar cells.

The lack of involvement of extrapancreatic nerves in the actions of peptide YY was confirmed by two other studies (54, 198) using isolated pancreata; these studies suggested that peptide YY acts via the Y1 receptor in rats (54) and the Y2 receptor in dogs (198).

**Galanin.** Galanin is a 29-amino acid, COOH-terminally amidated peptide that was first isolated by Tatemoto et al. (195) from the porcine intestinal mucosa. Immunoreactivity for galanin has been localized in pancreatic nerves and also in a subset of islets (2, 10, 35, 116, 121). Galanin inhibits secretion of insulin (103, 109, 116, 121, 174) and somatostatin (7, 20).

Ahren et al. (3) were the first to study the effect of galanin on pancreatic exocrine secretion in isolated rat pancreatic acinar cells. Numerous investigators have studied galanin’s effects and mechanisms of action (43, 59, 71, 163, 164, 214). As with other peptides, galanin’s effects on exocrine secretion are inconsistent, with no effect (3, 43, 71), inhibitory effects (3, 43, 59, 71, 163, 164, 214), and in some models stimulatory effects reported (164).

It is likely that the complexity of the system used for such studies influences the findings. Using the isolated mouse pancreatic lobule preparation, we recently demonstrated that, although galanin had no effect on basal amylase secretion, its effect on stimulated secretion was dependent on the stimulus used. Galanin did not affect carbachol-stimulated amylase secretion but inhibited amylase secretion stimulated by caerulein at “physiological” concentrations (0.1 nanomolar) (12). The stimulatory effect of caerulein was mediated by inhibition of insulin secretion and by acting on postganglionic cholinergic nerves or directly on islets. However, at supramaximal concentrations of caerulein (0.1 micromolar), galanin potentiated amylase release by inhibiting the somatostatin secretion evoked by caerulein at these high concentrations, i.e., suppress-
ing somatostatin’s inhibitory effect (11). It is noteworthy that these effects of galanin were not observed when we used isolated mouse acinar cells (unpublished data), highlighting the role played by the islet cells in regulating exocrine secretion.

Substance P. Substance P is present in the pancreas (68, 182) and is believed to bind to the neurokinin (NK) receptors (15, 21, 184) to influence pancreatic neural signaling, blood flow, and pancreatic exocrine function. As with other peptides, inconsistent findings are often reported. In vitro studies have shown that Substance P stimulates basal and secretagogue-stimulated amylase secretion (53, 68, 73, 91, 155, 181); however, no effect on basal amylase release from isolated mouse pancreatic acinar cells has also been reported (159). We have observed (unpublished data) that exogenous Substance P stimulates basal amylase secretion and potentiates caerulein (0.1 nanomolar)-stimulated amylase secretion by isolated mouse pancreatic lobules. However, at supramaximal concentrations of caerulein, exogenous Substance P had no effect on amylase secretion. In vivo studies have also provided conflicting data. Substance P stimulated basal amylase secretion (86) and potentiated CCK- and caerulein-stimulated amylase secretion in some dog studies (66, 73, 155), but others reported inhibited secretin- and caerulein-stimulated exocrine secretion (66, 86). Similarly, Substance P inhibited both CCK-stimulated amylase secretion and secretin-stimulated flow of pancreatic juice in the isolated vascular perfused rat pancreas (81). The proposed underlying mechanisms involve binding of Substance P to NK receptors on acinar cells, stimulation of intrapancreatic nerves, some of which are cholinergic (188), and (indirectly) via its action on glucagon release (24, 30).

VIP. VIP is structurally similar to secretin and glucagon (69). VIP-containing nerves in the pancreas are well documented and preferentially associated with postganglionic cholinergic nerves (17, 25, 97, 188). VIP’s action on pancreatic exocrine secretion is primarily stimulatory. VIP stimulated insulin and glucagon secretion in perfused pancreata of pigs, with the particular hormone secreted being critically dependent on glucose concentrations in the perfusate (69). In vivo, VIP stimulated amylase release from isolated rat pancreatic acinar cells, via its receptors located on acinar cells (120, 160, 170). In vivo, VIP stimulated rat and rabbit pancreatic exocrine flow rate and secretin levels but did not significantly alter amylase levels (6, 162). These findings suggest that VIP’s effects on pancreatic exocrine secretion are probably mediated via secretin secretion.

CGRP. In the pancreas, CGRP-immunoreactive neurons have been reported (74). Exogenous CGRP has been shown to stimulate basal amylase release and potentiate CCK- and bombesin-stimulated amylase secretion from isolated guinea pig pancreatic acinar cells via a cAMP-dependent mechanism (170, 219). In contrast, CGRP administration inhibited rat and dog exocrine secretion in vivo including amylase secretion stimulated by CCK and pentagastrin (57, 130), an effect associated with a rise in somatostatin. The likely mechanism of action involved somatostatin and also sympathetic noradrenergic efferent nerves via α-adrenergic receptors (122). Another study using perfused rat pancreas and isolated pancreatic acinar cells confirmed that CGRP inhibited stimulated secretion in vivo, but not in vitro (26). The effect of CGRP was probably indirect, possibly involving cholinergic muscarinic transmission.

NPY. NPY is a 36-amino acid peptide isolated initially from the porcine brain (192) and bearing strong sequence homology with pancreatic polypeptide and peptide YY. Like galanin, in the rat, NPY-immunopositive nerve fibers have been noted in close association with arterial and ductal structures (28, 186, 189). When the effects of NPY on pancreatic exocrine secretion were studied in the rat, in vivo and in vitro (131), it was found that NPY dose dependently inhibited pancreatic exocrine secretion stimulated by CCK in vivo. It did not, however, alter the bicarbonate concentration in secretin-stimulated pancreatic juice output. In vitro, NPY had no effect on isolated acinar cell secretion but inhibited potassium- and veratridine-stimulated amylase secretion from pancreatic lobule preparations. These findings led Mulholland et al. (131) to conclude that the actions of NPY are indirect and possibly related to alteration in intrapancreatic neurotransmission. Sumi et al. (187) found that NPY inhibited pancreatic exocrine secretion stimulated by secretin alone and in combination with CCK at doses that also caused a reduction in splanchnic blood flow. This suggested that NPY’s inhibitory effect may be due, at least in part, to its splanchnic vasoconstrictive effect.

Nitric oxide. Nitric oxide is a gaseous mediator with several actions including as a neurotransmitter. Nitric oxide is believed to exert a stimulatory influence on pancreatic exocrine secretion. However, this conclusion was based on a reduction of pancreatic secretion following inhibition of nitric oxide synthase activity (61, 80, 84, 85, 88, 114, 213). These studies showed that in animals the inhibition of nitric oxide synthase activity resulted in an inhibition of water, bicarbonate, and protein enzyme secretion (61, 80, 85, 88, 114, 213), whereas in humans the inhibition was restricted only to protein enzyme secretion (84).

On the basis of studies with isolated canine pancreatic acinar cells, Konturek et al. (85) suggested that the observed effect of nitric oxide on pancreatic exocrine secretion was probably secondary to its effects on blood flow. However, the results obtained by Holst et al. (61) seemed to indicate the existence of other possible mechanisms. The existence of additional mechanisms of action of nitric oxide was supported by the ability of L-arginine (nitric oxide synthase substrate) to stimulate basal amylase release from in vitro systems (acini and lobules) (80, 213).

Exogenous administration of a nitric oxide donor (sodium nitroprusside) to the isolated rat pancreas produced a dual effect: inhibition of basal amylase secretion from acinar cells and inhibition of acetylcholine release from intrinsic nerve terminals. Both these effects were believed to be Ca2+ dependent and possibly mediated by cyclic guanosine monophosphate (cGMP) (38). This dual effect on isolated, extrinsically denervated rat pancreata was also observed by Zoucas et al. (220) suggesting that intrapancreatic nitric oxide release was regulated by extrapancreatic nerves.

DiMagno et al. (34) studied the role of the different isoforms of nitric oxide synthase (neuronal, endothelial, and inducible) in vivo in gene-knockout mice using a nitric oxide synthase inhibitor and found that the constitutive nitric oxide synthase isoforms exerted opposite effects on pancreatic secretion. Endothelial nitric oxide synthase gene deletion mimicked nitric oxide synthase inhibition by inhibiting CCK-8 and carboclo-
stimulated secretion, whereas neuronal nitric oxide synthase gene deletion augmented CCK-8- but not carbachol-stimulated secretion.

The proposed mechanisms of regulation of pancreatic secretion by nitric oxide has been attributed to a generation of cGMP and also its ability to control the release of endogenous neurotransmitter in the pancreas and, subsequently, vagal (139) nerve-mediated enzyme secretion (215).

PACAP. PACAP was first discovered in the ovine hypothalamus by Miyata et al. (127). It has two molecular forms, PACAP-27 and PACAP-38. The reported effects on pancreatic exocrine secretion are exclusively stimulatory. In vivo, in rats, PACAP stimulated pancreatic exocrine flow rate as well as secretion without affecting secretin and VIP levels, implying a direct action by PACAP (6). In the rabbit pancreas, PACAP-27 stimulated amylase release (162). Similar stimulatory effects were noted in other species and ascribed to a cholinergic mechanism of action (137, 146, 147, 217). A direct effect of PACAP on the isolated guinea pig acinar cell has also been demonstrated, and CCK was found to have a synergistic effect (82).

Angiotensin II and the Role of the Renin-Angiotensin System

Leung et al. (105) demonstrated the presence of angiotensin II receptors (AT1 and AT2) in the endothelia of pancreatic blood vessels, the epithelia of the pancreatic ducts, and acinar cells using a histochemical approach. Recent studies concerning the expression and localization of the renin-angiotensin system in the pancreas have contributed to our understanding of the role of renin-angiotensin system in the regulation of acinar cell function (104). Administration of exogenous angiotensin II has been shown to stimulate the release of digestive enzymes from the acinar cell in a dose-dependent fashion, probably via the mediation of intracellular Ca2+ (200). The underlying regulatory mechanism(s) is yet to be clarified.

Conclusion

In conclusion, the findings reported in the literature are often disparate, which reflects not only the different species studied but the range of preparations used in the studies. Despite this, the evidence presented illustrates a complex regulatory system involving neurocrine, paracrine, and endocrine signaling coupled with modulation of blood flow to regulate the effects of humoral signals. The complexity and redundancy observed presumably reflects an intricate regulation of important physiological functions at a local and systemic level. Despite the fact that insulin plays a central role in orchestrating this multifaceted interplay of the humoral factors, the term insulinoacinar axis is a generalization. Since there is a complex interplay between the islet and acinar cell, the term islet-acinar axis remains more appropriate.

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DISCLOSURES

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ISLET-ACINAR AXIS


Potentiation of cholecystokinin-
creatic acinar membranes.
stead of receptors for NPY and PYY on vascular smooth muscle cells in rat pancreas.
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