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Influence of Neural Blockages and Proglumide on Rat Pancreatic Enzyme Secretion in Response to Intraluminal Fatty Acid (42579)

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Abstract. Effects of neural blockages on pancreatic enzyme secretion in response to infusing fatty acid into the lumen were investigated using anesthetized rats, equipped with bile–pancreatic and duodenal cannulae, to evaluate the relative contribution of the neural and the hormonal mediations in the pancreatic response. Oleate (0.2 ml) was injected as a bolus into the rat duodenum, and the trypsin output in bile–pancreatic juice was monitored to determine the pancreatic enzyme secretion response with continuous return of bile–pancreatic juice to the intestine. When anticholinergic agents such as atropine sulfate and scopolamine were administrated, although basal level in pancreatic enzyme secretion fell, the increase of pancreatic enzyme secretion from basal level after stimulation by oleate was not significantly different from that of the control (no blockage). However, the ganglion blocker, hexamethonium, inhibited the pancreatic enzyme secretion in response to oleate by 94%. An adrenergic blocker, guanethidine, also led to as much of a decrease as the ganglion blocker-induced decrease. Adrenergic α- and β-blockers partially, but not completely, inhibited the enzyme secretion. Adrenergic blockage also suppressed the basal level in pancreatic enzyme secretion. On the other hand, a specific CCK antagonist, proglumide, significantly inhibited pancreatic enzyme secretion induced by oleate in the presence of scopolamine. These observations suggest that pancreatic enzyme secretion in response to oleate is primarily mediated by CCK and that adrenergic modulation may play an important role in the CCK-mediated pancreatic enzyme secretion in response to oleate, although interpretation of these results may have some restriction related to anesthesia.

Pancreatic enzyme secretion is one of the most important steps in the digestion and absorption of dietary components. However, the details of the mechanisms concerned in the response of the enzyme secretion to dietary components or their digests are still unclear. Green and Lyman (1) first reported and Schneeman *et al.* (2) showed that intact protein, but not hydrolyzed protein, was a potent stimulant of pancreatic enzyme secretion in the rat. Many investigators have observed that intraluminal fatty acids also have a potent stimulatory effect on pancreatic enzyme secretion in rats (3–5). Rat pancreatic enzyme secretion induced by dietary protein is hypothesized to be due to CCK-mediated feedback regulation caused by the interaction of pancreatic protease and substrate (1, 6–8). On the other hand, considering the enzyme secretion induced by fatty acid, lipase and its substrate do not seem to have a similar mechanism of feedback control (9). There are many discussions as to whether neural or hormonal mediation is more dominant in the fatty-acid-induced pancreatic enzyme secretion. Valensuela *et al.* (10) reported that the cholinergic component mediates mainly pancreatic response to oleate in man. Solomon and Grossman (11) and Singer *et al.* (12–14) also showed in the transplanted canine pancreas that pancreatic enzyme secretion in response to oleate is mainly mediated by the neural system. However, Stubbs and Stabile (15) have suggested that the intestinal phase of pancreatic enzyme secretion is mainly CCK mediated, because proglumide, a specific CCK antagonist, can almost completely inhibit the pancreatic response to fat and amino acids in the intestine.

In this study, in order to elucidate the mechanism by which pancreatic enzyme secretion in response to intraluminal oleate is mediated, we have systematically investigated the effects of neural or hormonal blockages on the pancreatic response to oleate in rats.

Materials and Methods. *Chemicals.* Atropine methyl nitrate, methoxamine hydrochloride, oxprenolol hydrochloride, and porcine trypsin (type IX) were purchased from Sigma Chemical Co. Guanethidine sulfate (Ismelin)

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was from Ciba-Geigy (Japan). Hexamethonium chloride dihydrate, atropine sulfate, pentolinium di(L(+)-tartarate), scopolamine hydrobromide, and DL-propranolol hydrochloride were obtained from Wako Pure Chemicals. Scopolamine methylbromide, dibenamine hydrochloride and *N*-benzoyl-D-arginine*p*-nitroanilide hydrochloride were from Nakarai Chemicals Ltd. Proglumide was purchased from Research Biochemicals Inc. (Wayland, MA). Pentobarbital (Somunopentyl) was from Pitman–Moore, Inc. Other chemicals used were of the highest purity available from commercial sources.

Preparation of animals. Male Wistar rats weighing 300–350 g were used after a 12- to 16-hr fast. The neural blocker(s) was intraperitoneally (ip) injected as a bolus at the dose indicated and subsequent injections were given at 1-hr intervals during the experiment. One hour after the first blocker injection, rats were anesthetized with pentobarbital. A duodenal cannula was then inserted, and the main bile–pancreatic duct was ligated at the papilla of Vater, followed by insertion of a bile–pancreatic cannula. The surgical procedure has been described in detail elsewhere (5). Bile–pancreatic juice was collected via the bile–pancreatic cannula at 15-min intervals during the experiments, the volume was measured, and the juice was continuously returned to the intestine except for a 10-μl sample for the enzyme assay. All the experiments were performed under anesthesia by injection with pentobarbital (20 mg/kg-hr) at 1-hr intervals. One or two hours after the surgical preparations, intestinal infusions were performed. Amounts of oleate were infused into the proximal intestine via the duodenal cannula and bile–pancreatic juice was collected via the bile–pancreatic cannula for 2 hr as mentioned above. Since maximal stimulation of pancreatic enzyme secretion induced by oleate was obtained when infusing 200 μl of oleate under the experimental conditions, as shown in Fig. 1, we used the dose of 200 μl for the following experiments unless specified otherwise. Each dose of atropine sulfate (5 mg/kg), scopolamine hydrobromide (3 mg/kg), scopolamine methylbromide (2 mg/kg), atropine methyl nitrate (3 mg/kg), methoxamine (3.8 mg/kg), hexamethonium (15 mg/kg), pentolinium (3 mg/kg), guanethidine (7.5 mg/kg), dibenamine

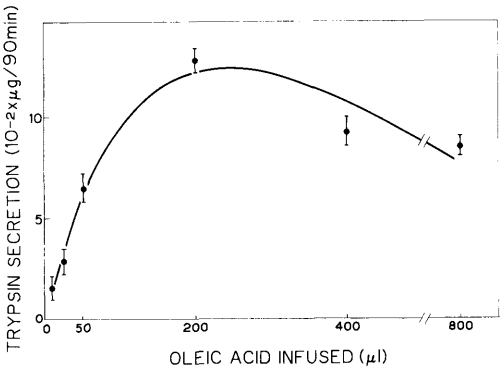

FIG. 1. Dose-dependent relationship between oleate-infused and pancreatic enzyme secretion in rats. Trypsin secretion (the net increase of trypsin output, porcine trypsin equivalent micrograms) for 90 min after the intraluminal infusion of indicated dose of oleate was presented. Values are means ± SE for five rats.

(7.5 mg/kg), propranolol (3.8 mg/kg), and oxprenolol (7.5 mg/kg) was injected 1 hr before the oleate infusion and subsequent injections of the same doses described above were given at 1-hr intervals during the experiments. These doses were determined according to previous descriptions (16, 17), except that we used 10 times the dose prescribed for the intravenous route because they were injected as a boluses intraperitoneally (18).

Proglumide solution was prepared according to the method described by Stubbs and Stabile (15). In the presence of scopolamine, proglumide (60 mg/kg) was injected intravenously 15 min before the intestinal infusion of oleate to rats prepared in the same way as described above. As a control, oleate was intestinally infused into some rats after they were given scopolamine (7.5 mg/kg-hr, ip) without proglumide.

Enzyme assay. Change in trypsin concentration in the collected samples of bile–pancreatic juice was monitored in order to determine pancreatic enzyme secretion (5). Under our experimental conditions, it was previously demonstrated that the time-course pattern of trypsin secretion changed in a manner parallel to that of lipase secretion and that trypsin activity and total trypsin output in bile–pancreatic juice were closely related (5). Trypsin activity was determined using benzoyl arginine-*p*-nitroanilide (BApNA) as a substrate (19) after being activated with procine enter-

okinase at 37°C for 40 min. Crystalline porcine trypsin was used as a standard.

Statistics. Data were analyzed statistically by Kruskal-Wallis' test (20).

Results. Fig. 1 shows that the amount of infused oleate was directly related to pancreatic enzyme secretion (the net increase of trypsin output for 90 min) until the oleate amount reached 200 μl. Therefore, in this study, the effects of cholinergic, adrenergic, and ganglion blockers and the hormone antagonist were investigated both on the basal level of pancreatic enzyme secretion and on the secretion stimulated by oleate, in which 200 μl of oleate was infused into the intestine (unless specified otherwise).

In a control study using rats into which no blockers were injected, basal pancreatic enzyme secretion for 90 min was 814 ± 99 μg (mean ± SE for six rats), when expressed with the trypsin output in bile–pancreatic juice (porcine trypsin equivalent). When 200 μl of oleate was infused as a bolus into the duodenum, pancreatic enzyme secretion was rapidly stimulated, and both the trypsin concentration of bile–pancreatic juice and the volume of bile–pancreatic juice reached peak levels 15–30 min after the infusion and then gradually decreased until basal levels were reached (preinfusion state) within 90 min after the infusion.

It was then estimated that the net increase of trypsin output during the 90 min after the infusion of oleate was 1278 ± 300 μg/90 min. The net increase was the value obtained when the basal trypsin output in each experiment was subtracted from the total trypsin output for 90 min. Effects of neural blockers and a hormonal antagonist on both the basal and the oleate-stimulated pancreatic enzyme secretions were each investigated for 90 min. Then, in the following experiments, both the basal trypsin secretion and the net incease by oleate for 90 min were calculated as described above and summarized in Table I. The time-course change of trypsin output is shown in each figure.

Effect of cholinergic blockage (Figs. 2 and 3 and Table I). When atropine sulfate (5 mg/kg-hr), scopolamine hydrobromide (5 mg/kg-hr), methyl scopolamine bromide (5 mg/kg-hr), or atropine methyl nitrate (5 mg/kg-hr)

TABLE I. EFFECTS OF NEURAL OR HORMONAL BLOCKERS ON PANCREATIC ENZYME SECRETION IN THE BASAL AND STIMULATED STATE BY INTRALUMINAL OLEATE INFUSION

Blocker	Site blocked	Trypsin secretion (μg/90 min)	
		Basal secretion	Net increase
Control		814.3 ± 99.1	1277.6 ± 303.01
Hexamethonium	Ganglion	176.0 ± 52.5*	74.4 ± 51.3*
Pentolinium	Ganglion	101.0 ± 40.4*	114.9 ± 29.0*
Scopolamine HBr (SC)	Cholinergic	357.7 ± 80.5*	1123.3 ± 337.3
Scopolamine methyl Br	Cholinergic	411.7 ± 79.7*	1768.1 ± 373.3
Atropine sulfate	Cholinergic	382.6 ± 50.3*	1251.6 ± 214.3
Atropine methyl nitrate	Cholinergic	191.5 ± 67.0*	428.5 ± 21.5*
Guanethidine	Adrenergic	19.6 ± 5.0*	33.9 ± 20.4*
Dibenamine	Adr. α	141.6 ± 48.4*	81.2 ± 68.5*
Propranolol	Adr. β	76.1 ± 62.4*	29.4 ± 77.1*
Methoxamine	Adr. β	454.5 ± 89.2*	231.9 ± 206.0*
Oxprenolol	Adr. β	286.6 ± 60.8*	429.1 ± 162.3*
Dibenamine + oxprenolol	α + β	108.1 ± 12.1*	29.5 ± 22.7*
Dibenamine + propranolol	α + β	62.1 ± 44.2*	47.3 ± 39.6*
SC + guanethidine	Chol. + Adr.	193.4 ± 49.9*	185.6 ± 73.3*
SC + dibenamine	Chol. + α	429.3 ± 111.2*	427.5 ± 225.8*
SC + propranolol	Chol. β	69.5 ± 21.0*	173.5 ± 32.4*
SC + proglumide	Chol. + CCK	208.7 ± 31.2*	259.2 ± 93.4*

Note. SC, scopolamine hydrobromide; Chol., cholinergic; Adr., adrenergic. Porcine trypsin equivalent micrograms for 90 min after the oleate infusion was presented. Net increase means the value of the total trypsin secretion subtracted from the basal secretion. Values are means ± SD for five experiments. *Significant difference compared with each control value.

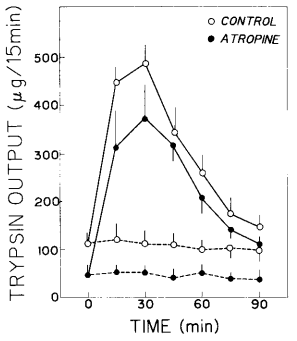

FIG. 2. Time-course change of trypsin output in response to intraluminal infusion of oleate in control (○) and under the administration of atropine sulfate (●) in the rats; each is stimulated by the oleate (hard line) and basal (broken line) states. Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Atropine sulfate (5 mg) was injected 1 hr before the infusion and subsequently injected at the same dose at 1-hr intervals during the experiments. Bile–pancreatic juice was collected via a bile–pancreatic cannula and was returned to the small intestine continuously except for 10 μl for use in the enzyme assay at 15-min intervals. The method of the enzyme assay is described in the text.

was administrated, the basal trypsin output for 90 min was reduced by 50–70% compared to that of the control. This reduction was due mainly to the reduction of the concentration of trypsin. These cholinergic blockers have no effect on the basal level of bile–pancreatic juice volume. As to stimulation of pancreatic enzyme secretion by oleate, cholinergic blockers, except methyl atropine, did not significantly decrease the secretion in response to oleate. This was clearly observed when the net increase of trypsin output was compared to that of the control (Table I and Fig. 2). Atropine methyl nitrate showed a much stronger suppressive effect on the trypsin output than did other cholinergic blockers used.

Effects of ganglion blockage. When hexamethonium (15 mg/kg-hr) or pentolinium (3 mg/kg-hr) was administered, both the basal level of pancreatic enzyme secretion and the secretion stimulated by oleate were almost completely blocked (Table I and Fig. 4).

Effect of adrenergic blockage. After intraperitoneal injection of guanethidine, a general (α- and β-) adrenergic blocker (7.5 mg/kg-hr), the basal level of trypsin output was reduced by 90%. The trypsin secretion induced by

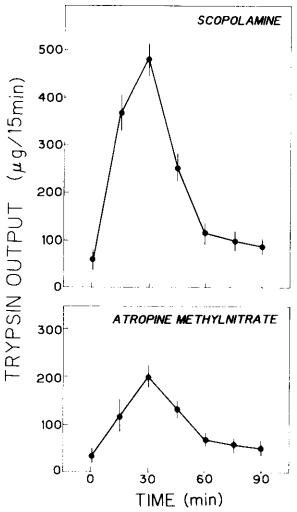

FIG. 3. Time-course change of trypsin output in response to intraluminal infusion of oleate under the administration of scopolamine hydrochloride (upper) or atropine methyl nitrate (lower) in rats. Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Scopolamine hydrochloride (3 mg/kg) or atropine methyl nitrate (3 mg/kg) was injected 1 hr before the infusion and subsequently injected at the same dose at 1-hr intervals during the experiments.

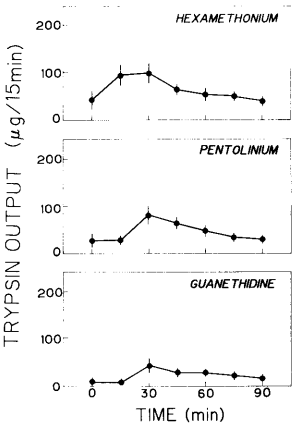

FIG. 4. Time-course change of trypsin output in response to intraluminal infusion of oleate under the administration of hexamethonium (upper), pentolinium (middle), or guanethidine (lower) in rats. Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Hexamethonium (15 mg/kg), pentolinium (3 mg/kg), or guanethidine (7.5 mg/kg) was injected 1 hr before the infusion and subsequently injected at the same dose at 1-hr intervals during the experiments.

oleate was inhibited almost completely, as was the case with the ganglion blockages (Fig. 4).

To specify whether the α- or β-adrenergic system is more dominantly involved in mediating the pancreatic enzyme secretion in response to oleate, the effects of α- and/or β-specific blockage were examined (Figs. 5 and 6). The α-blocker dibenamine suppressed the basal trypsin output by 80% and the oleate-induced net increase of trypsin output by 90%, from their control values, respectively. The β-blockers, propranolol, methoxamine, and oxprenolol, suppressed the basal trypsin output by 90, 40, and 60% and the net increase of trypsin output by 95, 80, and 90%, from their control values, respectively. When dibenamine (7.5 mg/kg-hr) and oxprenolol (7.5 mg/kg-hr) were administered together (α- and β-blockers), both the basal level of pancreatic enzyme secretion and the secretion stimulated by oleate were almost completely blocked. The same results were obtained when dibenamine (7.5 mg/kg-hr) and propranolol (3.8 mg/kg-hr) were administered together. When guanethidine and scopolamine were administered together, pancreatic enzyme secretion by oleate was higher in the case of guanethidine

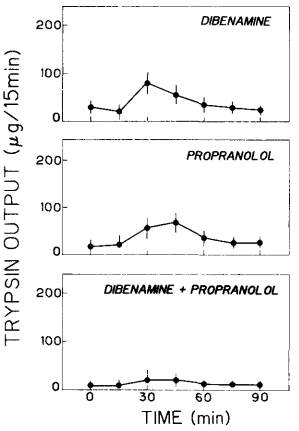

FIG. 5. Time-course change of trypsin output in response to intraluminal infusion of oleate under the administration of dibenamine (upper), propranolol (middle), or dibenamine plus propranolol in rats. Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Dibenamine (7.5 mg/kg), propranolol (3.8 mg/kg), or dibenamine (7.5 mg/kg) plus propranolol (3.8 mg/kg) was injected 1 hr before the infusion and subsequently injected at the same dose at 1-hr intervals during the experiments.

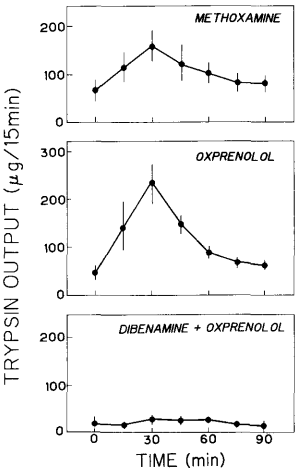

FIG. 6. Time-course change of trypsin output in response to intraluminal infusion of oleate under the administration of methoxamine (upper), oxprenolol (middle), or dibenamine plus oxprenolol in rats. Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Methoxamine (7.5 mg/kg), oxprenolol (3.8 mg/kg), or dibenamine (7.5 mg/kg) plus oxprenolol (3.8 mg/kg) was injected 1 hr before the infusion and subsequently injected at the same dose at 1-hr intervals during the experiments.

plus scopolamine than in the case of guanethidine alone. Similarily, when α- or β-blocker was injected together with cholinergic blocker, scopolamine hydrobromide, the inhibiting effects of α- and β-blockers were diminished (Table I and Fig. 7).

Effect of proglumide. Injection of proglumide suppressed the pancreatic response to oleate considerably, although some response was still observed in the presence of scopolamine (Fig. 8).

Discussion. Pancreatic enzyme secretion in response to intake of dietary components into the lumen is controlled by the interplay of neural and hormonal mechanisms. There is a debate as to which of the neural or hormonal mechanisms contributes more to the pancreatic response. These contributions may differ from species to species of animals used, and moreover there may also be large variations in the pancreatic responses according to the type of dietary component ingested. It has been shown that pancreatic enzyme secretion in response to fat is due mainly to free fatty acid but not due to glycerol, according to the experiments using dogs (21) and rats (5). While

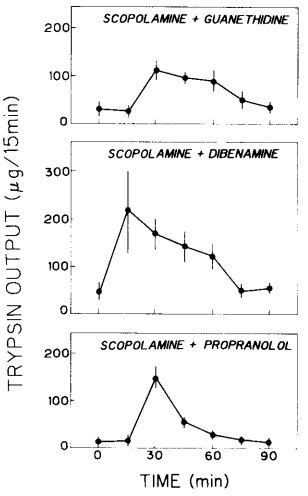

FIG. 7. Time-course change of trypsin output in response to intraluminal infusion of oleate under the administration of scopolamine, plus guanethidine (upper), dibenamine (middle), or propranolol (lower). Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Scopolamine (3 mg/kg), plus guanethidine (7.5 mg/kg), dibenamine (7.5 mg/kg), or propranolol (3.8 mg/kg).

the pancreatic enzyme response to intact dietary protein in the rat is believed to be mainly mediated by CCK (2, 6–8, 22, 23), the suggestion that CCK may not be a major mediator of the pancreatic response to fatty acid or amino acids in dogs and humans has been derived from the observations that atropine administration and vagotomy reduce pancreatic enzyme secretion both during the basal state and during the intraluminal infusion of fatty acid or amino acid (24–27), and from the failure to detect sufficient postprandial plasma CCK increase to account for the observed pancreatic responses (28–31). On the other hand, using a region-specific radioimmunoassay, Himeno *et al.* observed that CCK levels had been greatly elevated after intraluminal infusion of fat in man (32). Hopman *et al.* also observed that fat ingestion had significantly increased the plasma CCK concentration and showed that atropine did not affect the release of CCK (33).

Cholinergic blockages largely decreased the basal level of pancreatic enzyme secretion. These observations are very consistent with a previous report in rats (34) and support the suggestion that basal pancreatic enzyme secretion is maintained mainly by neural mechanisms. On the other hand, these cholinergic blockages have almost no effect on the net increase of trypsin output after oleate is infused. When the net increase of trypsin output 90 min after the infusion (the value obtained by subtracting the basal trypsin output from the total output) is compared, administration of cholinergic blockers, scopolamine hydrobromide, scopolamine methylbromide, and atropine sulfate, did not cause any significant decrease (Table I). Unlike other cholinergic blockers, atropine methyl nitrate inhibited both the basal and the stimulated pancreatic enzyme secretions considerably. This may be due to the ganglion blocking effect of methyl atropine in addition to its cholinergic blocking effect (35).

The observations that cholinergic blockage did not decrease oleate-induced pancreatic enzyme secretion in the rat are inconsistent with those in dogs (2, 3, 5) and in man (6). These discrepancies may be due to species differences. However, attention should be paid to the fact that the basal level of pancreatic enzyme secretion seems to be mediated mainly by neural mechanisms in the rat. Some scientists have observed significant differences in the total enzyme output in response to oleate

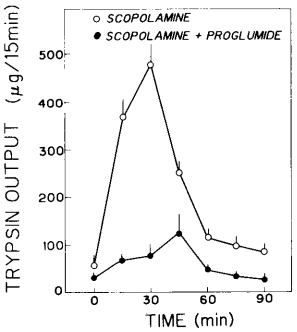

FIG. 8. Time-course change of trypsin output in response to intraluminal infusion of oleate under the administration of scopolamine (○) or scopolamine plus proglumide (●) in rats. Oleate (0.2 ml) was infused into the rat small intestine via a duodenal cannula at 0 time. Scopolamine hydrochloride (3 mg/kg) was injected 1 hr before the infusion and subsequently injected at the same dose at 1-hr intervals during the experiments in both the control and the test groups. In the test group, proglumide (60 mg/kg) was injected intravenously 15 min before the intestinal infusion of oleate.

between the cases of cholinergic blocker administration and control groups if the basal pancreatic enzyme secretion level is considerably higher in experimental animals or under some experimental conditions. It has been pointed out that there are large variations in basal pancreatic enzyme secretion among species or among experimental conditions (34). Petersen and Grossman (36) reported that an anesthetized rat has a much lower level of basal pancreatic secretion than a conscious rat; this is assumed to be caused by anesthesia and/or surgical trauma. However, even under anesthesia they observed normal pancreatic enzyme secretion after injection of CCK or secretin. Thus, our anesthetized rat system is favorable for detecting a net increase in pancreatic enzyme secretion in response to fatty acid in large variations of basal secretion.

We next examined the effects of other neural blockages to determine whether the increase of pancreatic enzyme secretion induced by oleate in the presence of cholinergic blockages is mediated by the hormonal mechanisms. The results were somewhat unexpected because adrenergic blockers alone effectively reduced pancreatic enzyme secretion both in the basal state and in the stimulated state. Little attention has been paid, as far as we know, to adrenergic modulation of pancreatic enzyme secretion in response to food stimuli, and it has been believed that hormonal and cholinergic mechanisms play major roles (37). Only a report by Demol and Sarles (38) showed that the α-blocker phentolamine impaired the pancreatic response to intestinal infusion of trypsin inhibitors. However, Green (39) failed to confirm their work. It is not determined whether pancreatic enzyme secretion in response to oleate is due to the same mechanism as the pancreatic response to trypsin inhibitors.

The result that ganglion blockage led to almost complete inhibition of pancreatic enzyme secretion in response to oleate, taken together with the fact that cholinergic blockage had no effect on oleate-stimulated secretion (Fig. 2 and Table I), also suggests that the adrenergic mechanism takes part in controlling pancreatic enzyme secretion to oleate. It seems that no other unknown neural factors are involved other than the α- and β-adrenergic systems because the α-blocker administered together with the β-blocker almost completely suppressed the response to oleate. This suppression is as much as that caused by a general adrenergic blocker or ganglion blocker. However, an attempt to determine which of the α- and β-adrenergic mechanisms is more dominant ended with somewhat unclear results. Even when excessive doses were administered, the α- and β-blockers led to partial, but not complete, inhibition of the pancreatic response to oleate, as shown in Figs. 5 and 6, respectively. There was a tendency for the inhibitory effect of the α-blocker to be slightly greater than that of several kinds of β-blocker, although the degree of the inhibition by the β-blockers largely varied. It should be noted that in the presence of scopolamine, the inhibiting effects of several adrenergic blockers were diminished. However, in our cases, it has not been clearly determined whether or not anesthesia or surgical trauma inhibits pancreatic enzyme secretion in response to fatty acid administration. If so, then in the case of conscious rats the relative contribution of the adrenergic modulation discussed above may be less than that in anesthetized rats. Further study will be needed on these points.

Based on these results, one could suppose that pancreatic response to oleate is dominantly mediated by a neural, especially an adrenergic, mechanism. However, somewhat paradoxical results were obtained from the experiments using proglumide, which is assumed to be a specific CCK receptor antagonist. In the presence of scopolamine, a cholinergic blocker, proglumide inhibited the pancreatic enzyme secretion response to oleate which was inhibited by adrenergic blockages and ganglion blockages as well. It may be reasonable to interpret the data as follows: pancreatic enzyme secretion to oleate is mediated primarily by CCK. However, integrity of the adrenergic system is indispensable for mediation by CCK of intraluminal stimuli to the pancreas by oleate. Much evidence has been found to show that proglumide is a specific CCK receptor antagonist *in vitro* and *in vivo* (40–42). Stubbs and Stabile (15) have claimed that CCK is of prime importance in the intestinal phase of pancreatic response in dogs, since they found that proglumide caused virtually complete inhibition of pancreatic enzyme secretion in response to intraluminal

amino acid and oleate. These results are consistent with our data. However, it should be noted that we observed that, as a side effect, intravenous injection of proglumide greatly increased the secretion volume of rat bile–pancreatic juice. The same phenomenon was observed by Louie *et al.* (43). Although specificity of proglumide as a CCK receptor antagonist should be examined further *in vivo* (it seems unreasonable that so much proglumide should be injected to show that it is working as a CCK-receptor antagonist), since proglumide has acted as a CCK receptor antagonist in this study, it seems that CCK release by oleate or sensitivity of the pancreas to CCK is due at least partly to the integrity of adrenergic mechanisms, whether directly or indirectly. There has been little information about the proposed interaction of adrenergic mechanism and CCK release or of adrenergic mechanism and sensitivity of the pancreas to CCK. More examinations are necessary to determine where the adrenergic system modulates in the course of CCK mediation from the intestine to the pancreas.

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