The efferent vagal fibers are also important, because with CCK to stimulate pancreatic secretion (61, 68). after a meal (6, 60), and secretin acts synergistically in these rat studies.

PYY inhibits CCK-stimulated pancreatic secretion through the area postrema in unanesthetized rats

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Peptide YY (PYY) inhibits CCK-8-secretin-stimulated pancreatic secretion in vivo. To investigate whether CCK-8-secretin-stimulated pancreatic secretion is mediated through a vago-vagal pathway and whether PYY inhibits this pathway through the area postrema (AP), chronic pancreatic, biliary, and duodenal catheters were implanted in AP-lesioned (APX) or sham-operated rats. The effects of APX on pancreatic secretion stimulated by bethanechol, pancreatic juice diversion (PJD), or CCK-8-secretin, were tested, with and without background PYY infusion, in unanesthetized rats. APX reduced basal pancreatic secretion by 15–20% (P < 0.01). APX had no effect on bethanechol-stimulated secretion and potentiating protein secretion stimulated by PJD (396 vs. 284%) and exogenous CCK-8-secretin. In sham-operated rats, background PYY potently inhibited CCK-8-secretin-stimulated pancreatic fluid (1.8 vs. 48.2%) and protein secretion (3.7 vs. 49.6%), but potentiated fluid (52.9 vs. 43.1%) and protein (123.9 vs. 68.9%) secretion in APX rats. Our findings demonstrate that PYY inhibits CCK-8-secretin-stimulated pancreatic secretion through an AP-dependent mechanism in sham-operated rats. The AP also contributes to basal pancreatic secretion.

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Peptide YY; cholecystokinin; area postrema lesion; pancreatic secretion; neural and hormonal mechanisms; pancreatic secretion; CCK receptors located on either the pancreatic acinar cells (38, 52, 68, 71). Although PYY1–36 inhibits CCK-stimulated pancreatic secretion in anesthetized rats (38) and conscious dogs (35, 65), it fails to inhibit CCK-stimulated amylase release in isolated rat pancreas preparations (26, 38). PYY1–36 also fails to inhibit pancreatic secretion by electrical stimulation of the distal end of the severed vagus nerve trunk in anesthetized rats (52) or when pancreatic secretion is driven by neural stimulation of the surgically isolated pig pancreas (26), suggesting that PYY acts as a more central site. A parallel observation has been made for PYY inhibition of gastric acid secretion. PYY is more potent in inhibiting a thyrotropin-releasing hormone analog-induced stimulation of gastric acid secretion in urethane-anesthetized rats when administered intracisternally rather than intravenously (73). To achieve the same level of potency to block the antisecretory of intravenous PYY, the dose of antibody for intravenous injection is 16 times higher than the intracisternal effective dose (73). These observations suggest that the site of PYY’s hormonal actions may be central.

Because PYY1–36 does not appear to inhibit CCK release in rats (31) and because afferent vagal fibers express functional CCK-A receptors (7, 34, 40, 45, 63), we hypothesize that PYY1–36 inhibits CCK-stimulated pancreatic secretion somewhere along the vago-vagal stimulatory pathway. The vago-vagal pathway begins with the afferent, CCK-sensitive fibers that pass through the nodose ganglion and project into the brain stem within the dorsal vagal complex (DVC; 29, 56), specifically the nucleus of the solitary tract (NTS), although some fibers may also present in the area postrema.
postrema (AP) (29). The AP, a region in the DVC with an incomplete blood-brain barrier, allows small peptide hormones to enter the DVC (24, 69). We previously demonstrated binding sites for PYY<sub>1–36</sub> and pancreatic polypeptide within the DVC that specifically bind peripherally infused hormones (24, 69, 70). These binding sites appear to be functional receptors, because micro-injection of PYY<sub>1–36</sub> into the DVC inhibits pancreatic secretion (71). The DVC also includes the dorsal motor nucleus of the vagus (DMV) with efferent fibers innervating the pancreas (56). Peripheral injection of PYY induced c-Fos expression in the DVC (5). However, for reasons stated above, it is unlikely that PYY inhibits pancreatic secretion distal to the efferent vagus nerve.

Taken together, these data suggest that a primary site of PYY’s regulatory effects may be the DVC and that access to the DVC requires an intact AP. Therefore, we hypothesize that removal of the AP will eliminate the major regulatory effects of PYY on the pancreas. In the present study, we ablated the AP in rats to prevent the action of circulating PYY on the DVC and thereby determine whether the DVC is the primary control site where PYY regulates CCK- and secretin-stimulated pancreatic exocrine secretion.

**MATERIALS AND METHODS**

**Chemicals**

Synthetic rat PYY<sub>1–36</sub>, CCK-8 sulfate, and secretin were purchased from Peninsula Laboratories (Belmont, CA). BSA and Bethanechol were purchased from Sigma-Aldrich (St. Louis, MO). Isoflurane was purchased from Abbott Laboratories (Abbott Park, IL). Ultrapure water was obtained from a Milli-Q water purification system. Intravenous tubing (0.020 in. OD and 0.025 in. ID) was purchased from Bolab Products (Lake Havasu City, AZ). Modified Bollman cages were custom built by the Cell Biology and Physiology Machine Shop as described (22).

**Animals**

All animal protocols were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh and the Veterans Affairs Medical Center of Pittsburgh. Male Wistar rats (250–275 g) were purchased from Harlan Sprague Dawley (Indianapolis, IN) and housed individually with free access to rat chow (Prolab RMH3000, St. Louis, MO) and tap water under a 12:12-h light-dark cycle.

**Ablation of the AP**

A total of 56 rats was used in this study. The AP-lesioned (APX) procedure was performed as we previously described (9). In brief, rats were anesthetized with isoflurane, placed in a stereotaxic frame, and the AP was exposed through a surgical incision between the occipital crest and midcervical region. Under a stereotaxic microscopic visualization, the AP was either aspirated with a blunted 25-gauge needle (APX group) or visualized for 10–15 min (sham-operated group). The musculature was then sutured, and the skin was closed. The rats recovered for 1 mo with weekly monitoring of body weight. All rats with APX survived and gained weight, but the average body weight for APX rats after 1-mo recovery was less than sham-operated rats (300 ± 3 vs. 340 ± 6 g, P < 0.01). However, this weight difference does not appear to affect pancreatic secretion (28, 38).

The extent of damage to the AP and underlying NTs was tested functionally 3 wk after surgery with a 0.5 M NaCl aversion test (9). On 3 consecutive days, rats had ad libitum access to water and 0.5 M NaCl. Control rats drank <5 ml of the salt solution per day. Rats that drank >15 ml of 0.5 M NaCl were considered to have functional ablation of the AP and were used in subsequent pancreatic function testing. After all experiments, the brain stem was examined histologically to provide anatomic conformation at the extent of the AP lesion.

**Chronic Pancreatic Cannulation Model**

In our pilot studies, we measured pancreatic secretion during postsurgery day 1 to day 12. Pancreatic secretion recovered by day 3, as observed by others (19, 21, 39, 42), a period shorter than functional recovery of some other visceral organs (3, 4). Therefore, 3 days or more before pancreatic function experiments, rats were anesthetized with isoflurane and prepared with pancreatic, biliary, duodenal, and intravenous catheters as previously described (22). Pure pancreatic juice and bile were continuously collected and returned to the duodenum by a peristaltic pump (Ismatec 7614 series mini-micro pump, Cole-Parmer Instruments, Chicago, IL) with a photoelectric controller (Sight-glass Scanner with control box, Moxley Skan-a-Matic, Glenmore, PA; Ref. 22). After surgery, rats were housed individually in modified Bollman cages. During the recovery period, all rats were given 3 days of intravenous ampicillin (40 mg·kg<sup>−1</sup>·day<sup>−1</sup>).

**Experimental Protocols**

Animals were fasted overnight. Basal pancreatic secretions were collected every 15 min for 60 min. Rats then received one of the treatments described below. Both pancreatic fluid and protein were measured for an additional 155 or 195 min. The fluid volume was calculated from weight changes of preweighed microcentrifuge tubes. Protein content was determined by ultraviolet absorbency at 280 nm using BSA as a standard (22).

After all physiological experiments were completed, rats were killed with an overdose of pentobarbital sodium. The brain was rapidly removed and snap frozen in liquid nitrogen. The brain was sectioned (20 μm) using a cryostat at −20°C. Sections were mounted on Superfrost slides (VWR Scientific, West Chester, PA) and stained with cresyl violet. Sections were examined using a light microscope to determine the extent of the APX. Pancreatic tissue samples from control and APX rats were fixed in 4% formalin, sectioned, stained with hematoxylin and eosin, and examined for histological changes.

A series of four experiments was performed in a randomized order in APX and sham-operated rats. A total of 35 APX rats and 21 sham-operated rats was used. Most rats were tested in two of the four protocols, with at least a 3-day interval between experiments.

**Effect of APX on basal pancreatic secretion.** To determine the effect of APX on basal pancreatic secretion, basal pancreatic secretion was collected without any infusion in APX (n = 35), sham-operated (n = 21), and intact rats (n = 18, another set of 18 weight-matched rats without any procedure except abdominal surgery).

**Effect of APX on Bethanechol-stimulated pancreatic secretion.** To determine if APX affects cholinergic response at the level of the pancreas, Bethanechol was infused to directly...
activate cholinergic receptors (28, 52). After the baseline collection period, bethanechol was infused at a rate of 3 mg·kg⁻¹·h⁻¹ for 135 min (APX: n = 7, sham operated: n = 5).

Effect of APX on pancreatic secretion during diversion of pancreatic juice. Experiments were performed to determine if APX affects pancreatic secretion after pancreatic juice diversion (PJD), a potent stimulant of endogenous CCK release (16, 30). After measuring basal pancreatic secretion (juice returned to the duodenum), the pancreatic juice, but not bile, was diverted to the exterior without being returned to the duodenum for next 135 min. Pancreatic juice was collected every 15 min for 135 min (APX: n = 7, sham operated: n = 5).

Effect of APX on CCK-8-secretin-stimulated pancreatic secretion. To determine if APX affects CCK-8-secretin-stimulated pancreatic secretion, graded doses of CCK-8 (14, 28, and 56 pmol·kg⁻¹·h⁻¹) plus secretin (1.25, 2.5, and 5.0 pmol·kg⁻¹·h⁻¹; APX: n = 6, sham operated: n = 6) were simultaneously intravenously infused at increasing doses every 60 min, as described by Jin et al. (28). This physiological combination of CCK-8 and secretin was chosen to allow us to compare our results with previous studies on inhibition of CCK-8-secretin-stimulated pancreatic secretion using PYY (28).

Effect of APX on PYY₁₋₃₆-mediated inhibition of CCK-8-secretin-stimulated pancreatic secretion. To determine if PYY₁₋₃₆ inhibits CCK-8-secretin-stimulated pancreatic secretion at the level of the DVC, PYY₁₋₃₆ at the dose of 50 pmol·kg⁻¹·h⁻¹ (APX: n = 8, sham operated: n = 8) or vehicle (APX: n = 6, sham: n = 6) was continuously infused after the basal collection; CCK-8-secretin was simultaneously infused at increasing doses for 60 min as described above.

Analysis of Data

Data are presented as means ± SE. Because APX decreased basal pancreatic secretion and to compare the effects of different treatments, the incremental changes during the 60-min period (the values of pancreatic fluid secretion and protein output with their own average baseline values subtracted) were averaged and reported as microliters per 15 min or milligrams per 15 min. To compare the maximum secretory response to bethanechol or PJD, the incremental peak secretion rate was tested for statistical significance. Comparison between treatments was performed using ANOVA with repeated measures (StatView 4.5, Abacus Concepts, Berkeley, CA). The multiple-range post hoc test or Student’s t-test was used to compare the difference among the means. P < 0.05 was considered to be significant difference.

RESULTS

The AP remained intact in all sham-APX rats (Fig. 1A) but was completely absent in all APX rats (Fig. 1B). APX rats typically had minimal or no damage to the subjacent NTS, and no APX rats had damage to the DMV. The histological appearance of pancreatic acinar cells, duct cells, and islets of Langerhans in pancreas from APX rats and sham-operated rats was identical (not shown).

Effect of APX on the Basal Pancreatic Secretion

Basal fluid secretion in APX rats was decreased by −16% compared with sham-operated rats (119.1 ± 4.4 vs. 141.7 ± 5.9 μl/15 min, P = 0.0019). Likewise, basal protein output in APX rats was less (−19%) with APX than in sham-operated rats (11.7 ± 0.5 vs. 14.5 ± 0.8 mg/15 min, P = 0.0015). The basal pancreatic fluid and protein secretion in intact rats were 139.1 ± 10.4 μl/15 min and 14.18 ± 1.3 mg/15 min. Therefore, the sham operating procedure did not affect the basal pancreatic secretion (P = 0.49 for fluid and P = 0.46 for protein).

Effect of APX on Bethanechol-Stimulated Pancreatic Secretion

In both sham-operated and APX rats, bethanechol significantly stimulated fluid secretion, and the magnitude of stimulation was similar (net peak fluid secretion 142.58 ± 16.3 vs. 161.99 ± 11.8 μl/15 min, P = 0.33). Similarly, a comparable increase in protein secretion was observed in both sham-operated and APX
rats (net peak protein secretion 35.09 ± 7.4 vs. 41.68 ± 4.1 mg/15 min, P = 0.42).

**Effect of APX on Pancreatic Secretion During PJD**

PJD produced increases in both pancreatic fluid and protein secretion in APX and sham-operated rats (Fig. 2). However, the increase of peak pancreatic fluid in APX rats (change = 214.2 ± 25.9 μl/15 min, increased 180%) was significantly higher than the increase observed in sham-operated rats (change = 126.3 ± 16.0 μl/15 min, increased 89%, P = 0.0176, Fig. 2C). The net change in peak protein secretion in APX rats (46.4 ± 7.0 mg/15 min, increased 396%) also increased compared with the sham-operated rats (41.2 ± 5.6 mg/15 min, increased 284%), but it failed to reach statistical significance (P = 0.59, Fig. 2D).

**Effect of APX on CCK-8-Secretin-Stimulated Pancreatic Secretion**

CCK-8-secretin stimulated pancreatic fluid secretion at higher doses (56 ± 5 pmol·kg⁻¹·h⁻¹ vs. basal, P = 0.0189, Fig. 3A); it also increased protein secretion at both 28.8 ± 2.5 and 56 ± 5 pmol·kg⁻¹·h⁻¹ (vs. basal, P = 0.0388) in sham-operated rats (Fig. 3B). However, when the same doses of CCK-8-secretin were infused in APX rats, it produced a significant increase in pancreatic fluid (vs. basal, P < 0.0001) and protein (vs. basal, P < 0.0001) secretion (Fig. 3, A, B, F, and G). In particular, the stimulated protein secretion in APX rats was much higher than the values in the sham-operated rats (APX vs. sham operated, P = 0.0379, Fig. 3).

**Effect of APX on CCK-8-Secretin-Stimulated Pancreatic Secretion During a Background Infusion with PYY₁₋₃₆**

The effects of APX on CCK-8-secretin with and without PYY₁₋₃₆-stimulated pancreatic secretion were summarized in Table 1 (data are presented as an average of original pancreatic secretion during a 1-h period). CCK and secretin failed to increase pancreatic fluid secretion (vs. basal secretion, P = 0.94) in sham-operated rats during the PYY₁₋₃₆ background infusion (Fig. 3, C–F). In other words, PYY₁₋₃₆ background infusion significantly inhibited CCK-8-secretin-stimulated protein secretion (vs. basal, P < 0.0001). How-

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**Fig. 2.** Effect of APX on pancreatic fluid (A and C) and protein (B and D) secretion during diversion of pancreatic juice (DPJ). The data in A and B represent the incremental changes of pancreatic secretion, and the data in C and D represent the peak pancreatic secretion that was the averaged values of combined highest secretion of each individual rat during a 15-min period. *P < 0.05, compared with basal secretion; **P < 0.01, compared with basal secretion; and #P < 0.05, compared with sham-operated rats.
neurohormonal pathways regulating CCK-secretin-stimulated pancreatic exocrine secretion and PYY-mediated inhibition. Top: central portion of the regulatory system centered in the dorsal vagal complex (DVC) including the AP, NTS, and dorsal motor nucleus of the vagus (DMV). The afferent and efferent vagal pathways are shown in bold lines. Bottom: peripheral actions of CCK and secretin. PYY enters the DVC through the AP and extends throughout the lightly shaded region enclosed by the dashed circle. PYY could act either on A) inhibitory neurons located in the AP (a), 2) interneurons in the NTS, or 3) dorsal motor neurons in the DMV. Removal of the AP eliminates the inhibitory effect of PYY on CCK-stimulated pancreatic secretion and PYY may act by removing the inhibitory interneurons from the AP 1) or by removing the portal of entry for PYY into the NTS and DMV, thereby preventing PYY from acting on interneurons in the NTS (b) or on the dorsal motor neurons (c). PYY does not appear to act on peripheral afferent vagal fibers, intrapancreatic ganglia (d) or on the acinar cells, because these components of the CCK-secretin mediated pathway remain intact after APX.

Table 1. Pancreatic fluid and protein secretion stimulated by CCK-8-secretin in the presence or absence of PYY in APX and sham-treated rats

<table>
<thead>
<tr>
<th></th>
<th>CCK + Secretin</th>
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<tr>
<td></td>
<td>Low dose</td>
</tr>
<tr>
<td>Fluid secretion, µl/15 min</td>
<td></td>
</tr>
<tr>
<td>Sham + vehicle</td>
<td>101.0 ± 11.1</td>
</tr>
<tr>
<td>Sham + PYY1–36</td>
<td>91.1 ± 13.4</td>
</tr>
<tr>
<td>APX + vehicle</td>
<td>100.0 ± 5.4</td>
</tr>
<tr>
<td>APX + PYY1–36</td>
<td>133.7 ± 23.7</td>
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</tbody>
</table>

| Protein secretion, mg/15 min |
| Sham + vehicle | 6.27 ± 1.24 | 7.85 ± 1.12 | 7.12 ± 1.10 |
| Sham + PYY1–36 | 2.35 ± 0.35 | 2.43 ± 0.57 | 2.14 ± 0.40 |
| APX + vehicle  | 8.64 ± 0.66 | 12.34 ± 0.97* | 14.15 ± 1.23† |
| APX + PYY1–36 | 13.19 ± 2.75† | 15.51 ± 1.95 | 20.97 ± 1.60† |

Values are means ± SE. Low dose: CCK 14 pmol·kg⁻¹·h⁻¹ + secretin 2.5 pmol·kg⁻¹·h⁻¹. Medium dose: CCK 28 pmol·kg⁻¹·h⁻¹ + secretin 2.5 pmol·kg⁻¹·h⁻¹. High dose: CCK 56 pmol·kg⁻¹·h⁻¹ + secretin 5.0 pmol·kg⁻¹·h⁻¹. PYY, peptide YY, APX, area postrema lesioned. *P < 0.01, †P < 0.0001 as compared with the values of sham groups.

ever, when a background of PYY1–36 was infused in APX rats, CCK-8-secretin significantly stimulated both pancreatic fluid (vs. basal, P < 0.001) and protein (vs. basal, P < 0.0001) secretion (Fig. 3, C–F). A temporary reduction in protein output between 45 and 90 min in the APX group (Fig. 3D) was observed. The difference between CCK-8-secretin-stimulated pancreatic secretion during background infusion of PYY in APX and sham-operated rats was significant (APX vs. sham-operated: fluid, P < 0.0001, and protein, P < 0.0001, Fig. 3, C and D). Furthermore, this increment of protein in the APX rats was higher than the stimulation of CCK-8-secretin without PYY in APX rats (low dose: P = 0.0232, high dose: P = 0.0003, Fig. 3G).

DISCUSSION

The present study defines a critical role for the AP and the DVC in the mechanism through which PYY1–36 regulates pancreatic exocrine secretion. These experiments demonstrate that APX increases pancreatic secretion elicited by exogenous CCK-8-secretin or by endogenous CCK secretion during PJD. Furthermore, APX eliminates the inhibitory effect of PYY on CCK-secretin-stimulated pancreatic secretion. These studies, therefore, support the hypothesis that CCK-8-secretin acts through a vago-vagal pathway (Fig. 4) and that PYY1–36 acts at the level of the AP to regulate this vago-vagal reflex (Fig. 4).

The choice of experimental conditions is always important when investigating the physiology of neurohormonal mechanisms. Although some previous studies demonstrated the involvement of the DVC in the modulation of pancreatic secretion, most of these experiments were performed under anesthesia with acute surgery (47, 48). Because anesthesia (51) and acute surgery (42) can markedly alter pancreatic secretion and because anesthesia and acute surgery per se also affect the neuronal activity in the nervous system (3, 4), we conducted these experiments in awake, chronically instrumented rats. Furthermore, all doses of chemical used in this study were chosen to reflect physiological dose ranges (22, 28, 33).

As illustrated in the schematic of Fig. 4, the majority of gastrointestinal afferent fibers terminates in the NTS, although a few also terminated in the AP (29). Heavy cross innervation has been demonstrated between the AP, NTS, and the DMV (37). The AP not only receives the vagal input, but also has high-density noradrenergic projections to the DMV, the source of the
parasympathetic innervation of pancreas. This anatomic relationship between the major components of the DVC allows the AP to regulate pancreatic secretion.

Because the mechanisms for controlling basal and postprandial pancreatic secretion may be different, we explored a possible role of the AP in regulation of both basal and postprandial pancreatic secretion. Basal pancreatic secretion was decreased in APX rats. This is in line with the decreased basal pancreatic secretion after vagotomy (11, 59), suggesting that the AP contributes, in some way, to basal vagal tone. The mechanism of decreased tonic cholinergic control in basal pancreatic secretion is not clear, but we have observed a blunted pancreatic secretory response to 2-deoxy-D-glucose in APX rats as well (14, 15). Whereas basal pancreatic secretion was diminished in APX rats compared with sham-operated rats, APX did not affect the pancreatic secretory response during stimulation with the muscarinic receptor agonist Bethanechol. This demonstrates that direct cholinergic stimulation of pancreatic secretion was not impaired by removal of the AP. Removal of the AP caused a marked elevation in pancreatic fluid output during the PJD compared with sham-operated rats. These results suggest that the AP may exert a level of chronic inhibition on CCK-mediated pancreatic fluid and protein secretion. This is supported by the subsequent experiments; stimulation with increasing doses of exogenous CCK and secretin caused an exaggerated fluid and protein secretion in APX rats. However, we cannot fully determine whether there are separate stimulatory and inhibitory elements in the AP or whether some of the observed changes reflect adaptation to the surgical lesions.

Previous studies have shown that perivagal capsaicin treatment, atropine, vagotomy, and a CCK-A receptor antagonist eliminated CCK-stimulated pancreatic secretion in anesthetized rats (49); however, these effects were not seen in awake rats (20). Furthermore, CCK-A receptors are located on pancreatic acinar cells (64, 67, 72), afferent vagal fibers (7, 34, 40, 44, 45, 63), and the brain stem (25, 41, 53) in rats, suggesting several potential sites for CCK's action. However, several recent studies suggest that CCK's primary physiologic actions are mediated through receptors located on capsaicin-sensitive afferent fibers of vagus (7, 8, 32, 40, 44). Vagal sensory afferents terminate in the medial region of the NTS and, to a lesser extent, in the AP (29, 57). CCK-A receptors are also found in these regions (41, 46), which may reflect central projections of the CCK receptors bearing afferent vagal fibers. Peripheral administration of CCK-8 activates NTS neurons, as reflected by an increase in c-Fos expression in these neurons (10, 43, 55, 74), and this is blocked by disruption of vagal afferents (43), suggesting that CCK was acting at a peripheral site rather than centrally. Other studies have also demonstrated physiological effects of CCK through the afferent vagus, including food intake, gastric emptying, and pancreatic secretion (32, 54, 62). In the present study, CCK-8-secretin stimulated pancreatic secretion in the presence or absence of the AP, suggesting that the primary site of CCK stimulation was peripheral and likely through the afferent vagal pathway.

The present study demonstrates the importance of the AP for modulation of CCK and secretin-stimulated pancreatic secretion and adds further support to the hypothesis that PYY1–36 interacts with a vago-vagal circuit through the AP to inhibit CCK-8-secretin-stimulated pancreatic secretion under physiological conditions. PYY1–36, released from the endocrine cells of the distal ileum and colon in response to a meal, is an important physiological inhibitor of CCK-stimulated pancreatic secretion in vivo (1, 2, 18). However, the mechanism mediating this effect of PYY1–36 has remained controversial because of the wide distribution of PYY1–36 receptors, differences in experimental design, use of different species, and inherent limitations of many of the previously used animal models (1, 17). For example, PYY1–36 inhibits CCK release in dogs (27, 36) but not in rats (21, 31). Furthermore, the role of the different receptor subtypes is also complex (17, 22). However, several lines of evidence suggest that PYY1–36 may act through a central site (24, 38, 52). First, both PYY and CCK receptors were located in the AP and NTS (24, 25, 41, 53). Second, PYY receptors were not found in pancreatic acinar cells (38, 58) nor does PYY inhibit neurally mediated pancreatic secretion distal to the efferent vagal nerve trunk (26). Thus the logical site for PYY inhibition of CCK-stimulated secretion is the DVC. Our current observation that PYY1–36 failed to inhibit pancreatic secretion elicited by CCK-8-secretin after removal of the AP represents the strongest evidence to date that the primary action of PYY1–36 is through the DVC. These observations add further support to the hypothesis that PYY is the “anti-CCK hormone” in awake rats, as proposed by others (12, 23, 50), and suggest that the mechanism by which PYY inhibits the effect of CCK on pancreas is primarily mediated through the AP.

In marked contrast to the inhibitory effect of PYY1–36 in rats with intact AP, PYY1–36 further potentiates CCK-8-secretin-stimulated pancreatic secretion after APX (Fig. 3G). Although the exact mechanism for PYY1–36 to stimulate pancreatic secretion or potentiate CCK-8-secretin’s stimulatory effects on exocrine pancreas in APX rats is not clear, others have observed that under some conditions, PYY1–36 may increase pancreatic exocrine secretion. Tohno et al. (66) infused carbohydrate into the distal ileum of awake dogs, causing the release of immunoreactive PYY and found that the intestinal transit and gastric emptying slowed while the amylase secretion increased. Our recent observations (22) also demonstrated that PYY1–36 stimulated pancreatic secretion when PYY1–36 alone is perfused at increasing doses in fasted rats. The current observations suggest that APX further unmasked a peripheral stimulatory effect of PYY on exocrine pancreas.

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Perspectives

Understanding the neurohormonal control of the pancreas and visceral organs, especially the brain modulation, is complex, but it is important because it defines potential pathological pathways and targets for new therapies. The present study provides a major step in our understanding of this mechanism by demonstrating that the AP is the major site of PYY1–36-mediated inhibition of CCK-8-secretin-stimulated pancreatic secretion (Fig. 4). These studies also demonstrate that removal of the AP unmask a stimulatory effect of circulating PYY1−36. Furthermore, these studies demonstrate that under physiological conditions, CCK acts primarily through a vago-vagal stimulatory pathway. Coordination of visceral functions through centralized reflexes with hormonally mediated inhibitory feedback loops using peripheral peptides such as PYY1−36 may be more important than previously recognized. Indeed, similar central and peripheral feedback mechanisms may be operating with pancreatic polypeptide, somatostatin, and other peptides that regulate visceral function.

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