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A Role of Endogenous Somatostatin in Exocrine Secretion Induced by Intrapancreatic Cholinergic Activation

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A role of endogenous somatostatin in pancreatic exocrine secretion induced by intrapancreatic cholinergic activation was studied in the isolated rat pancreas perfused with modified Krebs-Henseleit solution. Intrapancreatic neurons were activated by electrical field stimulation (EFS: 15 V, 2 msec and 8 Hz). Pancreatic exocrine secretion, including volume flow and amylase output, and release of somatostatin from the pancreas were respectively determined. Somatostatin cells in the islet were stained with an immunoperoxidase method. EFS significantly increased pancreatic volume flow and amylase output, which were reduced by atropine by 59% and 78%, respectively. Intraarterial infusion of either pertussis toxin or a somatostatin antagonist resulted in a further increase in the EFS-evoked pancreatic secretion. EFS also further elevated exocrine secretion in the pancreas treated with cysteamine, which was completely restored by intraarterial infusion of somatostatin. EFS significantly increased not only the number of immunoreactive somatostatin cells in the islet but also the concentration of immunoreactive somatostatin in portal effluent. It is concluded from the above results that intrapancreatic cholinergic activation elevates pancreatic exocrine secretion as well as release of endogenous somatostatin. Endogenous somatostatin exerts an inhibitory influence on exocrine secretion induced by intrapancreatic cholinergic activation via the islet-acinar portal system in the isolated pancreas of the rat.

Key Words: Somatostatin, Intrapancreatic cholinergic neurons, Pancreatic secretion, Rats

INTRODUCTION

It has been reported that the exocrine pancreas is partially supplied by the blood flow which passes through the Langerhans' islet (Henderson & Daniel, 1979; Lifson et al, 1985; Schönfeld et al, 1994). This finding indicates that a portal system exists between the endocrine and the exocrine parts of the pancreas (the islet-acinar portal system) and that islet peptides could reach pancreatic acinar cells in high concentrations. It has been experimentally proved that insulin, an islet hormone, gives a great influence on acinar cell functions through the islet-acinar portal system (Williams & Goldfine, 1985; Garry et al, 1989; Park et al, 1993; Lee et al, 1994; Lee et al, 1996a).

Somatostatin, another islet peptide, is known to inhibit pancreatic exocrine secretion induced by various stimulants (Chariot et al, 1978; Singh, 1986; Lee et al, 1994). It is, however, unclear at the present time if endogenous somatostatin plays an inhibitory role in pancreatic exocrine secretion through the islet-acinar portal system. It has been reported that cholinergic activation results in stimulation of pancreatic exocrine secretion as well as somatostatin release (Guzman et al, 1979; Kimura et al, 1982; Ahren et al, 1986). Since exogenous somatostatin inhibits pancreatic exocrine secretion induced by cholinergic activation (Chariot et al, 1978; Singh, 1986; Garry et al, 1989), it seems to be possible that the effect of cholinergic activation on pancreatic exocrine secretion could be reduced by somatostatin which is con-

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comitantly released from the islets during cholinergic activation and reaches exocrine cells through the islet-acinar portal system.

We have already published that intrapancreatic cholinergic activation results in stimulation of exocrine secretion in the rat pancreas (Lee et al, 1996b). The present study, therefore, was aimed to investigate if the pancreatic exocrine secretory response to intrapancreatic cholinergic activation could be modified by endogenous somatostatin released concomitantly from the islet. It was also examined if endogenous somatostatin gives influences on the pancreatic exocrine response to the intrapancreatic cholinergic activation via the islet-acinar portal system. The isolated perfused pancreas model was employed in the present study to eliminate possible influences of somatostatin released from the other organs in the body.

METHODS

Experimental animals

Male Sprague-Dawley rats, weighing 250~300 g, were anesthetized with an intraperitoneal injection of 25% urethane (Sigma, St. Louis, MO, USA) at a dose of 7 ml/kg after 24 hour-fasting but with free access to water. The rats were sacrificed by an intravenous overdose of urethane after isolation of the pancreas.

Preparation of the totally isolated vascularly perfused pancreas

The isolated pancreas was prepared according to the method described previously (Penhos et al, 1969; Park et al, 1993). In brief, the abdominal aorta was carefully dissected and cannulated with a PE-50 tubing (0.58 mm ID, 0.97 mm OD; Clay Adams, Parsippany, NJ, USA) just above the celiac artery, while the aorta was tightly ligated below the superior mesenteric artery. The pancreatic duct was cannulated at the duodenal end with a PE-10 tubing (0.28 mm ID, 0.61 mm OD; Clay Adams). The isolated pancreas was perfused with modified Krebs-Henseleit solution (pH 7.4, 305 mosmol/kg water) through the celiac and superior mesenteric arteries at a flow rate of 1.2 ml/min by using a multistaltic pump (Buchler, Kansas, MO, USA). The hepatic portal vein was cannulated with a tygon microbore tubing (1.27 mm ID, 2.28 mm OD; Fisher Scientific, Pittsburgh, PA, USA) to drain the perfusate. The perfusate contained 0.1% bovine serum albumin (Sigma), 3% Dextran T-70 (Sigma), 5.6 mM glucose and it was continuously oxygenated with 95% O_2 containing 5% CO_2. Insulin (Sigma) at a concentration of 100 nM was added to the perfusate to intensify an effect of electrical field stimulation (EFS) on pancreatic exocrine secretion (Lee et al, 1996b). The isolated pancreas, including the duodenum, was placed in a temperature-controlled experiment chamber at 37°C, which was also continuously supplied with Krebs-Henseleit solution at a flow rate of 0.35 ml/min and oxygenated. After an equilibration period of 30 min, pancreatic juice as well as portal effluent in 15 min-samples were sequentially collected throughout the entire period of the experiment.

Electrical field stimulation of the isolated pancreas

EFS was applied to the isolated perfused rat pancreas for 45 min after the basal period of 30 min via a pair of coiled platinum electrodes immersed in the experiment chamber with a distance of 5 cm. EFS was performed by using biphasic square waves with parameters of 15 V, 2 msec and 8 Hz. Atropine (Sigma) at a concentration of 2 μM was dissolved in the perfusate starting 45 min before EFS until the end of the experiment.

Pharmacological blocking of the action of endogenous somatostatin

The action of endogenous somatostatin was eliminated by adding either pertussis toxin (Sigma), a well-known non-specific somatostatin inhibitor in pancreatic acinar cells (Koch et al, 1985; Viguerie et al, 1988), at a concentration of 200 ng/ml or Cyclo-(7-Aminoheptanonyl-Phe-D-Trp-Lys-Thr[BZL]) (Sigma), a specific somatostatin antagonist in pancreatic acinar cells (Fries et al, 1982), at a concentration of 10 nM to the perfusate starting 45 min before EFS until the end of the experiment. For depletion of somatostatin in Langerhans' islets (Szabo & Reichlin, 1981; Sorenson et al, 1983; Silvestre et al, 1986), cysteamine (2-Mercaptoethylamine hydrochloride; Sigma) was subcutaneously injected to rats at a single dose of 300 mg/kg at 24 hr before the experiment. To observe an effect of exogenous somatostatin on the EFS-evoked pancreatic exocrine secretion, synthetic somatostatin (Peninsula, Belmont, CA, USA)

was intraarterially infused to the pancreas isolated from the cysteamine-treated rat at a concentration of 100 pM starting 45 min before EFS until the end of the experiment.

Immunocytochemistry

The isolated perfused rat pancreas was fixed in Bouin solution and processed according to a standard procedure for paraffin embedding. Serial paraffin sections were made and immunolabeled as described previously (Park & Bendayan, 1992). Briefly, the sections were incubated with rabbit anti-somatostatin antibody (1:1,500, INC Corp, Stillwater, MN, USA). After incubation with primary antibody, the tissue sections were treated with biotin-labeled anti-rabbit antibody (1:500, Vector Lab, Burlingame, CA, USA) according to the avidin-biotin-peroxidase complex immunocytochemical technique (Hsu et al, 1981). Immunoperoxidase reaction was developed by substrate solution of diaminobenzidine tetrahydrochloride (Sigma).

Measurements

Volume flow of pancreatic juice was determined by measuring the length of pancreatic juice collected in a microtube with a capacity of 3.8 μl/cm. Amylase activity in pancreatic juice was measured by the method of Rick and Stegbauer (1974). The concentration of immunoreactive somatostatin in portal venous effluent was determined by radioimmunoassay. The 4 ml of portal venous perfusate was extracted on a column of XAD-2 resin as previously described by Lee et al (1994). Synthetic somatostatin-14 was added in 4 ml of the perfusate and extracted in parallel with the samples. The extracted standards exhibited a dose-dependent inhibition of tracer binding and formed a linear standard curve in a logit-log plot. The concentration of somatostatin in the unknown sample was calculated by antilog conversion of its log concentration. ^{125}I-[Tyr]-somatostatin prepared as described by Lee et al (1994) and a goat anti-somatostatin serum (1:50,000) were used for the present assay.

Statistical analysis of data

All data are illustrated as means ± SE. The statistical analysis was evaluated by the Student's *t* test. Difference was considered significant when *p* value is less than 0.05.

RESULTS

Effects of EFS on spontaneous pancreatic exocrine secretion

During the basal period, the isolated perfused rat pancreas spontaneously secreted a minute amount of juice (2.25 ± 0.32 μl/45 min) and amylase activity (38.63 ± 6.35 U/45 min). Application of EFS to the isolated pancreas resulted in significant increases ($p < 0.001$) in volume flow and amylase output from the basal levels to peak levels of 14.61 ± 1.12 μl/45 min and 202.56 ± 20.46 U/45 min, respectively. Atropine (2 μM) markedly inhibited ($p < 0.001$) the EFS-evoked pancreatic volume flow and amylase output by 59% and 78%, respectively (Fig. 1).

Effects of endogenous and exogenous somatostatins on the EFS-evoked pancreatic exocrine secretion

Pertussis toxin, Cyclo-(7-Aminoheptanonyl-Phe-D-Trp-Lys-Thr[BZL]) and cysteamine did not change the basal level of pancreatic exocrine secretion. As shown in Fig. 2, however, pertussis toxin significant-

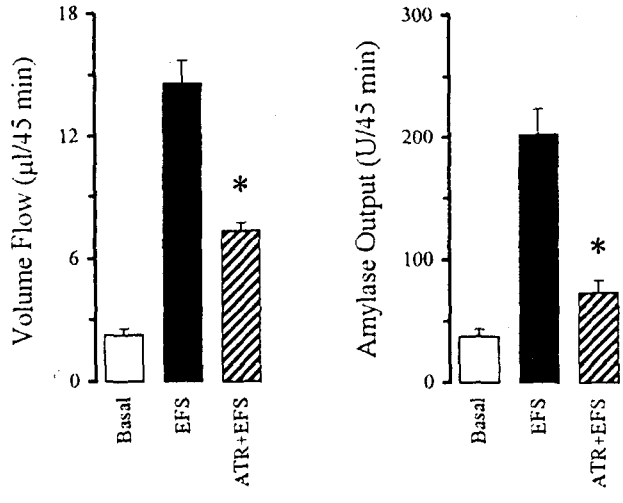

Fig. 1. Effect of atropine (ATR) on pancreatic volume flow and amylase output evoked by electrical field stimulation (EFS). Each value represents mean ± SE of 6 pancreata. Atropine (2 μM) significantly reduces (*$p < 0.001$) the EFS-evoked pancreatic volume flow and amylase output.

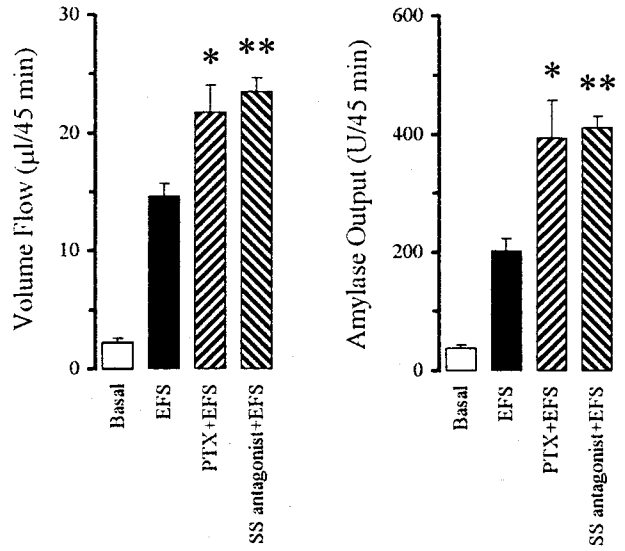

Fig. 2. Effects of pertussis toxin (PTX) and Cyclo-(7-Aminoheptanonyl-Phe- D-Trp-Lys-Thr[BZL]), a somatostatin (SS) antagonist, on the EFS-evoked pancreatic volume flow and amylase output. Each value represents mean ± SE of 6 pancreata. Both pertussis toxin and the somatostatin antagonist significantly increases ($*p<0.05$, $**p<0.01$) the EFS-evoked pancreatic volume flow and amylase output.

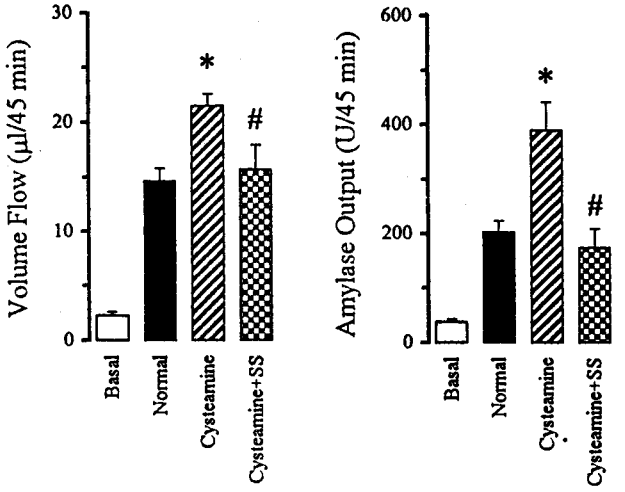

Fig. 3. Effect of somatostatin on the EFS-evoked pancreatic volume flow and amylase output in the cysteamine-treated pancreas. Each value represents mean ± SE of 6 pancreata. The pancreatic exocrine responses to EFS are significantly increased ($*p<0.01$) in the cysteamine-treated pancreas. The cysteamine effect is significantly suppressed ($^{\#}p<0.05$) by somatostatin (SS; 100 pM).

ly further elevated ($p<0.05$) the EFS-evoked volume flow and amylase output to 21.72±2.28 μl/45 min and 393.35±64.25 U/45 min, respectively. Cyclo-(7-Aminoheptanonyl-Phe-D-Trp-Lys-Thr[BZL]) also significantly raised ($p<0.01$) the EFS-evoked volume flow and amylase output to 23.50±1.17 μl/45 min and 410.92±19.62 U/45 min, respectively. In the cysteamine-treated pancreas, the EFS-evoked volume flow and amylase output markedly increased ($p<0.01$) to 21.44±1.09 μl/45 min and 388.87±51.4 U/45 min, respectively. Synthetic somatostatin (100 pM) significantly suppressed ($p<0.05$) the EFS-evoked volume

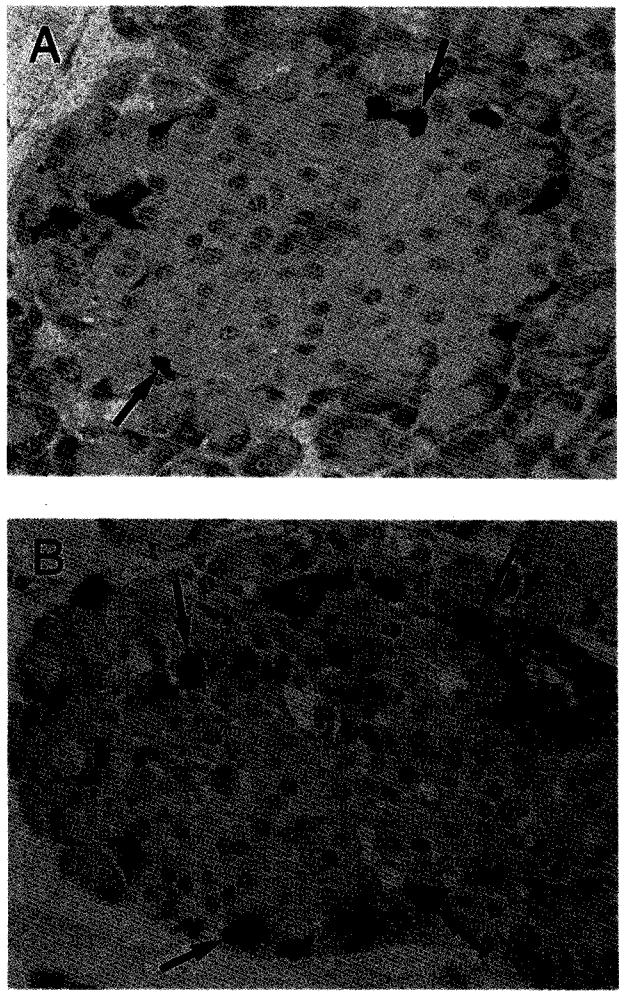

Fig. 4. Effect of EFS on somatostatin immunoreactive cells in the Langerhans' islet of the isolated rat pancreas. The cells stained of strong somatostatin immunoreactivity are identified at the periphery of the islet in the control (A) and stimulated (B) pancreas (arrows). The number of cells with somatostatin immunoreactivity in the islet remarkably increased in the stimulated pancreas. Magnification ×350.

flow and amylase output to 15.68±2.14 μl/45 min and 173.44±33.86 U/45 min, respectively, in the cysteamine-treated pancreas (Fig. 3).

Morphometric evaluation of somatostatin cells in islets

In general, somatostatin cells were distributed at the periphery of the Langerhans' islets. The number of somatostatin cells in the islets of the isolated pancreas significantly increased ($p<0.05$) from 4.89 ±1.13 cells/islet in the basal state to 8.40±1.25 cells/islet in the second 15 min-period of EFS (Fig. 4, 5).

The concentration of somatostatin-like immunoreactivity in portal venous effluent

The mean concentration of somatostatin-like immunoreactivity in portal venous effluent significantly increased ($p<0.001$) from the basal level of 0.89± 0.18 pM to a peak level of 1.94±0.15 pM in the second 15 min-period of EFS (Fig. 6).

DISCUSSION

In the present study, application of EFS to the isolated perfused pancreas resulted in a marked increase in exocrine secretion, including volume flow and amylase output, as reported previously (Lee et al, 1996b). In order to intensify the effect of EFS on pancreatic exocrine secretion in this study, insulin was added to the perfusate at a concentration of 100 nM because cholinergic action to the exocrine pancreas was reportedly enhanced by insulin (Lee et al, 1996b). Atropine inhibited the EFS-evoked pancreatic volume flow and amylase output by 59% and 78%, respectively. The inhibition of the EFS-evoked amylase secretion by atropine has been already reported in the isolated segments of the rat pancreas (Pearson et al, 1984; Varga et al, 1990). These results indicate that the effect of EFS on pancreatic exocrine secretion is mainly mediated by cholinergic activation. The incomplete inhibition of the EFS-evoked pancreatic exocrine secretion by atropine suggests that intrapancreatic non-cholinergic excitatory neurons, probably peptidergic excitatory neurons (Bishop et al, 1980; Moghimzadeh et al, 1983), may be also activated by EFS. Participation of the intrapancreatic peptidergic neurons in the EFS-evoked pancreatic exocrine secretion is remained to be elucidated in the future study.

Since somatostatin, an islet hormone, is released by

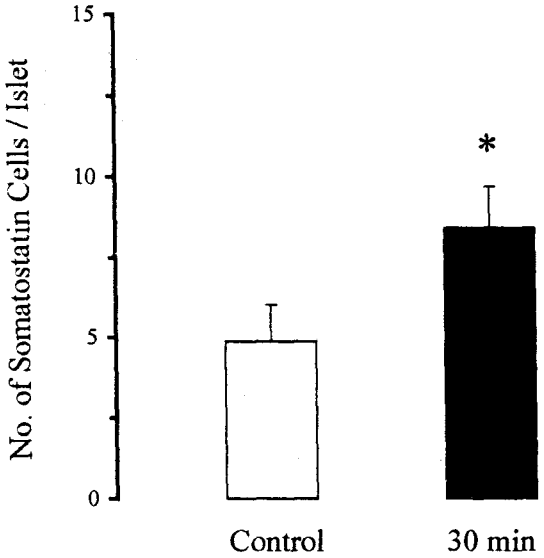

Fig. 5. Effect of EFS on the number of somatostatin immunoreactive cells in the Langerhans' islet of the isolated rat pancreas. Each value represents mean±SE of 40 islets in 3 pancreata. The number of somatostatin immunoreactive cells in the islet significantly increased (*$p<0.05$) in the second 15 min-period (30 min) of EFS.

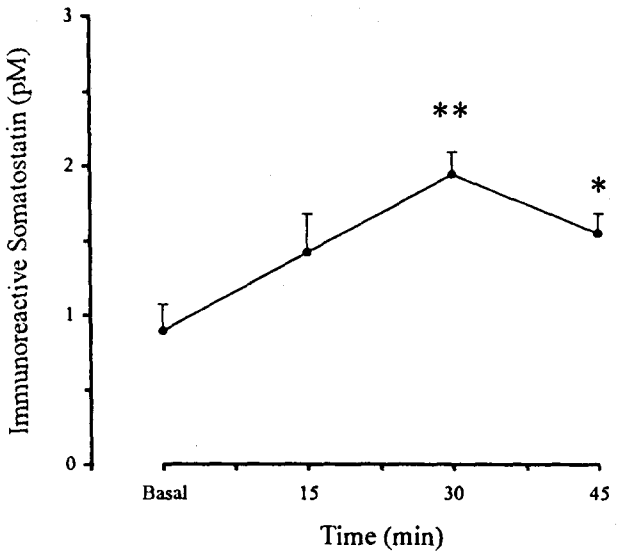

Fig. 6. Effect of EFS on the mean concentration of somatostatin-like immunoreactivity in portal venous effluent. Each value represents mean±SE of 10 pancreata. EFS significantly increases (*$p<0.01$, **$p<0.001$) the mean concentration of somatostatin-like immunoreactivity to the peak level in the second 15 min-period of EFS.

cholinergic activation (Guzman et al, 1979; Kimura et al, 1982; Ahren et al, 1986) and suppresses pancreatic exocrine secretion stimulated by cholinergic activation (Chariot et al, 1978; Singh, 1986; Garry et al, 1989), it is hypothesized that the effect of EFS on pancreatic exocrine secretion may be reduced by endogenous somatostatin which is concomitantly released by EFS. To prove this hypothesis, the action of endogenous somatostatin on pancreatic secretion was blocked by somatostatin inhibitors in this study. The most important finding of the present investigation is that not only pertussis toxin, a non-specific somatostatin inhibitor in pancreatic acinar cells (Koch et al, 1985; Viguerie et al, 1988) but also Cyclo-(7-Aminoheptanonyl-Phe-D-Trp-Lys-Thr[BZL]), a specific somatostatin antagonist in pancreatic acinar cells (Fries et al, 1982) further elevate the EFS-evoked pancreatic volume flow and amylase output. The EFS-evoked pancreatic volume flow and amylase output also increased in the pancreas in which endogenous somatostatin was depleted by cysteamine, a well-known somatostatin-depleting agent (Szabo & Reichlin, 1981; Sorenson et al, 1983; Silvestre et al, 1986). In addition, exogenous somatostatin completely restored the EFS-evoked pancreatic exocrine secretion in the cysteamine-treated pancreas. The results strongly indicate that the EFS-evoked pancreatic exocrine secretion increases when the action of endogenous somatostatin is eliminated. Taken together these results, it is suggested that intrapancreatic cholinergic activation may release endogenous somatostatin, which reduces the stimulatory effect of intrapancreatic cholinergic activation on pancreatic exocrine secretion.

In order to verify that endogenous somatostatin is released by EFS in this study, somatostatin-like immunoreactivities in portal effluent and islets were determined by radioimmunoassay and immunocytochemistry, respectively. The concentration of somatostatin-like immunoreactivity in portal effluent was elevated twofold during application of EFS to the isolated pancreas. The number of somatostatin immunoreactive cells in Langerhans' islets was also markedly increased by EFS. The results strongly indicate that EFS increases synthesis and release of endogenous somatostatin from somatostatin cells in the islets. The increase in somatostatin release by EFS is in a good agreement with results obtained by vagal stimulation in dogs (Ahren et al, 1986; Guzman et al, 1989) and by a cholinergic agonist in rats (Kimura et al, 1982). It is, however, at variance with Nishi's report (1987) in which vagal stimulation rather inhibits somatostatin release from the isolated perfused rat pancreas. Unfortunately, the Nishi's isolated pancreas preparation includes the stomach from which somatostatin release is reportedly inhibited by vagal stimulation (Nishi et al, 1985; Schubert et al, 1987). Thus, it is possible that the inhibition of the somatostatin concentration in portal venous effluent during vagal stimulation in the Nishi's preparation could reflect release of somatostatin from the stomach rather than from the pancreas. The mechanism by which EFS increases the number of somatostatin immunoreactive cells in the islet is unknown at the present time. It is, however, assumed that some somatostatin cells may not be in function in the basal state and that EFS might induce the functionless cells to synthesize somatostatin. The assumption remains to be proved in the future study.

In the present study, we employed the isolated perfused pancreas model in which the intrapancreatic circulation is completely separated from the systemic circulation. Therefore, the results of the present study indicate that endogenous somatostatin released from the Langerhans' islets, like insulin (Garry et al, 1989; Park et al, 1993), also reaches the exocrine part of the pancreas via the islet-acinar axis.

It is concluded from the above results that the activation of the intrapancreatic cholinergic neurons not only exerts a stimulatory effect on pancreatic exocrine secretion but also release of endogenous somatostatin, and that endogenous somatostatin released from Langerhans' islets reaches the exocrine part via the islet-acinar axis and reduces pancreatic exocrine secretion induced by the intrapancreatic cholinergic activation in the isolated perfused rat pancreas.

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