Pancreatic phospholipase A$_2$ from the small intestine is a secretin-releasing factor in rats

JAMES P. LI, TA-MIN CHANG, DAVID WAGNER, AND WILLIAM Y. CHEY
Konar Center for Digestive and Liver Diseases, University of Rochester Medical Center, Rochester, New York 14624

Received 3 April 2000; accepted in final form 10 April 2001

Pancreatic phospholipase A$_2$ from the small intestine is a secretin-releasing factor in rats. Am J Physiol Gastrointest Liver Physiol 281: G526–G532, 2001.—A secretin-releasing activity exists in the upper small intestine and pancreatic juice in the rat and the dog. Group I pancreatic phospholipase A$_2$ (PLA$_2$) in canine pancreatic juice and porcine pancreatic PLA$_2$ stimulate the release of secretin from both STC-1 cells and a secretin-producing cell (S cell)-enriched preparation isolated from rat duodenal mucosa. We investigated the distribution and release of pancreatic PLA$_2$-like immunoreactivity in the gastrointestinal tract and the role of PLA$_2$ on the release of secretin and pancreatic exocrine secretion in response to duodenal acidification in anesthetized rats. PLA$_2$-like immunoreactivity was detected in the mucosa throughout the gastrointestinal tract. High concentrations of PLA$_2$ were found in both the small intestine and the pancreas. Duodenal acidification significantly increased the release of PLA$_2$ from the upper small intestine (385% over basal secretion). Intravenous infusion of an anti-PLA$_2$ serum (anti-PLA$_2$) dose-dependently inhibited the release of secretin and pancreatic exocrine secretion in response to duodenal acid perfusion. Preincubation of the concentrate of intestinal acid perfusate (10-fold) from donor rats with the anti-PLA$_2$ significantly suppressed its stimulation of secretin release and pancreatic exocrine secretion in recipient rats. We conclude that pancreatic PLA$_2$ also functions as a secretin-releasing factor in the small intestine that mediates acid-stimulated release of secretin in rats.

SECRETIN IS A major gut hormone that regulates pancreatic water and bicarbonate secretion (9, 10, 14). Secretin is released from S cells of the upper small intestine in response to luminal stimuli, including gastric acid, fatty acid, bile salts, and other dietary elements (10). Some neuropeptides and neurotransmitters, such as pituitary adenylate cyclase-activating polypeptide (PACAP; see Ref. 27), gastrin-releasing peptide (GRP; see Ref. 30), or serotonin (29), also stimulate or are involved in the release of secretin. It has been reported that secretin-releasing peptides exist in both the upper small intestine (31) and pancreatic juice (32) to mediate the release of endogenous secretin in the dog (42) and rat (32). Chang et al. (8) have purified two secretin-releasing factors (SRFs) from canine pancreatic juice. Both are 14-kDa polypeptides that are structurally homologous to canine pancreatic phospholipase A$_2$ (PLA$_2$). These two secretin-releasing peptides (8) and purified porcine pancreatic PLA$_2$ (4) were found to stimulate secretin release from STC-1 cells and S cell-enriched cell preparations isolated from rat duodenal mucosa. However, it has not been studied whether the secretin-releasing peptide activity in the small intestine is attributed to PLA$_2$.

It has become evident that PLA$_2$ are a heterogeneous family of lipolytic enzymes that can be classified into at least five subtypes of mammalian origin (12). Group I, II, and III PLA$_2$ are low-molecular-weight PLA$_2$ of 14 kDa referred to as secretory, extracellular enzymes. Group IV PLA$_2$ are high-molecular-weight PLA$_2$ of 60–110 kDa referred to as cytosolic PLA$_2$, whereas bee venom PLA$_2$ constitute the group V enzyme. Recent data have indicated that PLA$_2$ play a number of important roles in cells and tissues (13). Pancreatic PLA$_2$ belongs to the group I PLA$_2$ and plays a central role in the digestion of dietary and biliary phospholipids. It is also involved in stimulation of cell growth (15), contraction of smooth muscle (41), and regulation of progestosterone (39) and prostaglandin (44) release. We hypothesized that PLA$_2$ may function as a modulator of intestinal endocrine cells to play an important role in stimulation of secretin release in the rat.

The aim of the present study was to investigate the distribution of phospholipase A$_2$-like immunoreactivity (PLA$_2$-LI) in the gastrointestinal tract and the pancreas, the release of PLA$_2$ from the upper small intestine and pancreas after duodenal perfusion of acid, the effect of a specific anti-PLA$_2$ serum (anti-PLA$_2$) on pancreatic exocrine secretion and the release of secretin in response to duodenal acidification, and the effect of the antibody on SRF activity in duodenal acid perfusate in anesthetized rats.

MATERIALS AND METHODS

Animal preparation. Male Sprague-Dawley rats weighing between 220 and 280 g were fasted for 24 h with free access to drinking water before surgery. Under anesthesia with...
intrapertoneal injection of 25% urethane at a dose of 120 mg/100 g body wt, a midline abdominal incision was made. A polyethylene tube (ID 3.0 mm, OD 4.0 mm) for duodenal infusion was inserted in the proximal duodenum 5 mm distal to the pylorus through the stomach followed by ligation of the pylorus. A jugular vein catheter was prepared with a polyethylene tube (PE-10, ID 0.58 mm, OD 0.96 mm). The tube was kept patent by infusion of 0.15 M NaCl at a rate of 1 ml/h. In the donor-recipient study, a 20-cm upper small intestinal loop was made by placing an additional cannula (ID 3.0 mm, OD 4.0 mm) in the jejunum 15 cm distal to the ligament of Treitz for collection of the perfusate. A polyethylene tube (PE-10, ID 0.28, OD 0.61 mm) was inserted in the pancreatic duct via the ampulla for collection of pancreatic juice. A second PE-10 tube was inserted in the bile duct proximal to the pancreatic duct for diversion of bile to the exterior. The abdominal wound was covered by a piece of wet gauze soaked with isotonic saline.

Experimental design. Experiments were performed 30 min after surgery. After 90-min collection of basal pancreatic secretion, 0.02 N HCl in saline was infused intraduodenally at a rate of 4.5 ml/h for 60 min in five rats. To study the effect of anti-PLA2 on acid-induced pancreatic exocrine secretion and the release of secretin, anti-PLA2 at 0.1, 0.3, and 0.5 ml/rat was injected via the jugular vein 30 min before duodenal infusion of acid in five rats each. Normal rabbit serum (NRS) was injected intravenously at 0.5 ml/rat before intraduodenal infusion of 0.02 N HCl began in five rats as controls. The antibody used in this experiment was the same as the one used for RIA for PLA2 described below. In the donor-recipient study, the upper small intestinal loop was washed with 40 ml of warm 0.15 M NaCl followed by perfusion of the loop with 0.02 N HCl at 0.3 ml/min for 1.5 h while both bile and pancreatic juice were diverted. The acid-perfusate was continuously collected from the jejunal cannula in an ice-chilled beaker and then centrifuged at 3,000 g and 4°C for 25 min. The supernatant solution was lyophilized and concentrated 10-fold, adjusted to pH 7.0, and then incubated with anti-PLA2 or NRS (1:10) at 37°C for 30 min. The materials were further filtered through an Amicon PM-10 membrane (Grace, Danvers, MA) to remove the antibody and antibody-antigen complex. The filtrate was reinfused in the upper small intestine of recipient rats after a 90-min collection of basal pancreatic secretion.

To determine the release of PLA2-LI by duodenal acidification, an aliquot of 2 ml of the perfusate collected during the basal period or duodenal acid perfusion was mixed with 0.1 ml of 2% BSA in saline and stored at –20°C before determination of PLA2-LI by RIA. To determine if PLA2 has different susceptibility in the duodenal lumen during saline and acid perfusion, porcine pancreatic PLA2 at a concentration of 1 ng/ml was added to perfusion solution of saline or acid. After a 30-min perfusion with saline alone in the basal period, PLA2 in saline, HCl alone, or PLA2 with or without HCl was perfused intraduodenally in three groups of three rats each as described above. The perfusate was collected during basal and experimental periods in 30-min intervals. The perfusate was treated and stored as described below for RIA of PLA2.

To determine the distribution of PLA2 in the gastrointestinal tract, five rats were killed by cervical dislocation after 24 h of fasting. The stomach, duodenum, jejunum-ileum, colon, and pancreas were immediately taken and washed separately with 0.15 M NaCl at 4°C. Each tissue was homogenized in 5 vol of 10 mM Tris•HCl, pH 7.4, at 4°C using a Polytron at maximum output for 30 s. The homogenate was centrifuged at 108,000 g for 1 h at 4°C. The supernatant solution was stored at −70°C for RIA of PLA2.

RIA of PLA2. RIA of PLA2 was carried out using a specific anti-PLA2 serum raised in our laboratory. The antiserum was raised in New Zealand White rabbits by immunization with purified porcine pancreatic PLA2 (4) emulsified in Freund’s adjuvant and boosted monthly with the enzyme emulsified in Freund’s incomplete adjuvant (5, 6). After five booster injections, the titer of the antibody increased to 1:10⁶. The antibody is specific for PLA2-I and has no cross-reaction with any known gastrointestinal regulatory peptides or islet hormones, including rat secretin, CCK-8, human gastrin-17-I, glucagon, porcine GRP, insulin, rat pancreatic polypeptide, vasoactive intestinal peptide, and PACAP-38. The competitive tracer-binding curves with standard PLA2 and some of these peptides are shown in Fig. 1. The anti-PLA2 serum also had no cross-reaction with reptilian and bee venom PLA2 (all obtained from Sigma), as shown in Fig. 2. An RIA method was developed using purified porcine pancreatic PLA2 as the standard. Purified PLA2 (5 μg) was radioiodinated using the chloramine T-catalyzed method (19). The labeled enzyme was
then purified by gel filtration through a Sephadex G-50 superfine column (1.3 x 58 cm) run in 50 mM sodium phosphate, pH 7.5, containing 0.15 M NaCl, 0.5% BSA, and 0.02% NaN₃. Purified ¹²⁵I-labeled PLA₂ had a specific activity of 260.6 μCi/nmol. The sample or standard was incubated with anti-PLA₂ (at 1:10⁶ dilution) and the pellet (containing anti-PLA₂) was吹vaped at 1,650 g for 1 h with occasional mixing and then was centrifuged at 1,650 g for 30 min. The supernatant solution (containing free PLA₂ counts) and the pellet (containing antibody-bound PLA₂ counts) were separated, and both were counted in a Wallac model 1271 gamma counter with automatic data reduction using the RIACALC software provided by the manufacturer. The assay has a minimum detection limit of 10 pg PLA₂ and intra- and interassay variations of 7% and 9%, respectively.

Determination of pancreatic secretion and plasma concentration of secretin. Pancreatic juice was collected continuously by inserting the pancreatic duct cannula in a glass micropipette (Drummond Scientific, San Francisco, CA) in 30-min intervals. The volume of the fluid retained in the micropipette was obtained and stored at −70°C. Plasma secretin level was determined by RIA method described previously (6).

Data analyses. All values were expressed graphically as means ± SE. The percentage (%) increase in pancreatic secretion over the basal value was calculated by comparison between the values obtained in the last 60-min treatment period and the last 60-min basal period. The statistical differences in these data were analyzed using one-way ANOVA. Tukey’s post hoc test was applied for multiple comparisons of the means. A difference between two means with P values of <0.05 is regarded as statistically significant.

RESULTS

Distribution and release of PLA₂ in the gastrointestinal tract and the pancreas. RIA of PLA₂ in the tissue extracts indicated that PLA₂ distributed throughout the gastrointestinal tract and the pancreas (Table 1). The contents of PLA₂ in the pancreas and the small intestine were similar, although PLA₂ in the duodenum was slightly less than that in the jejunum-ileum and the pancreas. PLA₂ in the stomach and the colon was much less compared with that in the pancreas and the small intestine.

Perfusion of the upper small intestinal loop with 0.02 N HCl significantly increased the concentration of PLA₂ in the intestinal perfusate (from 0.42 ± 0.04 to 1.49 ± 0.63 ng/ml, n = 5, P < 0.05; Fig. 3). When PLA₂ in saline was perfused intraduodenally, there was no statistically significant difference in the apparent recovery of the exogenous PLA₂. Similarly, the average concentration of PLA₂-LI found in the perfusate of PLA₂ with

Table 1. Pancreatic PLA₂-like immunoreactivity in the gastrointestinal tissue and the pancreas of rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>PLA₂-Like Immunoreactivity, ng/g tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.91 ± 0.16</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1.59 ± 0.41</td>
</tr>
<tr>
<td>Jejunum + ileum</td>
<td>2.79 ± 0.39</td>
</tr>
<tr>
<td>Colon</td>
<td>0.50 ± 0.14</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.70 ± 0.39</td>
</tr>
</tbody>
</table>

Values are means ± SE of 5 rats in each tissue. Phospholipase A₂ (PLA₂)-like immunoreactivity was determined by RIA.

Table 2. Stability of porcine pancreatic PLA₂ perfused through the duodenum

<table>
<thead>
<tr>
<th>Condition</th>
<th>PLA₂-LI in Perfusate, ng/ml</th>
<th>Increase Over Basal or Control, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal (saline)</td>
<td>0.12 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Saline + PLA₂</td>
<td>1.05 ± 0.14</td>
<td>0.93</td>
</tr>
<tr>
<td>Diluted HCl</td>
<td>1.10 ± 0.21</td>
<td>0.98</td>
</tr>
<tr>
<td>Diluted HCl + PLA₂</td>
<td>2.08 ± 0.20</td>
<td>0.98*</td>
</tr>
</tbody>
</table>

Values represent means ± SE for 9 perfusate samples. PLA₂-LI, PLA₂-like immunoreactivity. Perfusion of PLA₂ in saline and in HCl had no significant difference in the apparent recovery of the exogenous PLA₂. *Increase over HCl control.

Perfusion of the upper small intestinal loop with 0.02 N HCl significantly increased the concentration of PLA₂ in the intestinal perfusate (from 0.42 ± 0.04 to 1.49 ± 0.63 ng/ml, n = 5, P < 0.05; Fig. 3). When PLA₂ in saline was perfused intraduodenally, there was no time-dependent decrease in PLA₂ immunoreactivity in the perfusate. As shown in Table 2, the average concentration of PLA₂-LI of the nine samples collected was 1.05 ± 0.14 ng/ml, which was 0.93 ng/ml above the average basal concentration, indicating a 93% recovery of the exogenous PLA₂. Similarly, the average concentration of PLA₂-LI found in the perfusate of PLA₂ with

Fig. 3. Release of pancreatic PLA₂ from the upper small intestine (A) and the pancreas (B) in response to duodenal acidification. Basal, basal PLA₂ level after 24 h of fasting; HCl, 0.02 N HCl (4.5 ml/h id). Upper small intestinal acid perfusate and pancreatic juice were continuously collected for 60 min during acid perfusion. PLA₂ levels were determined by RIA. Values are means ± SE of 5 rats in each group. *P < 0.05 compared with basal values.

AJP-Gastrointest Liver Physiol • VOL 281 • AUGUST 2001 • www.ajpgi.org
Pancreatic PLA2 antibody at 0.1, 0.3, and 0.5 ml/rat or normal rabbit serum (NRS) at 0.5 ml/rat was injected iv 30 min before infusion of 0.02 N HCl id for 1.5 h. Pancreatic exocrine secretion in the last 60 min was compared with basal secretion in 60 min. A: volume. B: bicarbonate output. Values are means ± SE from 5 rats in each group. *P < 0.05 and **P < 0.01 vs. basal pancreatic secretion.

or without HCl (2.08 ± 0.20 ng/ml) was 0.98 ng/ml over that of the HCl control, corresponding to a 98% recovery of exogenous PLA2. Although acid perfusion did not influence the PLA2 concentration in pancreatic juice (Fig. 3), the output of PLA2 was significantly increased because the volume of pancreatic fluid, as shown in Fig. 4, was markedly elevated (72% over basal secretion) in response to acid.

Effect of anti-PLA2 on pancreatic exocrine secretion and the release of secretin in response to duodenal acidification. Basal pancreatic secretion of fluid (17.6 ± 3.6 μl/30 min) and bicarbonate (0.54 ± 0.14 μeq/30 min) was stable during the study period. Duodenal infusion of 0.02 N HCl significantly increased pancreatic secretion of fluid (73.2 ± 10.7% over basal secretion, P < 0.01) and bicarbonate output (144.1 ± 27.8% over basal, P < 0.01). Intravenous injection of anti-PLA2 at 0.1, 0.3, and 0.5 ml did not influence basal pancreatic exocrine secretion (data not shown) but dose-dependently inhibited the acid-stimulated pancreatic fluid and bicarbonate secretion (Fig. 4). The plasma level of secretin also decreased in a dose-related manner after anti-PLA2 administration (Fig. 5). NRS did not influence either pancreatic secretion or the release of secretin (Figs. 4 and 5).

Pancreatic secretion and release of secretin in response to intestinal acid perfusate with and without preincubation with anti-PLA2 in recipient rats. Intraduodenal administration of intestinal acid perfusate increased pancreatic secretion of fluid volume (72.2 ± 11.3% over basal secretion) and bicarbonate output (140.7 ± 28.9% over basal) and caused an elevation of plasma secretin concentration to 6.2 ± 1.2 pM. To test if PLA2-LI present in the duodenal acid perfusate contributes to this SRF activity (30), the perfusate was preincubated with either NRS or anti-PLA2 and then ultrafiltrated. As shown in Fig. 6, intraduodenal perfusion in the recipient rats of the donor acid perfusate, which was preincubated with NRS, resulted in an increase in plasma secretin concentration to 5.6 ± 0.8 pM and an increase of fluid secretion of 61.5 ± 7.6% and bicarbonate output by 108.7 ± 12.7% over basal. These increases were not significantly different from those produced by the untreated perfusate described above. In contrast, the acid perfusate preincubated with anti-PLA2 failed to elevate plasma secretin concentration (1.5 ± 0.6 pM) and produced only a small increase in pancreatic secretion of fluid volume (10.1 ± 5.1% over basal) and bicarbonate output (44.0 ± 19.0% over basal) in the recipient rats. Thus anti-PLA2-treated perfusate elicited less fluid volume and bicarbonate output by 81.2 ± 8.9 and 62.0 ± 9.9%, respectively, than NRS-treated perfusate.

DISCUSSION

The results of the present study have indicated that pancreatic PLA2 is distributed in the small intestine mucosa and may function as an SRF during duodenal acidification. Our previous studies (28, 31) have shown that duodenal acidification in the rat elicited the release of an SRF activity in the duodenal lumen that can be recovered from the acid perfusate. Infusion of a concentrate of ultrafiltrated duodenal acid perfusate in the duodenum of a recipient rat stimulates the release of secretin and pancreatic exocrine secretion of fluid and bicarbonate. We have demonstrated in the present study that pancreatic PLA2-LI is present in the luminal perfusate, and its concentration is increased upon duodenal acidification in the rat. Because exogenous PLA2 in saline or acid perfused intraduodenally did not result in different recovery of PLA2-LI (Table 2), the increase in PLA2-LI concentration must be the result of an increase in the release of endogenous PLA2. Immuno-neutralization of PLA2 with a specific anti-PLA2 serum result in a significant inhibition of the increases of plasma secretin concentration and pancreatic exocrine secretion of fluid and bicarbonate elicited by duodenal acidification. Pretreatment of the concentrated perfusate from donor rats with anti-PLA2 resulted in a substantial decrease in the SRF activity of the perfusate. The observation suggests that a PLA2-LI in the acid perfusate is a constituent of the SRF activity and thus
corroborates well our previous observations that canine (8) and porcine (4) pancreatic PLA2 stimulate secretin release from secretin-producing cells. The source of the pancreatic PLA2-like SRF appeared to be in the upper small intestine as pancreatic juice was diverted in both donor and recipient rats in the present study. This view is supported by the findings that pancreatic PLA2 is widely distributed in the intestine and is released in the duodenal lumen upon acid perfusion during pancreatic juice diversion. It should be noted that the presence of pancreatic PLA2 in nonpancreatic tissues, including the stomach and the intestine, has been documented previously (25, 37, 40, 45). mRNA for PLA2-I has been detected in the mucosa of human ileum (34) and guinea pig stomach (47). Moreover, luminal secretion of PLA2 activity has been documented in the rat small intestine (1, 2) and guinea pig gastric juice (45). It should be noted that PLA2-LI in the intestinal acid perfusate could not be derived from gastric juice as the pylorus was ligated in the present study. In addition, it is unlikely that the detection of PLA2-like immunoreactivity in the intestinal lumen was the result of mucosal damage because we infused a diluted acid (0.02 N HCl) so that, during acid infusion, the luminal pH was maintained between 3.0 and 4.0 because of duodenal bicarbonate secretion (unpublished observation). Moreover, we have previously shown by electron microscopy in dogs that duodenal perfusion with 0.1 N HCl does not cause mucosal damage (7).

The mechanism of action of pancreatic PLA2 as an SRF is not clear at present. Although a small amount of IgG has been shown to be transported across human jejunal mucosa (22), it is unlikely that a sufficient amount of anti-PLA2 is transported to the intestinal lumen to inhibit the release of secretin and exocrine pancreatic secretion upon duodenal acidification. An alternative explanation is that PLA2 may also be released and acts locally at the basolateral interstitial space of the intestinal mucosa. Our previous study (28) indicated that the release and action of SRF during duodenal acidification are neurally mediated, depending on the vagal afferent pathway. It is possible that, in addition to the release in intestinal lumen, PLA2 is also released locally and acts on mucosal vagal afferent fibers to stimulate secretin release. The presence of a PLA2-specific receptor (11, 26) and action of secretory PLA2 in neurons has been documented (37). On the other hand, luminally released PLA2 may penetrate the intestinal mucosa and acts on S cells directly and/or indirectly through the vagal afferent pathway. The neural action of PLA2, either locally released or derived from the lumen, would then be sensitive to anti-PLA2 that reaches the lamina propria in the intestinal mucosa where mucosal afferent nerve fibers are found. However, these modes of action by PLA2 remain hypothetical and may be tested in our future study.

It is not unusual for pancreatic PLA2 to be involved in the regulation of secretin release. PLA2 is a family of lipolytic enzymes that release fatty acid specifically from the sn-2 position of phospholipids and are classified into several groups according to their primary structures (12, 13, 46). Several important functions have been identified for various PLA2s, including phospholipid digestion and metabolism, host defense, and signal transduction (13). Pancreatic PLA2 is a group I PLA2 and a well-defined digestive enzyme. The results of recent studies have indicated that this enzyme is also present in nonpancreatic tissues (36, 40) and is involved in regulation of other cellular functions, including secretion of progesterone (39), prostaglandin production (44), gene expression of type II PLA2 (24), stimulation of smooth muscle contraction (23, 41), and stimulation of cell proliferation (15–17). Thus our observations that pancreatic PLA2 stimulates secretin release from secretin-producing cells (4, 8) and may function as an SRF (present study) have provided an addition to the functional list of this enzyme. It is not surprising, therefore, that pancreatic PLA2 is involved in the regulation of secretin release.

It should be noted that, based on the results of this study, we could not rule out the possibility that other SRF exist and also play a role in acid-stimulated release of secretin. This is quite analogous to that of CCK-releasing factors in regulation of the release of CCK (35, 38). Two luminal CCK-releasing factors, luminal CCK-releasing factor (43) and diazepam-binding inhibitor (18), have been purified, sequenced, and shown to release CCK and elevate pancreatic protein secretion through a CCK-dependent mechanism. In addition, monitor peptide isolated from rat pancreatic juice (21) also stimulated the release of CCK from CCK-producing cells (3, 33) and from rats in vivo (20,
We have attempted to isolate SRF from rat intestinal acid perfusate. So far, we have identified a few fractions possessing SRF activity that have no cross-reaction with PL\textsubscript{A2} antibody and have chromatographic properties different from that of PL\textsubscript{A2} (unpublished observation). Therefore, it is likely that SRF also exists in multiple forms to mediate acid-stimulated secretin release.

In summary, the results of the present study demonstrate that pancreatic PL\textsubscript{A2} is distributed throughout the gastrointestinal tract and was abundant in the pancreas and the small intestine. Duodenal infusion of diluted acid stimulated the release of PL\textsubscript{A2} from the upper small intestine to elicit the secretion of secretin, which was abolished by intravenous administration of anti-PL\textsubscript{A2}. SRF activity in duodenal acid perfusate is an SRF in regulation of the release of secretin and pancreatic exocrine secretion in response to duodenal acidification in the rat.

We are grateful to Laura Braggins and Frank Roth for technical assistance.

This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-25962.

REFERENCES


