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Comparison of Pancreatic Exocrine Secretion via Endogenous Secretin by Intestinal Infusion of Hydrochloric Acid and Monocarboxylic Acid in Anesthetized Piglets

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Abstract The secretory response of the exocrine pancreas via endogenous secretin (IRS) by intraduodenal instillation of hydrochloric acid (HCl) and various monocarboxylic acid solutions was studied in anesthetized piglets. The secretion induced by HCl solutions of various concentrations containing 250 mM NaCl occurred when pH of the solutions was lower than 1.5. After instillation of the HCl solution of pH 1.0, juice flow and protein output increased 26 times and 9 times, respectively, as compared with basal levels. Such pancreatic responses paralleled an increase in plasma IRS concentration in the portal vein. The pancreatic response induced by a lactic acid solution occurred when pH of the solutions was lower than 3.8. The juice flow and protein output stimulated by a lactic acid solution of 250 mM and pH 2.0 were 16 and 8 times higher than the basal levels. The responses to the lactic acid solution of pH 2.0 increased concentration dependently, and were followed by an increase in IRS concentration in the portal vein. The pancreatic exocrine responses induced by other monocarboxylic acid solutions (250 mM) of pH 2.0 were in the following order: formic acid > lactic acid > pyruvic acid ≫ acetic acid > butyric acid > propionic acid. Lactamide, an analogous substance of lactic acid, did not evoke any pancreatic secretion. The results indicate the possibility that pancreatic exocrine response induced by HCl is dependent upon hydrogen ion, while the response induced by monocarboxylic acid is not always dependent on dissociation constant of acid.

Key words: pancreatic exocrine secretion, secretin release, intestinal acidification, monocarboxylic acids, anesthetized piglets.

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Secretin contained in the duodenal epithelium is released into blood in response to acidification of the luminal fluid of the duodenums, thus resulting in increased pancreatic juice flow and bicarbonate secretion. THOMAS and CRIDER (1940) reported that there was a pH threshold above which luminal acidification did not stimulate pancreatic exocrine secretion. This early observation has been confirmed by several investigators (MEYER *et al.*, 1970a; GROSSMAN and KONTUREK, 1974). Recently, it was also found that the pH threshold for the release of secretin digestion was 4.5 (CHEY and KONTUREK, 1982). The magnitude of pancreatic exocrine response induced by intraluminal acidification was shown to be a function of the rate of acid load to the duodenum in the conscious dog (PRESHAW *et al.*, 1966). MEYER *et al.* (1970a) further demonstrated that, in conscious dogs, the degree of pancreatic response was proportional to the rate of entry of acid titratable at pH 4.5 as well as the length of intestine exposed to acids, and that inorganic acids were more effective than organic acids. To account for the differences in the stimulating properties among weak acids, MOORE (1977) has proposed another explanation that the hydrogen ion receptor resides in the interior of the sensing cell. However, it has not been clearly shown how weak acids behave in acid sensing cells distributed in the intestinal mucosa. Moreover, the secretory mechanism of secretin induced by duodenal acidification with weak acid is still less understood.

The present study was designed to compare the pancreatic exocrine secretion and plasma secretin levels induced by intestinal instillation of hydrochloric acid (HCl) and various monocarboxylic acid solutions adjusted to various pH values in anesthetized piglets. Based on the present findings, we suggest that pancreatic exocrine response induced by monocarboxylic acids is not always dependent on dissociation constant of acid. Preliminary accounts of the work described in this paper have already been published in an abstract (HARADA *et al.*, 1985).

MATERIALS AND METHODS

Animals. The experiments were carried out in piglets (Landrace barrows) weighing 20–23 kg. The animals were fasted for 18 h, with free access to water.

Surgical procedures. No premedication was given. Anesthesia was induced with 2.5% halothane, and after the onset of surgical anesthesia, halothane was substituted with intravenous infusion of pentobarbital sodium (Abbot Lab. North Chicago, Il.). The stomach, the duodenum and the pancreas were exposed through a mid-line incision. The pylorus was ligated and a polyethylene tube was inserted into the stomach for excretion of gastric fluid. A segment of the proximal part of the small intestine including the duodenum and jejunum (about 50 cm in length) was selected and cannulated both proximally and distally. A polyethylene cannula was inserted into the bile duct, toward the hilum of the liver for excretion of bile. A metal cannula was also inserted into the pancreatic duct, close to its entrance into the duodenum, and was used for collection of pure pancreatic juice. Blood samples were obtained through a polyethylene catheter placed in the portal vein. Rectal

temperature was maintained at about 38°C with a heat lamp and heating pad.

Experiments. Experiments were started not sooner than 1 h after surgery. After a basal period of 30 min, a bolus of control or test solutions (2 ml/kg body wt.) prewarmed to 38°C in a water bath was instilled slowly into the duodenal part through the cannula within 7 min by means of a syringe. Generally, each solution was maintained in the intestine for about 20 min. The luminal contents were then gently flushed out and the intestinal lumen was rinsed with 30 ml of saline solution at 38°C. The next test solution was not introduced into the intestine until at least 1 h after drainage of the foregoing solution.

Samplings. Blood specimens were obtained at frequent intervals from the portal vein catheter and transferred into chilled tubes containing 500 kIU aprotinin (Trasylol, Bayer, leverkusen, Germany) and 1.2 mg EGTA-2Na per ml of blood. Samples were centrifuged at 4°C and plasma stored at −20°C until assay. Pancreatic juice flow was measured as follows: a calibrated tube (10.6 μl/cm), made of silicon rubber (2.5 mm o.d.) was attached to the free end of the pancreatic duct cannula. Every 10 min, the tube was replaced and the rate of flow down the tube was monitored.

Solution. Infusion solutions were prepared by dissolving reagent grade chemicals in distilled water. Each test solution was adjusted to desired pH with NaOH (2 M) or HCl (1 M). The osmolality (mOsmol/kg H_2O) of each test solution at pH 7.0 and 2.0 was as follows (shown in parenthesis): HCl solution containing 150 mM NaCl (290 at pH 7.0 and 300 at pH 2.0) and 250 mM (470, 485); lactic acid solution of 150 mM (255, 165), 250 mM (420, 250), 500 mM (850, 490), and 1,000 mM (2,900, 980); acetic acid solution of 250 mM (510, 300); butyric acid solution of 250 mM (480, 280); formic acid solution of 250 mM (290, 300); lactamide solution of 250 mM (260, 290); pyruvic acid solution of 250 mM (240, 400). An HCl solution containing 250 mM NaCl at pH 1.0 was also used (680 mOsmol/kg H_2O). Osmolality was measured with an osmometer (Knauer Electronic, Germany). In some animals, synthetic porcine secretin (Peptide Inst. Inc., Osaka, Japan) was tested.

Laboratory analysis. Protein concentration in pancreatic juice was determined by the method of LOWRY *et al.* (1951) using bovine serum albumin as a standard. Bicarbonate concentration in pancreatic juice was measured by adding 200 μl of juice to 10.0 ml of HCl (0.01 M), boiling for 10 min, cooling and back titrating the residual HCl with 0.1 M NaOH (pH meter, TOA, Tokyo). The immunoreactive secretin (IRS) of plasma was measured with a secretin RIA kit using porcine secretin standard (Daiichi Radioisotope Lab., Tokyo). No cross reactions were detected with gastrin, pancreatic glucagon, or pancreatic polypeptide. A weak cross reaction was noted with VIP, the percent immunoreactivity being 0.002%. The sensitivity of this assay was 25 pg/ml plasma, calculated as the 95% confidence limit of the blank.

Statistics. Each calculated value was expressed as the mean ± S.E., and the difference of means was analyzed by Student's *t*-test.

RESULTS

Relationship among juice flow, bicarbonate output, and protein output in pancreatic juice

Figure 1 depicts the relationship between juice flow and bicarbonate output (A) and the relation between juice flow and protein output (B) in pancreatic juice induced by intraduodenal instillation of HCl solution containing NaCl (250 mM) at pH 1.0 or lactic acid (150–1,000 mM) solutions at pH 2.0 and intravenous infusion of secretin (0.3–300 pmol/kg body wt.). The regression equation for juice flow (y) against the bicarbonate output (x) was given as $y=0.87x+1.65$ ($r=0.97$) (Fig. 1A). However, no clear relationship between juice flow and protein output was obtained, the responses varied widely from experiment to experiment (Fig. 1B). The results indicate that changes in juice flow qualitatively parallel those of bicarbonate output. For this reason, juice flow was adopted as an indicator of fluid secretion in the present experiment.

Secretory response induced by hydrochloric acid

It is well known that pancreatic exocrine secretion is induced by intraduodenal instillation of acid solution. To compare the responses induced by monocarboxylic acids with that induced by HCl solution containing NaCl (250 mM), the following experiments were performed as a control observation.

As shown in Fig. 2, the pancreatic secretion by HCl solution containing 250 mM NaCl did not appear not only at pH 7.0 but also at pH 2.0. However, a slight increase in secretory response appeared by instillation of the solution of pH 1.5. After instillation of the solution of pH 1.0, pancreatic juice flow rapidly increased and reached a peak value after 20 min, which was 26 times higher than the basal level. During the next 10 min, the secretion decreased to about 36% of the peak value. The peak value of protein output was obtained at 10 min after the instillation. The value corresponded to 9 times the basal level. During the next 10 min, the secretion rapidly decreased to about 37% of the peak value. The total amounts of pancreatic juice and protein output for 30 min after the instillation were 628.7 ± 136.8 μl/30 min and 499.4 ± 87.3 μg/30 min, respectively. On the other hand, plasma IRS concentration in the portal vein was not induced by the instillation of the solution of pH 7.0 and 2.0. But after the instillation of the solution of pH 1.0, IRS concentration increased rapidly, reaching a peak value after 20 min. The value was 3 times that of the basal level. During the next 10 min, the concentration decreased abruptly and returned to the resting level. This secretory pattern of IRS was very similar to that found in the pancreatic secretion.

Secretory response induced by lactic acid

Figure 3 shows the time course of pancreatic juice flow, protein output and plasma IRS concentration in the portal vein induced by lactic acid solutions maintained at various pH values. The secretory response was not induced in the

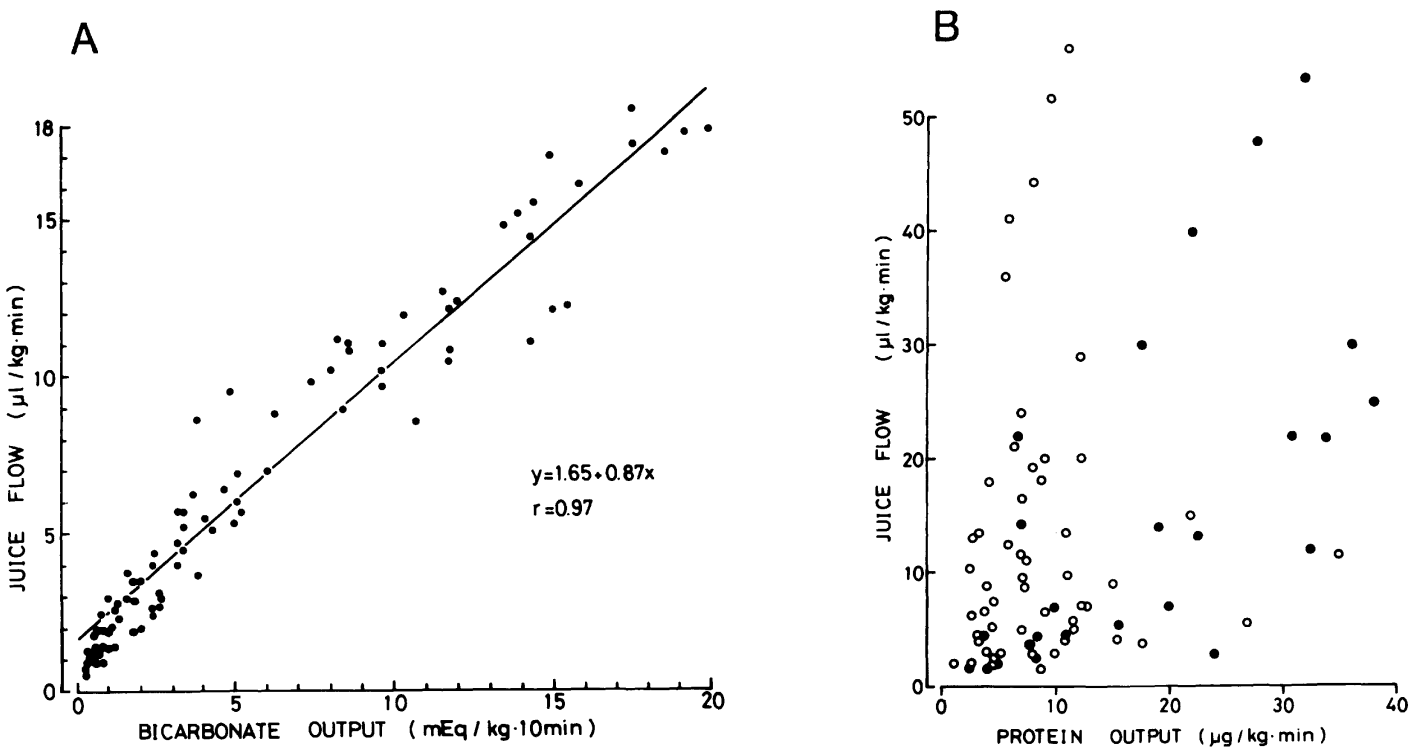

Fig. 1. Relation between juice flow and bicarbonate output (A) or protein output (B) in pancreatic juice induced by intraduodenal instillation of HCl solution containing NaCl at pH 1.0 or lactic acid solutions at pH 2.0 and intravenous infusion of secretin (0.3–300 pmol/kg body wt.: ○ in B).

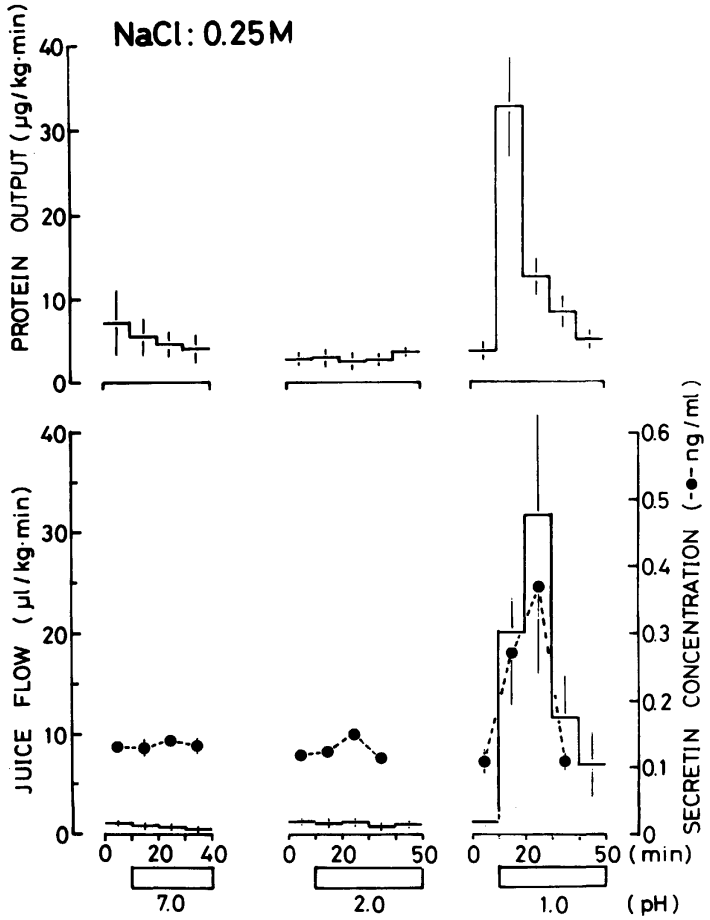

Fig. 2. Time course of pancreatic juice flow, protein output, and plasma secretin (IRS) concentration in the portal vein induced by intraduodenal instillation of HCl solution containing NaCl (250 mM) at pH 7.0, 2.0, and 1.0. Each value represents the mean ± S.E. ($n=5$ at pH 7.0 and 1.0; $n=4$ at pH 2.0).

250 mM lactic acid solution adjusted to pH 7.0 and 3.8 (Fig. 3A). However, instillation of the solution adjusted to pH 2.8 caused a rapid increase in pancreatic secretion which reached a peak value after 20 min. During the next 10 min, the secretion decreased to about 60% of the level and returned to the resting levels after 40 min. The pancreatic secretion by the lactic acid solution of pH 2.0 was much larger than that by the solution of pH 2.8. The peak value of juice flow, protein output and IRS concentration was augmented 16, 8, and 3 times, respectively, compared with the basal levels. These secretory responses were enhanced by instillation of the solution of pH 1.0 (not shown in this figure).

The pH-dependent secretory response observed by the 250 mM solution of lactic acid was compared with that induced by a higher concentration of lactic acid

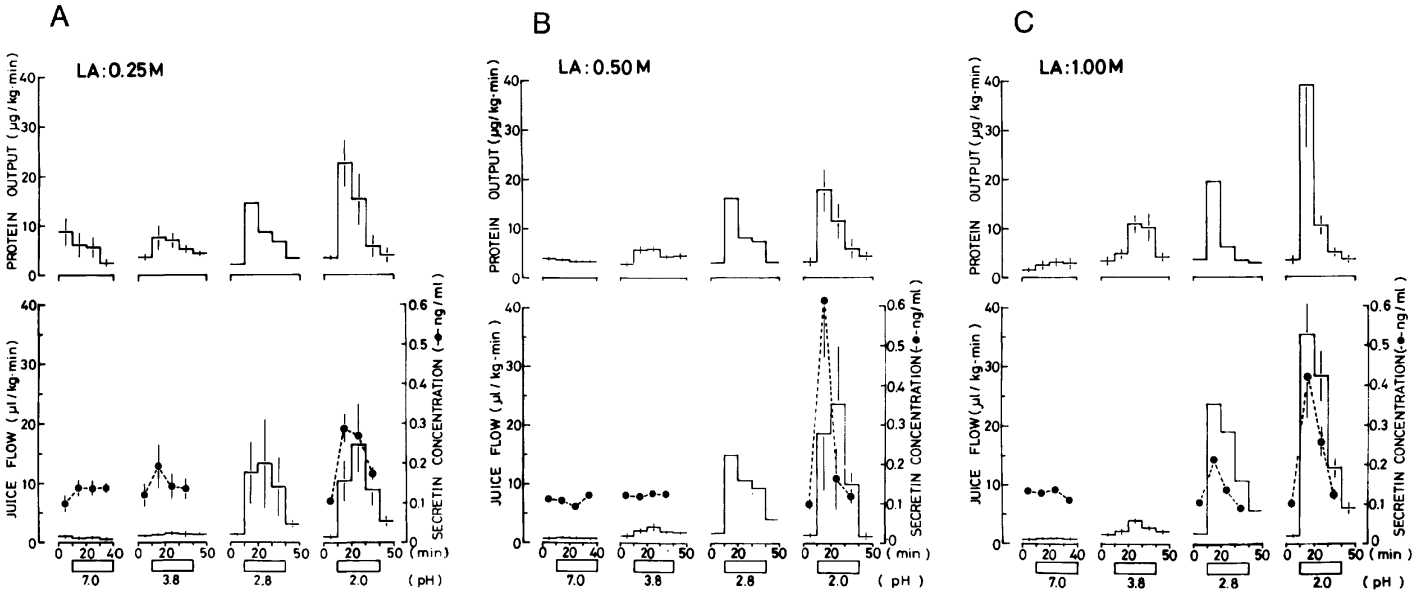

Fig. 3. Time course of pancreatic juice flow, protein output, and plasma IRS concentration in the portal vein induced by intraduodenal instillation of lactic acid solutions maintained at various pHs (A: 250 mM, B: 500 mM, and C: 1,000 mM). Each value represents the mean ± S.E. ($n=6$ at pH 7.0 and 2.0 in A; $n=5$ at pH 3.8 in A; $n=3$ at pH 2.8 in B and C; $n=4$ at others).

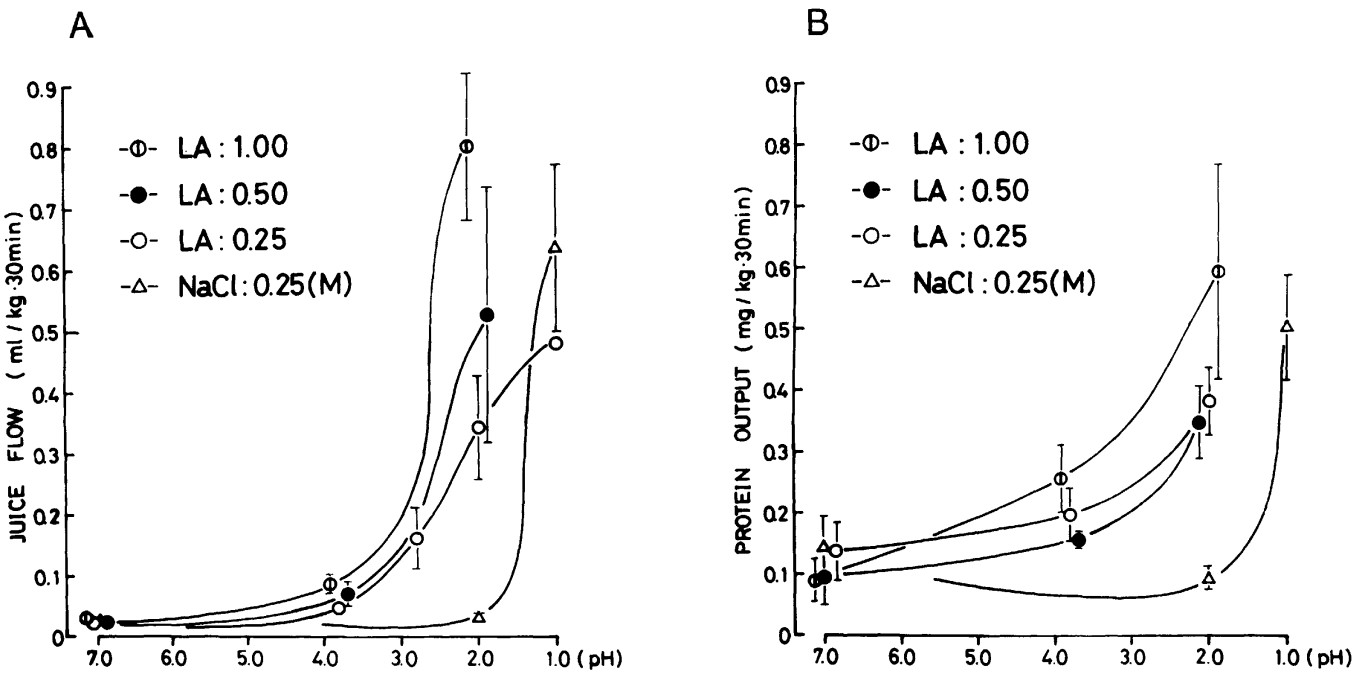

Fig. 4. A pH dependence of juice flow (A) and protein output (B) induced by intraduodenal instillation of lactic acid solutions (250, 500, and 1,000 mM) and HCl solution containing NaCl (250 mM). Each value indicates the mean ± S.E. for 30 min. The data presented in Figs. 2 and 3 are used.

(Fig. 3B, C). An instillation of 500 or 1,000 mM solution of lactic acid of pH 7.0 did not induce any pancreatic secretion. Instillation of the higher concentration of lactic acid solution of pH 3.8 caused a slight increase in the pancreatic secretion. Total pancreatic juice flow and protein output for 30 min by 1,000 mM solution were significantly larger than those by 250 mM solution ($p<0.05$) (Fig. 4). The pancreatic secretion was augmented dose-dependently by instillation of various concentrations of lactic acid kept at pH 2.0 (Fig. 4). Total pancreatic juice flow for 30 min induced by 500 and 1,000 mM solution increased 1.5 and 2.4 times compared with that by 250 mM, respectively. Total pancreatic protein output showed an almost similar pattern to that of the total pancreatic juice flow. However, pH-dependency of the pancreatic secretory response induced by HCl solution containing NaCl was clearly different from that by lactic acid solution (Fig. 4). These pancreatic secretory patterns were in accord with changes in the IRS concentration.

Pancreatic secretory response by other monocarboxylic acids

Pancreatic secretory responses induced by other monocarboxylic acids such as formic acid, acetic acid, propionic acid, butyric acid, and pyruvic acid, were examined using 250 mM solutions adjusted to pH 7.0 and 2.0 (Table 1). Total pancreatic juice flow for 30 min after intraintestinal instillation of formic acid solution at pH 2.0 corresponded to 19.7 times the value at pH 7.0. The value was slightly higher than that by 250 mM lactic acid ($p>0.05$) and corresponded to two-thirds of that by a HCl solution of pH 1.0 containing 250 mM NaCl. The response

Table 1. Secretory responses of exocrine pancreas and IRS induced by various monocarboxylic acid solutions (250 mM) at pH 7.0 and 2.0.

		Juice flow (μl/(kg·30 min))		Protein output (μg/(kg·30 min))		IRS response
		pH 7.0	pH 2.0	pH 7.0	pH 2.0	
Formic acid	(4)	18.7±2.9	369.2±76.3**	80.6±28.2	316.4±70.0*	3.25
Acetic acid	(4)	25.8±5.7	100.9±23.7*	57.0±12.0	209.0±29.9**	1.47
Propionic acid	(4)	22.8±5.2	43.6±15.5	71.0±20.0	164.7±55.4	1.51
Butyric acid	(4)	24.4±5.6	51.2±23.7	120.0±31.0	199.0±48.6	1.24
Lactic acid	(6)	17.9±5.0	340.2±90.7**	137.6±49.9	489.9±45.9**	2.90
Pyruvic acid	(4)	27.0±5.6	187.1±59.4	81.9±26.0	547.9±274.0	—
Lactamide	(2)	36.0	22.7	85.0	120.0	1.1
HCl	(5)	21.8±6.2	628.7±136.9**	98.8±28.1	499.4±87.3**	3.75

Numbers in parentheses indicate the number of animals. Responses induced by HCl solution containing NaCl (250 mM) indicate values of pH 7.0 and 1.0. IRS response is indicated by response time, calculated from peak value after stimulation by each solution of pH 2.0 against basal value before stimulation. Mean±S.E. of the mean. *$p<0.05$ and **$p<0.01$ as compared with value of pH 7.0.

for 30 min by pyruvic acid at pH 2.0 was 6.9 times that at pH 7.0 ($p<0.05$). The responses by acetic acid, propionic acid, and butyric acid solutions of pH 2.0 were very small and increased only 3.9, 2.1, and 1.3 times, respectively, as compared with each response at pH 7.0. The changes in plasma IRS concentration showed a similar tendency with the secretory response of juice flow by each acid as shown in Table 1 (IRS response). Total protein output at pH 7.0 varied more or less by each acid. The protein output response induced by lactic acid at pH 2.0 was significantly larger than that by formic acid ($p<0.05$). The secretory response by pyruvic acid tended to be higher compared to that by lactic acid. The ratio of protein to pancreatic juice ($\mu g/\mu l$) was calculated from the total amount of each response for 30 min at a pH 2.0. The ratio for formic acid (0.86) was lower than those for lactic acid (1.44) and pyruvic acid (2.93), and was almost the same as those for HCl solution of pH 1.0 containing NaCl (0.84) and secretin administration (0.80). On the other hand, lactamide, an analogous substance with lactic acid, did not induce any pancreatic secretion.

DISCUSSION

Difference in pH dependence between HCl and lactic acid stimulation. The present experiment revealed that pH-dependence in the pancreatic secretory response induced by intraduodenal instillation of HCl solutions is clearly different from that induced by lactic acid solutions in the anesthetized piglets. The threshold existed around pH 1.3 in the case of HCl solutions containing NaCl and around pH 3.8 in the case of lactic acid solutions. Above these pH values secretin was not released in amounts sufficient to stimulate pancreatic exocrine secretion. FAHRENKRUG *et al.* (1977) also observed that only the mean with pH 1.0 which resulted in an intraduodenal pH ranging from 1.0 to 1.7 caused an increase in plasma IRS and pancreatic flow rate in anesthetized pigs. While some investigators have reported no demonstrable threshold below pH 7.0 for pancreatic juice flow via secretin release (PINCUS *et al.*, 1948; HONG *et al.*, 1967), it has been shown that a threshold exists around pH 4.5 in the conscious dog (THOMAS and CRIDER, 1940; MEYER *et al.*, 1970a; GROSSMAN and KONTUREK, 1974; CHEY and KONTUREK, 1982). The discrepancies in these findings may be attributed to the experimental conditions rather than to the differences in the species. As all our experiments were performed in anesthetized piglets, the possibility that anesthesia might have retarded the secretin release and/or pancreatic exocrine secretion cannot be excluded. BEN-ARI *et al.* (1969) observed that anesthesia by pentobarbital Na depressed basal pancreatic exocrine secretion and the response to secretin in the dog. Although the gastrointestinal hormones were believed to be the major factors in the controlling of pancreatic secretion, it is now recognized that cholinergic reflexes that relate to the intestine and the pancreas also play an important role (DEBAS *et al.*, 1975; MODLIN *et al.*, 1979; SINGER *et al.*, 1980). YOU *et al.* (1982) reported that atropine inhibited the pancreatic secretion induced by secretin, but not the intestinal release of secretin by

perfusion with HCl. The duodenal mucosa of pig is found to be rich in osmoreceptors (HOUPT *et al.*, 1983). DOOLEY and VALENZUELA (1984) demonstrated that human duodenum contains receptors for volume and osmolality that stimulate both pancreatic enzymes and bicarbonate secretions. Both mechanisms are atropine sensitive, suggesting that they are mainly neurally mediated. If it exists at all, it is probably only a minor phenomenon in the present experiments, because intestinal acidification resulted in a dramatic plasma IRS increase and pancreatic exocrine secretion, and hyperosmotic solution of lactic acid at pH 7.0 did not cause any secretory responses. The shift of pH threshold to a lower range in HCl solution compared with other investigations described above may probably be due to the effect of anesthesia. The pH threshold in the case of monocarboxylic acid may also shift to a lower range as well as that of HCl solution under anesthetic condition, although comparable evidence has not yet been obtained.

Potencies of pancreatic exocrine response induced by monocarboxylic acid. It is proposed that the rate of pancreatic bicarbonate secretion is a function of the rate of entry of a titratable acid, and weak acids as well as strong acids showed this relation between titratable acid and response (MEYER *et al.*, 1970a). In the present experiment, pancreatic exocrine response induced by monocarboxylic acid was examined in anesthetized piglets. The order of relative magnitude of response, as expressed as the ratio of the mean value of juice flow for 30 min induced by each acid solution at pH 2.0 to the value induced by acids at pH 7.0 was as follows: formic acid (19.7×) > lactic acid (19×) > pyruvic acid (6.9×) ≫ acetic acid (3.9×) > butyric acid (2.1×) > propionic acid (1.3×). However, no clear reciprocal proportion between the response and pK_a was observed, because this order did not always correspond to the order of pK_a value in each acid solution, that is: pyruvic acid (2.49) < formic acid (3.75) < lactic acid (3.86) < acetic acid (4.76) < butyric acid (4.82) < propionic acid (4.88). The order of protein output response was very different from the order of juice flow response. It is suggested that some acids may be able to release other gut peptides in addition to secretin, because protein concentration in pancreatic juice is different from that in juice induced by each acid.

Generally, it is assumed that acid sensing cells in the intestinal mucosa are responsive to luminal hydrogen ion concentration or activity. MEYER *et al.* (1970b) postulated that overall pancreatic bicarbonate response was determined by integration of 1) the number of sensing cells activated, a function of the length of gut acidified below threshold pH, and 2) the intensity of stimulation of each sensing cell, a function of pH in the immediate environment of the sensing cell. On the other hand, MOORE (1977) has proposed that the hydrogen ion receptor resides in the interior of the sensing cell and a hydrogen ion would cross the plasma membrane of the cell by two mechanisms to reach these internal receptors: 1) as a dissociated hydrogen ion, and 2) as an undissociated weak acid that would dissociate at the higher pH of the cell interior, thereby generating hydrogen ions. To test the hypothesis that the permeability of weak acids across the intestinal mucosa affects their ability to stimulate pancreatic bicarbonate output, SOLOMON *et al.* (1978)

compared pancreatic bicarbonate secretion in response to intestinal perfusion with an acid presumed to be impermeable, acidified bovine serum albumin. They suggested that the molecular size of weak acid anions had little or no effect on the hydrogen ion concentration in the intestinal mucosal receptor involved.

The fact that there was no clear reciprocally proportional relationship between the response and pK_a for each acid suggests the following: 1) secretin release from secretin cells having hydrogen ion sensor is evoked by the presence of hydrogen ion above a certain concentration; 2) the dissociation of hydrogen ion from each monocarboxylic acid is different from the theoretical dissociation of hydrogen ion in the acid solution; 3) the practical dissociation is affected by mucosal environment of duodenal epithelium. MEYER *et al.* (1970b) proposed the concept of "titratable acid." However, the pancreatic exocrine response to monocarboxylic acid is not always based on the titration curve of the acid, so that a new concept representing the cooperative functions between the given acid and the sensing cells is thought to be necessary.

It is known that some gut peptides, including secretin, are released from the mucosa of the upper small intestine in response to the action of hydrogen ion in the lumen (BARBEZAT and GROSSMAN, 1975; SCHUSDZIARRA *et al.*, 1979; CUBER *et al.*, 1985). In our experiments, it was clearly different in the ratio of protein to juice between HCl or secretin and monocarboxylic acid. Instillation of lactic acid solutions of 500 and 1,000 mM caused an increase in plasma VIP concentration in the portal vein (unpublished data). Some gut peptides causing pancreatic exocrine response may, at least partially, contribute to the action of endogenous secretin. Recently, it was reported that secretin cells release secretin in response not only to acid, but also to Na oleate (FAICHNEY *et al.*, 1981), bile salts (HANSSEN *et al.*, 1980; BONDESEN *et al.*, 1985), or 1-phenylpentanol (CHEY *et al.*, 1983). This raises the question whether hydrogen ion-independent secretory process is present in the secretin cell (HARADA *et al.*, 1985). Thus, further investigations are required to clarify the stimulus-secretion coupling mechanism in secretin cells.

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