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Primary pancreatic secretinoma: further evidence supporting secretin as a diarrheogenic hormone

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Abstract

Objectives—To document the existence of primary pancreatic secretinoma in patients with watery diarrhea syndrome (WDS) and achlorhydria and establish secretin as a diarrheogenic hormone.

Background—Vasoactive intestinal peptide (VIP) has been widely accepted as the main mediator of WDS. However, in 1968, Zollinger et al reported 2 female patients with pancreatic neuroendocrine tumors, WDS, and achlorhydria. During surgery on the first, a 24-year-old patient, they noticed distended duodenum filled with fluid and a dilated gallbladder containing dilute bile with high bicarbonate concentration. After excision of the tumor, WDS ceased and gastric acid secretion returned. The second, a 47-year-old, patient's metastatic tumor extract given intravenously in dogs, produced significantly increased pancreatic and biliary fluid rich in bicarbonate. They suggested a secretin-like hormone of islet cell origin explains WDS and achlorhydria. These observations, however, predated radioimmunoassay, immunohistochemical staining, and other molecular studies.

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Methods—The first patient's tumor tissue was investigated for secretin and VIP. Using both immunohistochemistry and laser microdissection and pressure catapulting technique for RNA isolation and subsequent reverse transcription polymerase chain reaction, the expression levels of secretin, and VIP were measured.

Results—Immunoreactive secretin and its mRNA were predominantly found in the tumor tissue whereas VIP and its mRNA were scarce.

Conclusions—The findings strongly support that the WDS and achlorhydria in this patient may have been caused by secretin as originally proposed in 1968 and that secretin may act as a diarrheogenic hormone.

Keywords

mRNA; pancreatic neuroendocrine tumor; secretin; vasoactive intestinal polypeptide; watery diarrhea syndrome

Watery diarrhea syndrome (WDS) associated with neuroendocrine tumors of the pancreas (PNETs) has been recognized since 1958 when Verner and Morrison[1] reported 2 patients with PNETs exhibiting severe watery diarrhea, hypokalemia, dehydration, and renal failure. They suggested that a hormonal mediator derived from the tumor was causing massive watery diarrhea. In 1973, Bloom et al[2] reported 4 patients with Verner-Morrison Syndrome who had high plasma immunoreactive vasoactive intestinal peptide (VIP) levels and PNETS containing numerous immunoreactive VIP cells. Surgical resection of the tumors led to complete cessation of watery diarrhea.[3] Moreover, in both conscious pigs[4] and human volunteers,[5] watery diarrhea was induced by intravenous (IV) administration of VIP in doses that mimicked plasma level of VIP in patients with WDS. Furthermore, IV VIP in the same dose range was shown to increase small intestinal secretion of water and chloride[6] and to inhibit small intestinal and colonic absorption of water and sodium in humans.[7] As a result of these accumulated observations, the NET became known as VIPoma, and VIP has been considered as the prime mediator of the watery diarrhea in WDS.[7]

In 1968, Zollinger et al[8] reported 2 female patients with PNETs who displayed WDS and basal achlorhydria. In the first patient at operation on May 24, 1967, a nodular, baseball-sized tumor in the superior margin of the neck of the pancreas and an olive-sized, encapsulated tumor within the substance of the tail of the pancreas were removed by resection of the body and tail of the pancreas.[8] At exploration in the first patient, a 24-year-old female—her clinical history, surgical operative finding and investigative data were described in detail in their original publication in 1968—they found a markedly dilated duodenum filled with fluid and was rapidly refilled with fluid after removal by suction and a tensely distended gallbladder containing a very dilute watery bile fluid with high bicarbonate and chloride concentration.[8] They hypothesized that marked biliary-pancreatic hypersecretion of fluid accounted for the increased volume of fluid in the duodenum and proximal jejunum. The watery diarrhea completely ceased and achlorhydria was reversed to gastric acid secretion after surgical resection of the tumor. In addition to pancreatic tumors, the first patient had a previous history of hyperparathyroidism and left renal nephrolithiasis in early 1965, requiring subtotal parathyroidectomy to correct hypercalcemia. Zollinger et

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al[8] described “the patient’s family history was significant only on her father’s side. The paternal grandmother had hyperparathyroidism. The paternal grandfather, 3 uncles and 3 of 5 aunts had all been treated for peptic ulcer disease. Most significantly, the father and one of his brothers had ulcerogenic tumors (gastrinomas) of the pancreas. In addition, the latter had hyperparathyroidism as well.” These clinical features are consistent with the presence of multiple endocrine neoplasia Type 1 (MEN1)[9] in this patient. The patient remained healthy without watery diarrhea in 1985, the last known contact. Although her pancreatic tumor extract, an acid/saline extract, given intravenously to dogs failed to stimulate pancreatic secretion, the extract of a large metastatic tumor of the second patient, a 47-year-old female with a malignant PNET, the size 5 times as large as that of the first patient, produced a marked increase in pancreatic secretion of fluid rich in bicarbonate and decrease in protein concentration, consistent with the classic action of secretin on the exocrine pancreas.[10,11] The second patient was also found to have achlorhydria and an enlarged gallbladder during the initial laparotomy and at autopsy.

In a subsequent report in 1972, Sanzenbacker et al[12] found similar exocrine pancreatic secretory responses in dogs to the primary PNET extracts of 2 additional patients with WDS. The tumor extracts also increased bile flow and concentrations of both bicarbonate and chloride in anesthetized dogs,[13] a characteristic action of secretin on biliary secretion.[11] The extracts also caused significant inhibition of gastric acid secretion in dogs.[8,12] Based on these observations, they suggested a secretin-like hormone of islet cell origin as the etiologic factor and that their clinical findings were attributable to secretin-producing islet cell tumors of the pancreas. However, there was no specific antisecretin serum available in late 1960s or early 1970s to identify secretin producing tumor cells or measure immunoreactive secretin levels in blood.

Indeed in 1975, Schmitt et al[14] reported a 26-year-old male with metastatic PNET and massive watery diarrhea who exhibited very high immunoreactive secretin level in plasma, [15,16] hypochlorhydria, marked pancreatic hypersecretion of water and bicarbonate, and numerous secretin-like immunoreactive tumor cells. At autopsy, similar to the 2 patients as described by Zollinger et al,[8] the gallbladder was found distended, containing 60 mL of markedly dilute bile. Additional findings were dilatation of the duodenum and remaining upper small intestine. Each of these latter findings is consistent with secretin’s inhibitory effect on the contractile activity of the duodenum and upper small bowel.[17]

We searched for paraffin-embedded tissues of these pancreatic tumors from 3 institutions[8,12,14] to determine if the tumor tissues expressed mainly secretin and the gene that encodes it. Only one paraffin block from the 24-year-old White female[8] was found in the Department of Pathology at The Ohio State University, Wexner Medical Center, Columbus, OH. We studied the tumor tissue to determine if the tumor cells positively react to specific and high titer antisecretin sera[18,19] and to determine if the gene encoding human secretin can be detected to determine whether this may have been the factor responsible for watery diarrhea in this patient. We have also reviewed relevant literatures to assess secretin as a potential diarrheogenic hormone.

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MATERIALS AND METHODS

Materials

The paraffin embedded tissue block of the index tumor was studied and compared with a known VIPoma as a control and adjacent normal pancreas identified at the same institution in 2003. The latter patient presented with severe watery diarrhea and hypokalemia, a serum fasting VIP of 598 pg/mL (normal range: 0–84 pg/mL), gastrin of 152 pg/mL (normal range: 0–100 pg/mL), and pancreatic polypeptide of 745,000 pg/mL (normal: <500 pg/mL).

Immunohistochemical Studies

Two rabbit antisecretin sera were employed for the study. Peroxidase immunohistochemical staining was performed to examine the expression of secretin and VIP. Briefly, paraffin embedded tissue was sectioned (4mm) and placed on positively charged slides. The slides were then placed in a 60°C oven for 1 hour, cooled, deparaffinized, and dehydrated through graded solutions of increasing ethanol concentration in water and xylene. All slides were quenched for 5 minutes in a 3% hydrogen peroxide aqueous solution to block for endogenous peroxidase. Antigen retrieval was performed by heat-induced epitope retrieval (HIER), in which the slides were placed in a 1X solution of Target Retrieval Solution (Dako, S1699) for 25 minutes at 96°C using a vegetable steamer (Stanley Black & Decker, New Britain, CT) and cooled for 15 minutes in solution. Slides were stained with the Intellipath Autostainer Immunostaining System (Biocare Medical, LLC, Concord, CA). All incubations on the autostainer were performed at room temperature.

The primary antibodies were diluted with an antibody diluent (Dako North America, Inc., Carpinteria, CA) at the following dilutions: VIP (1:18,000; Abcam, Cambridge, MA) and secretin (1:1,500; Chey et al[18]). The specific antisecretin serum was raised in rabbits and characterized as described previously.[19] Tumor tissue was incubated with each antibody for 60 minutes. MACH 3 Rabbit HRP-Polymer (Biocare Medical, M3R531L) was applied twice for 20 minutes each. Staining was visualized with the liquid DAB+ chromogen (Dako, K346811) using a 5-minute development. Slides were counterstained in Richard Allen hematoxylin, dehydrated through graded ethanol solutions, cleared with xylene, and coverslipped. Positive and negative controls were stained appropriately.

Immunofluorescence histochemistry studies were performed also on both tumor and normal pancreatic tissue samples using specific primary antibodies and fluorescence tagged secondary antibodies as described previously.[20,21] In brief, the paraffin sections were deparaffinized followed by heat-induced epitope retrieval. After blocking, the sections were incubated in primary antibodies: secretin (1:50; Abcam) and VIP (1:500; Abcam). Fluorescence tagged secondary antibody detection and counterstaining was performed with Alexa Fluor 488 or 568 secondary antibodies (1:200, Life Technologies, Grand Island, NY) as described previously.[21]

Laser Capture Microdissection and Pressure Catapulting (LMPC)

Paraffin embedded normal pancreatic tissues and tumor tissues were stained using quick hematoxylin and eosin staining method and used for RNA isolation and subsequent reverse

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transcription polymerase chain reaction (RT-PCR) to measure the expressions of secretin and VIP transcripts. Briefly, 5μm sections from formalin fixed paraffin embedded pancreas sections were placed on UV-treated thermoplastic (polyethylene napthalate)-covered glass slide (PALM Microlaser Technologies AG, Bernreid, Germany) followed by incubation in a 50°C oven for 2 minutes. The sections were immediately deparaffinized, stained, and dehydrated. After dehydration, cells of interest were captured using LMPC. LMPC was performed using the laser microdissection system from PALM Technologies (Carl Zeiss MicroImaging GmbH, Germany) containing a PALM MicroBeam and RoboStage for high-throughput sample collection and a PALM RoboMover (PALM Carl Zeiss MicroImaging GmbH) as described.[22–24] Approximately $1 \times 10^6 \mu m^2$ of tissue area from normal or tumor tissues were captured (Fig. 1). Typical settings used for laser cutting were UV energy of 56–65 and UV focus of 80.[23] Cut elements were catapulted into 25μL of the extraction buffer from Arcturus Paradise Extraction and Isolation kit (Applied Biosystems, Foster City, CA). Upon completion of microdissection, the captured material was spun down into a 0.2 mL PCR tube and the extract was then held at 80°C until RNA isolation.

RNA Isolation and Real-time PCR Analysis

Laser capture microdissection captured tissue elements in extraction buffer were incubated at 37°C for 16 hours. After incubation, the total cellular RNA was isolated using Arcturus Paradise Extraction and Isolation kit (Applied Biosystems) and purified RNA was digested with amplification grade deoxyribonuclease I (DNase I; Invitrogen, Carlsbad, CA) for 15 minutes at room temperature to remove any genomic DNA contamination. The purified RNA was used to synthesize cDNA via the Reverse Transcription System using Superscript Vilo cDNA synthesis kit (Invitrogen). RT-PCR was done using SYBR Green PCR Master mix (Thermo Fisher Scientific, Waltham, MA) as described earlier.[23] The following primers were used for the amplification of human secretin and VIP transcripts, respectively:

Secretin [GenBank accession number NM_021920.2]

5′-CTG GAT GCC CCT GGA CGG GA-3′

5′-CTC TCC CCC ATC CTG CCC CC-3′

VIP [GenBank accession number NM_003381.3]

5′- TGA GAA GCA CCA GCA GGC AGT −3′

5′- TGT GCC TCT CGC CCA GTC GT −3′

Statistics

The expression levels of secretin mRNA in the index tumor and normal pancreatic tissue were compared using Student's *t* test. The VIP mRNA levels were compared among the index tumor, normal pancreatic tissue, and an established VIPoma tissue using analysis of variance and post hoc analysis of Newman and Keuls. Any difference with $P < 0.05$ was regarded as statistically significant.

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RESULTS

Abundant Presence of Secretin in Index Tumor

Sections of the tumor show a well differentiated tumor with a pushing border, composed of cells arranged in nests, acini, and a trabecular pattern. The cells are polygonal with oval to round nuclei containing coarsely stippled chromatin and inconspicuous nucleoli. The cytoplasm was eosinophilic and moderately abundant. No necrosis was present and mitotic figures were not identified (Fig. 2A). The tumor exhibited very strong immunohistochemical expression of secretin throughout the tumor (Fig. 2B). No secretin-like immunoreactivity was detected in the adjacent normal pancreatic tissue (not shown). Some VIP-positive cells were also detected in the tumor tissue; however, staining was much less intense than that with secretin (Fig. 2C). This might have been attributable to cross-reaction to secretin, as the same antiserum used was also able to stain a few human duodenal mucosal cells not expected to contain VIP (not shown). Nevertheless, the anti-VIP serum clearly detected VIP-like immunoreactivity in a typical VIPoma tissue (Fig. 2D). Similarly, in the immunofluorescent study with another antisecretin serum (Abcam), abundant secretin was detected in the index tumor tissue (Fig. 3A). On the other hand, both the VIPoma tissue (Fig. 3B) and the adjacent normal pancreatic tissue (not shown) showed no secretin immunoreactive cells. Numerous VIP-positive cells were found in the VIPoma tissue (Fig. 3C). The adjacent normal pancreatic tissue was all VIP deficient (not shown), while the index tumor stained weakly and sparingly with anti-VIP serum (Fig. 3D), much less in number than those by immunohistochemical staining (Fig. 2C).

Abundant Secretin mRNA and Markedly Low VIP mRNA in the Index Tumor

To address any concerns there may be with antisera specificity, gene expression was quantified in the index tumor tissue. The index tumor and adjacent normal pancreatic tissue sections were subjected to LMPC (Fig. 1) and the RNA extracts were subjected to RT-PCR to determine mRNA levels. As shown in Figure 4A, the index tumor expressed abundant secretin mRNA, far exceeding the background level seen in the adjacent normal pancreatic tissue. On the other hand, VIP mRNA in the index tumor was detected in much lower level than that detected in the VIPoma tissue, and was not significantly different from that detected in the adjacent normal pancreatic tissue (Fig. 4B). These results establish that the source of secretin detected in the index tumor tissue was endogenous.

DISCUSSION

The index tumor tissue exhibited numerous cells containing immunoreactive secretin and significantly higher secretin mRNA than that in normal human pancreas, whereas neither was found in a control VIPoma. Furthermore, when compared with the control VIPoma, VIP mRNA expression in the index tumor was scanty. In the VIPoma, secretin gene expression was at lower detection limits. The surgical resection of the index tumor from the pancreas resulted in a complete cessation of WDS and resumption of normal gastric acid secretion, indicating that both watery diarrhea and suppressed gastric acid secretion were attributable to secretin in humans.[11] Moreover, the patient remained asymptomatic for at least 18 years. The results of our studies and the information obtained from the studies on a subsequent

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patient with metastatic PNET with very high plasma immunoreactive secretin,[14] strongly suggest that some patients with WDS could be attributable to a high circulating secretin level. Such a tumor could be more appropriately termed a secretinoma. The patients described exhibited the well-recognized biological effects of secretin including inhibition of gastric acid secretion,[11] stimulation of biliary and pancreatic secretion of water and bicarbonate,[10,13,25] diversion of bile into the gallbladder and relaxation of the gall bladder,[26] and inhibition of small intestinal motility with resultant dilatation of the duodenum and proximal jejunum[17] (Table 1). To our knowledge, this is the first patient with WDS and strong molecular evidence of a primary pancreatic secretinoma in the relative absence of the other well-known diarrheogenic hormone, VIP.

Secretin as a Diarrheogenic Hormone

The following clinical and experimental observations in humans suggest strongly that circulating secretin in excessive amounts can cause watery diarrhea and disordered intestinal mucosal transport of water and certain electrolytes.

Pancreatic Hypersecretion of Water and Bicarbonate in a Patient With WDS—

A 26-year-old White male with a malignant PNET and severe WDS reported by Schmitt et al[14] exhibited daily fecal liquid volume in excess of 14,000 mL. The pH and bicarbonate concentration of fecal liquid were as high as 8.79 and 104 mEq/L, respectively. These values remain the highest ever been reported in patients with WDS in the literature, reflecting a marked pancreatic hypersecretion of bicarbonate. His spontaneous pancreatic secretion collected by duodenal aspiration of fluid for volume and bicarbonate was as much as 557 mL/h and 54.9 mEq/h, respectively. These values were comparable to the maximum pancreatic secretion of water and bicarbonate of human volunteers produced by IV infusions of secretin at doses of 10 to 25 clinical units/kg/h[27] (Fig. 5), indicating that the patient's pancreas was secreting water and bicarbonate at the maximum rate driven by circulating endogenous secretin at high concentration. Thus, his daily pancreatic secretion of water and bicarbonate were estimated to be over 13,000 mL and 1317.6 mEq, respectively. Importantly, the patient had plasma immunoreactive secretin level of 5000 pg/mL, the highest value ever been reported.[11,14] His frozen pancreatic tumor was loaded with immunoreactive secretin cells,[14] coincided with a high content of immunoreactive secretin, 10 ng/gm of the tissue. Moreover, constant nasogastric aspirations of voluminous, lightly bile-stained gastric fluid because of frequent duodenalgastric reflux of duodenal fluid resulted in cessation of massive watery diarrhea, suggesting strongly that overload of biliary-pancreatic fluid in the small and large intestine contributed mainly the development of watery diarrhea. Although plasma VIP level was elevated, VIP is not a potent agonist of pancreatic secretion. Rather it is a partial agonist[28] as the maximal bicarbonate secretion in response to VIP is 17% of that achieved by secretin in dogs and the potency is about 1/100 of secretin in perfused pig pancreatic preparations.[29] This is in agreement with observations that in patients with classic WDS and elevated plasma VIP[30] and 2 patients with documented VIPoma (Chey and Chang, unpublished observation), basal and secretin-stimulated pancreatic secretions were normal.

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Pancreatic Hypersecretion of Fluid Rich in Bicarbonate by IV Secretin Can Cause Watery Diarrhea—In dose-response studies of secretin on pancreatic secretion of water and electrolytes in humans with IV secretin at doses 10 to 25 clinical units/kg/h, Wormsley[27] found 4 volunteer subjects experiencing explosive, painless watery diarrhea within 1 hour after stopping both IV secretin, and aspiration of duodenal fluid. In another study, Tompkins et al[13] reported 1 patient with T-tube in the common bile duct developed explosive watery diarrhea after receiving an IV bolus injection of secretin even at one clinical unit/kg without aspiration of duodenal fluid. This dose of IV secretin in bolus injection can raise plasma secretin level as high as over 1000 pg/mL[16] that is about one hundred times higher than the postprandial plasma secretin level in humans[11] or in dogs.[11]

Effect of Secretin on the Small Intestinal Mucosal Transport of Water and Electrolytes in Humans

Secretin in Pharmacologic Doses Causes Abnormal Jejunal Mucosal Transport of Water and Electrolytes in Humans—Using a triple lumen tube perfusion technique,[31] Sanzenbacker et al[12] found in normal healthy volunteers that IV secretin at 4 clinical units/kg/h caused an excessive secretion of water, sodium, and potassium into the jejunal lumen. In similar studies in human volunteers,[32,33] IV bolus injection of secretin at 1 or 2 clinical units/kg significantly inhibited jejunal absorption of water and sodium.

Secretinoma

There have been at least 6 patients with WDS,[8,12,14,30,34] who may be characterized as possible secretinomas. All were reported to exhibit dilated gallbladders with dilute bile. This finding may be an important clinical distinguishing feature between causes of WDS (Table 1). No known gut hormone or peptide other than secretin stimulates bile secretion as potently as secretin or cause dilation of the gallbladder. The potency of VIP stimulating bile secretion is about one-fourth of that of secretin in humans.[35] Table 1 summarizes clinical and laboratory evidence supporting secretin as a diarrheogenic hormone. The major pathophysiologic features of the various diarrheogenic hormones are compared in Table 2.

The actual incidence of secretinoma as a cause of WDS, however, cannot be known as plasma secretin levels have been rarely measured in patients with WDS. Moreover, because the majority of VIPoma of the pancreas contain more than one peptide,[36,37] it is not known how many of them have secretin-producing tumor cells coexisting with VIP-producing cells in patients with WDS. When the two peptides coexist in the same tumor, patients may produce more severe WDS than those with either VIP or secretin alone.

We realize that there were limitations in the interpretation of the present investigation. First, there was no measurement of plasma secretin. This is the sine qua non to establish a hormone as potentially causing a clinical syndrome. The case reported and studied, predated to secretin radioimmunoassay. Secretin level may have been elevated had it been measured. Second, a bioassay using a tumor extract of the index patient did not elicit a secretin effect on bile and pancreatic secretion in dogs. The inactivity of the tumor extract might be explained as noted by Zollinger et al,[8] “on the basis of a limited amount of starting material

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for extraction”…or “differences in extract activity as a variation in the activity of the tumors themselves.” Third, although a positive immunochemical staining may not always be associated with a clinical syndrome, the presence of abundant secretin mRNA in index tumor is a specific evidence that genuine secretin was present. Moreover, the physiologic characteristics observed strongly support secretin as the causative hormone. Finally, we did not perform immunohistochemical staining the tumor for gastrin. Gastrinoma is highly unlikely given the basal achlorhydria, return of acid secretion after the tumor removal and the negative bioassay reported in the original paper.

In conclusion, Zollinger et al[8] seemed to be correct in their initial hypothesis that secretin was the cause of their patient’s WDS. The supporting evidence is threefold: (i) the positive secretin-like effect on basal bile electrolyte concentrations, resolution of achlorhydria after tumor resection, and the marked gallbladder distention in the absence of biliary obstruction in the index case, (ii) strongly positive immunohistochemical staining for secretin, and (iii) the presence of abundant secretin mRNA in the index tumor.

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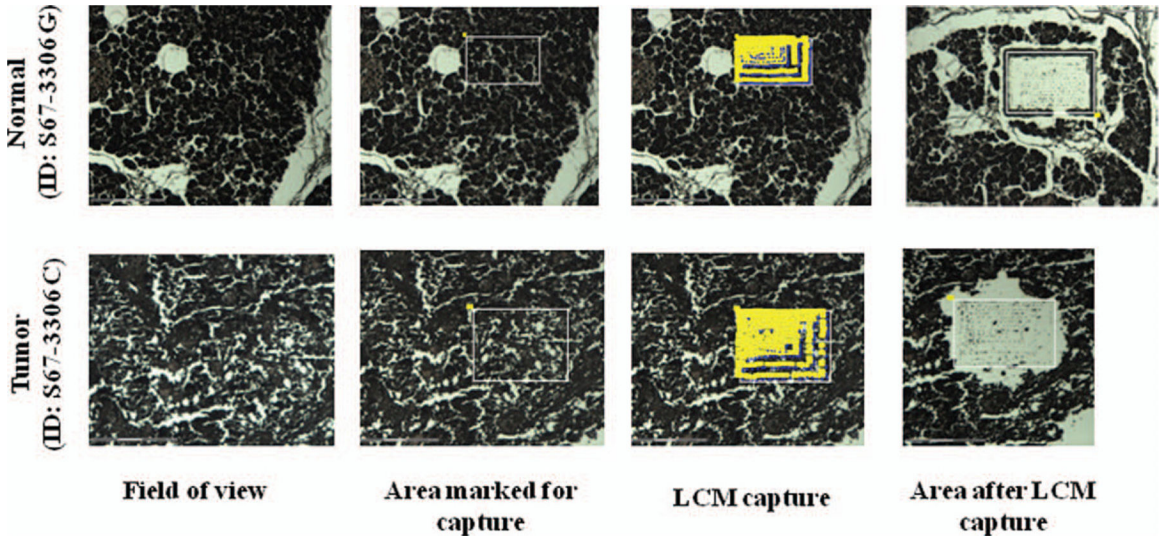

FIGURE 1.

Laser capture microdissection (LCM) of normal and pancreatic tumor tissue for RT-PCR studies. From left to right the panels represent normal pancreatic tissue (upper panels) or tumor tissue (lower panels) before and after marking for capture and catapult, laser-assisted cutting and separation of the identified area, and the tissue section after elements have been catapulted, respectively.

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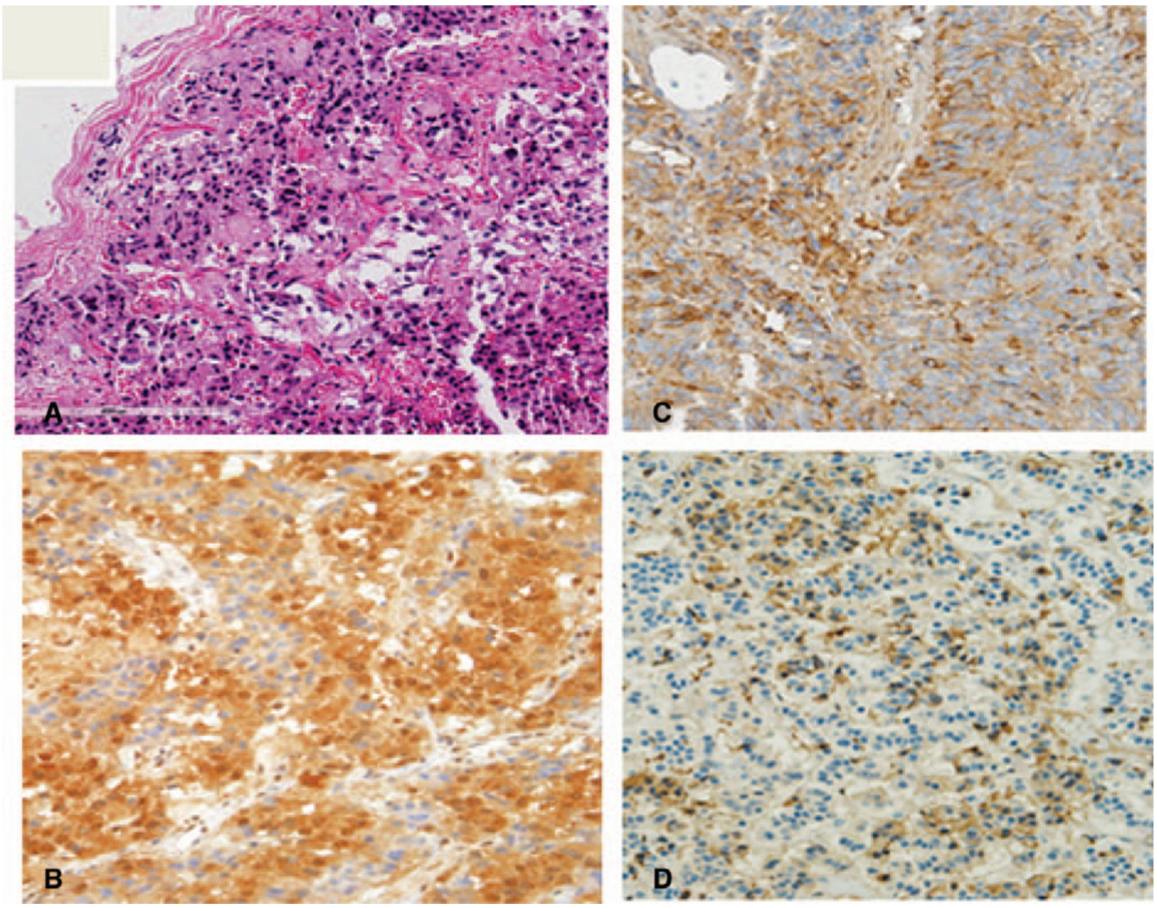

FIGURE 2.

Histochemical and peroxidase immunohistochemical staining of pancreatic tumor tissues. A, H&E stain of the index tumor. B, secretin-like immunoreactivity in the index tumor. C, VIP-like immunoreactivity in the index tumor. D, VIP-like immunoreactivity in a confirmed VIPoma tissue.

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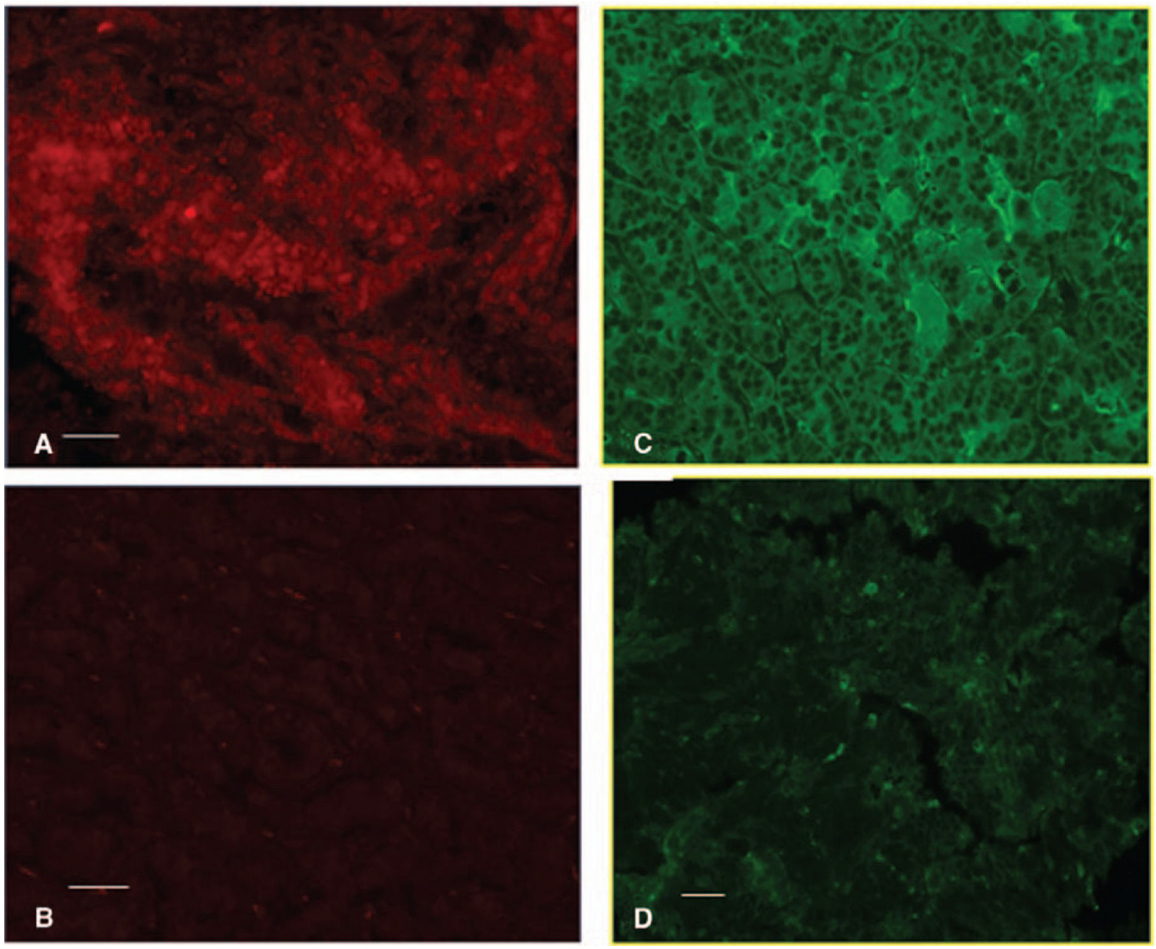

FIGURE 3.

Immunofluorescence staining of the index tumor and VIPoma tissues with antisecretin and anti-VIP sera. A, Secretin-like immunoreactivity was detected (red fluorescence) in the index tumor but not in a VIPoma tissue (B). C, VIP-like immunoreactivity (green fluorescence) was strongly positive in a VIPoma tissue. D, the index tumor displayed VIP-positive cells sparingly.

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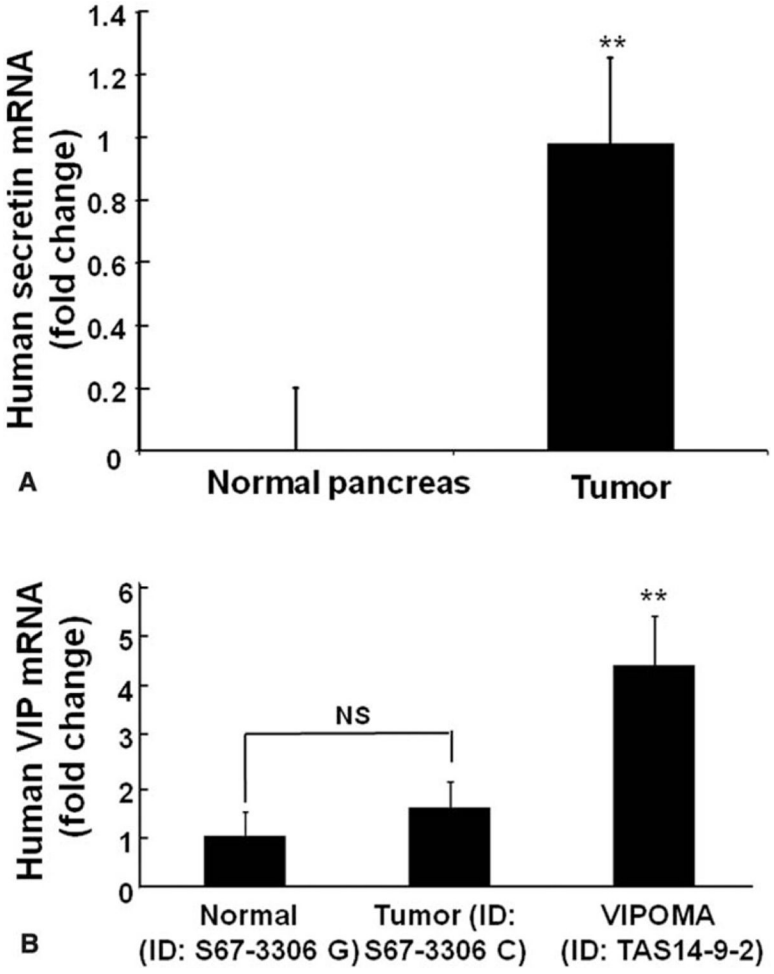

FIGURE 4.

Comparison of secretin and VIP mRNA levels in normal pancreatic and tumor tissues. A, Comparison of secretin mRNA level in normal pancreatic tissue to that found in the index tumor. The data represent mean ± SE determined from 5 captured tissue sections. The symbol ** denotes significant difference between the expression levels of normal and tumor tissue with $P < 0.01$. B, Comparison of VIP mRNA levels in normal pancreatic tissue, index pancreatic tumor, and a VIPoma. Data represent mean ± SE determined from 5 captured tissue sections. The symbol ** indicates $P < 0.01$, showing significant different levels between the VIPoma and normal pancreatic tissues. NS denotes not significantly different.

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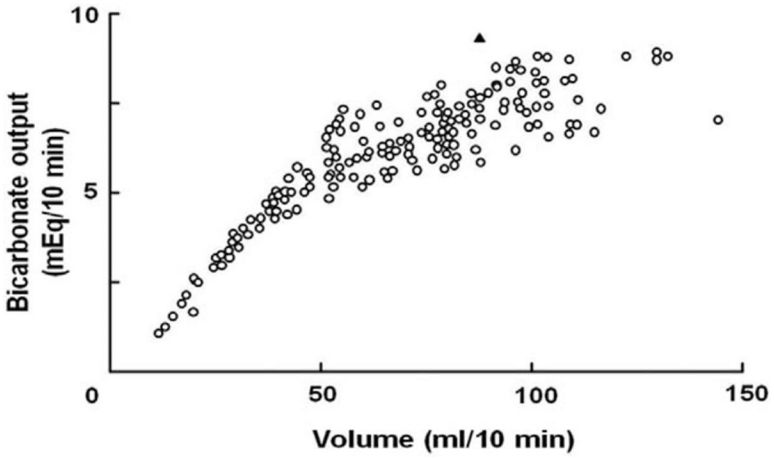

FIGURE 5.

Spontaneous pancreatic secretion of bicarbonate and water in a 26-year-old WDS patient[14] with very high plasma secretin level (5000 pg/mL) (shown in the filled triangle) in comparison with maximum pancreatic secretion (shown in circles) achieved by increasing pharmacologic doses of secretin in human volunteers.[28]

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TABLE 1.

Clinical and Laboratory Evidences Supportive for Secretin as a Potential Diarrheogenic Hormone

Clinical Observations	Experimental Observations
Pancreatic non-beta islet cell tumor with WDS[8,11,14]	Tumor extracts stimulate canine pancreatic-biliary H2O and HCO_3^- secretion[8,11,12]
Spontaneous maximum pancreatic hyper-secretion of water and bicarbonate[14]	Marked elevation of secretin level in plasma in a WDS patient[14]
Dilated duodenum[8,14] continually refilled with fluid during laparotomy[8]	Secretin in pharmacologic dose causes watery diarrhea in humans[13,27]
Markedly distended gallbladder[8,12,14,30,34] with high bicarbonate concentration in bile[8]; Achlorhydria[8,11] or hypochlorhydria[14]	Tumor[8,14] contains many secretin cells; and expresses secretin mRNA, but no VIP mRNA (present study)
Tumor removal ceased WDS[8] and gastric acid secretion returned[8]	

The superscript numbers indicate reference numbers.

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TABLE 2.

Action Mechanisms of Diarrheogenic Hormones

Action	VIP	Gastrin	Secretin
Gastric hypersecretion[a]	No	Yes	No
Pancreatic/biliary hypersecretion[b]	No	No	Yes
Intestinal secretion[c]	Yes	Yes	Yes
Intestinal absorption: suppression[d] or abolition[e]	Yes[e]	Yes[d]	Yes[d]
Colonic absorption: suppression[f] or abolition[g]	Yes[g]	No	NT

Superscripts indicate changes in:

a: H_2O, HCl, Na^+

b: H_2O, $NaHCO_3$

c: H_2O, Na^+, Cl^-

d,e: H_2O, Na^+

f,g: H_2O, Na^+

NT: not tested.