Kor J. Physiol (1991) 25(1),27-35

Cholinergic Control of Pancreatic Secretion: The Effects of Atropine on Plasma Cholecystokinin and Secretin Release

Yang Hyeok Jo, Duck Joo Rhie, Young Soon Chang, Sang June Hahn, Sang Soo Sim, Myung Suk Kim and Chung Chin Kim

Department of Physiology, Catholic University Medical College, Seoul, Korea

= ABSTRACT=

Generally, it has been known that cholecystokinin (CCK) release into the plasma is under cholinergic control, but secretin release is not. Thus in anesthetized dogs we studied the effect of atropine (50 μg/kg followed by 50 μg/kg/hr) on pancreatic secretion and plasma concentrations of bioactive CCK and immunoreactive secretin in response to intraduodenal perfusion of sodium oleate (1, 3 and 9 mmol/hr). The volume, protein output and bicarbonate output of the secretion were increased by sodium oleate and this oleate-induced secretion was decreased significantly by atropine administration. However the increased plasma CCK and secretin levels by sodium oleate were not changed by atropine. These results indicate that atropine suppressed sodium oleate-induced pancreatic secretion through inhibiting cholinergic mechanism directly rather than decreasing the release of pancreatic secretory hormones. In another set of experiments, bilateral cervical vagi were stimulated electrically to observe the changes of pancreatic secretion and the above two plasma hormone levels in the presence or absence of atropine. In the vagally stimulated dogs, the volume, protein output and bicarbonate ouput of the pancreatic secretion were increased significantly. Both plasma secretin and CCK were concomitantly released significantly by vagal stimulation. Atropine significantly depressed the pancreatic secretory response as well as the release of these two pancreatic secretory hormones. Therefore, we conclude that in the presence of atropine the depressed pancreatic response to vagal stimulation is at least, in part, due to decreased release of endogenous CCK and secretin. In the vagally stimulated animals, however, the involvement of direct cholinergic influence on pancreatic exocrine gland remains to be answered.

Key Words: Pancreatic exocrine secretion, Sodium oleate, Electrical vagal stimulation, Cholecystokinin, Secretin

INTRODUCTION

Administration of atropine decreases pancreatic secretory response to intestinal stimulants (Chey et al, 1979; Vazquez-Echarri et al, 1986; Jo et al, 1987) as well as to vagal stimulation (Kim et al, 1989) in dogs. The inhibitory mechanism of atropine on pancreatic exocrine secretion is uncertain. The atropine effect could be interpreted as either due to an impaired release of pancreatic secretory hormones such as CCK (Kim et al, 1989) and secretin, or to an interruption of an cholinergic influence on the pancreas (Jo et al, 1987). Plasma CCK response to atropine administra-

Received Mar 21, 1991; Accepted May 19, 1991.

This paper was supported by NON DIRECTED RESEARCH FUND, Korea Research Foundation, 1989 and in part by the Research Fund of the Catholic Medical Center, Seoul, Korea.

tion seems to vary depending on the pancreatic secretory stimulants in dogs. For instance, in the vagally stimulated dog, the increased plasma CCK level was suppressed by atropine (Kim et al, 1989), however, intraduodenal fat-induced CCK release was not (Jo et al, 1987). On the other hands, in man, the CCK response to intestinal fat could be inhibited (Maton et al, 1984) or not (Valenzuela et al, 1983; Brugge et al, 1987) by systemic atropinization. One likely explanation for these conflicting findings may be attributable to the limited sensitivity of CCK radioimmunoassay (Walsh, 1987). The recent availability of sensitive bioassay for CCK (Liddle et al, 1984) has allowed us to address the role of the cholinergic nervous system in the control of CCK release. In contrast, the release of secretin has been reported not to be altered by atropine in dogs (Lee et al, 1978; Guzman et al, 1979).

The aims of the present study were (1) to ascertain whether the release of CCK by intestinal fat is indeed independent of cholinergic control, (2) to confirm that release of CCK by electrical vagal stimulation is dependent on cholinergic control, and (3) to verify the participation of plasma secretin in these pancreatic secretory processes. For these purposes, in anesthetized dogs we measured pancreatic exocrine secretions in response to intraduodenal perfusion of sodium oleate or to electrical vagal stimulation in the presence or absence of atropine. The changes of plasma CCK and secretin concentration were also measured by bioassay and radioimmunoassay, respectively.

METHODS

Animal preparation

Twelve mongrel dogs of both sexes, weighing 10~19 kg, were fasted for 20 hr except allowing free access to water. The dogs were anesthetized with α-chloralose (100 mg/kg) via cephalic vein and supplemental doses (30 mg/kg) were administered as needed. The animals were then intubated and ventilated mechanically with supplemental oxygen. A rubber tube was inserted into stomach to drain the gastric secretion during the experiment. Through the midline abdominal incision, a cannula was inserted into the proximal part of the common bile duct and the distal part was ligated. The main and accessory pancreatic ducts were exposed meticulously with minimum tissue damage. The main pancreatic duct was ligated at the portion of duodenal opening, and the accessory pancreatic duct was cannulated to collect pancreatic juice. For the infusion of sodium oleate into the duodenum, a rubber cannula was inserted into the duodenum through the anterior wall of the stomach. Then the pylorus was ligated lightly with an umbilical tape to prevent back leakage of the perfusate into the stomach. To drain the perfusate from the duodenum, another rubber tube was inserted into the distal duodenum at the level of the Treitz' ligament. These tubes were exteriorized with the free ends of the bile and pancreatic cannulas through the abdominal incision. An intravenous catheter filled with 0.15 M saline solution was cannulated into the portal vein via the splanchnic vein. Two additional intravenous catheters were inserted into both femoral veins for dripping Hartmann solution and for infusing atropine, respectively. For electrical vagal stimulation, both cervical vagus nerves were exposed carefully through the midline incision on the anterior surface of the neck. Bipolar stimulating electrodes were placed on each vagus nerve isolated by parafilm from the surrounding tissue. The electrodes were connected to a stimulator (S88, Grass Instrument Co., MA, U.S.A.). One hour was allowed to stabilize the animal's condition.

Experimental procedure

In the dogs which were studied on the effects of intraduodenal sodium oleate, 0.15 M saline was initially infused into the duodenum through the tube placed in the proximal duodenum at a rate of 2.2 ml/min, for 30 min

using a infusion pump (Model 975, Harvard Apparatus, MA, U.S.A.). This was followed by the infusion of sodium oleate at loads of 1, 3 and 9 mmol/hr sequentially every 30 min. Sodium oleate solution was prepared by emulsifying sodium oleate with water and was adjusted to an osmolarity of 300 mOsm with NaCl. Pancreatic secretion was collected continuously in 30 min samples, and portal blood (15 ml) was sampled at the end of each collection period. After another 1 hr of stabilizing period, the identical experiments were repeated on the same animal after atropine sulfate. Atropine sulfate was administered into the femoral vein at a bolus dose of 50 μg/kg with the starting of sodium oleate perfusion and thereafter continuous infusion (50 μg/kg/hr) was followed.

In the dogs which were studied on the cholinergic vagal effects, both vagus nerves were stimulated electrically for 10 min with a parameter of 3 V, 8 Hz and 1 ms. Electrical vagal stimulation was applied after 30-min basal collection of pancreatc secretion. Blood was sampled from portal vein at 0,5,10,15 and 20 min after the electrical stimulation began. Pancreatic juice was collected for 30 min including the electrical vagal stimulatory period. Following an additional 1-hr stabilization, identical procedures were carried out with the same dose of atropine sulfate as described above. Atropine infusion started with the beginning of electrical vagal stimulation.

Pancreatic juice was collected in preweighed microcentrfugetube (1.5 ml) and the volume was estimated by weighing the samples taking a density of pancreatic juice as 1.0. Protein concentration in pancreatic juice was determined by measuring the absorbance at 280 nm in a spectrophotometer. with bovine serum albumin as a standard (Chariot et al, 1990). Bicarbonate concentration was measured by the Van Slyke volumetric method (Hotz et al, 1975). Blood sampled in chilled heparinized glass tubes was centrifuged (1500 g, 15 min) at 4°C to obtain plasma. The plasma was stored at -20°C for further bioassay of CCK and radioimmunoassay of secretin.

Hormone assay

Plasma (4 ml) was assayed for CCK bioactivity as described previously (Liddle et al, 1984: Rhie & Kim, 1991). Briefly, isolated rat pancreatic acini (Williams et al, 1978; Kim & Kim, 1989) were incubated with either known concentrations of CCK-octapeptide (CCK-8) or CCK extracted from plasma. The extraction of CCK was performed by adsorption of plasma onto a Sep-Pak C18 cartridge (Waters Associates, MA, U.S.A.). The solution for eluting CCK was 1 ml of ethanol and 1% trifluoroacetic acid (4 : 1, vol./vol.). The sample was then evaporated crudely under flow of nitrogen in vacuum evaporator (Vortex-Evaporator, Buchler Instruments Ind., NJ, U.S.A.) and was lyophilized. A standard curve for amylase released as a function of CCK-8 concentration was constructed to determine the activity of CCK in the plasma extract. The activity of amylase was measured with commercial kit (Amylase, Wako Pure Chemical Ind., Osaka, Japan). The activity of plasma CCK was expressed as CCK-8 equivalents. Plasma concentration of secretin was determined by radioimmunoassay described previously (Chang & Chey, 1980).

Statistical analysis

All the results were expressed as the mean $\pm$ SE. One-way analysis of variance was used for evaluating pancreatic secretory response to 9 mmol/hr of sodium oleate and vagal stimulatory response and was followed by comparison with the Newman-Keuls multiple range test. Repeated measures analysis of variance were adopted for pancreatic dose-response effect of sodium oleate and hormonal changes in response to sodium oleate perfusion or electrical vagal stimulation. P values less than 0.05 were considered statistically significant.

RESULTS

Effects of intraduodenal sodium oleate on pancreatic exocrine secretion and on plasma CCK and secretin levels

Intraduodenal perfusion of sodium oleate caused dose-dependent increases in pancreatic juice flow, protein output and bicarbonate output (Fig. 1). The increases in bioactive CCK and secretin level of the plasma obtained from the portal vein occurred concomitantly (Table 1). The release of pancreatic secretory hormones in response to intraduodenal sodium oleate was not altered by atropine administration (Table 1), whereas three parameters of pancreatic secretion were significantly decreased (Fig. 2).

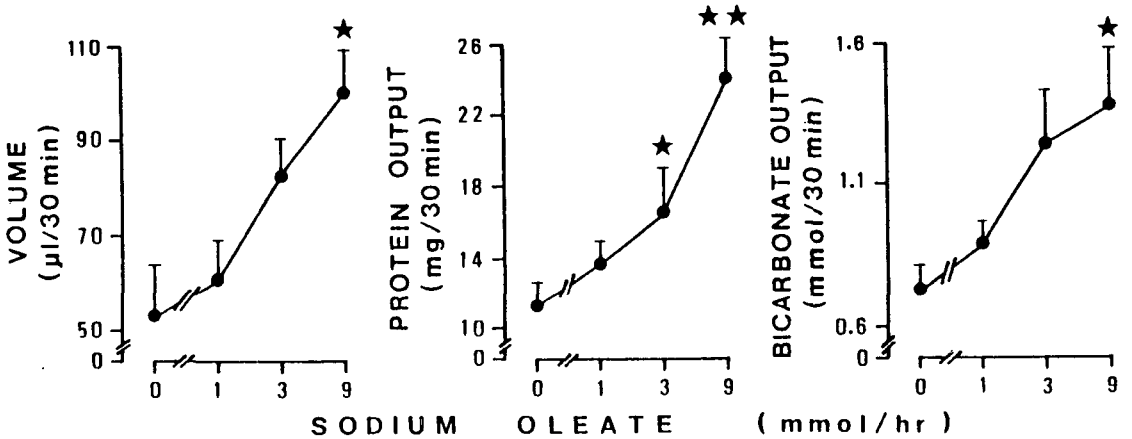

Fig. 1. The pancreatic exocrine secretion in response to 3 doses of sodium oleate perfused sequentially through duodenum in six anesthetized dogs (mean±SE). One, three and nine mmol/hr of sodium oleate were perfused for 30 min, respectively. The pancreatic secretion in volume, protein output and bicarbonate output were stimulated with sodium oleate dose-dependently ($P<0.05$, $P<0.01$ and $P<0.05$ respecitvely). Star represents significant difference from basal value (0 mmol/hr of sodium oleate).
★: $P<0.05$ ★★: $P<0.01$

Table 1. Effect of intraduodenal perfusion of sodium oleate on plasma bioactivity of cholecystokinin (CCK) and concentration of secretin. Atropine (50 μg/kg followed by 50 μg/kg/hr) did not affect the changes of these hormonal levels. Data were expressed with mean ± SE.

Sodium oleate (mmol/hr)	CCK (CCK-8 equivalents, pM)		Secretin (pM)	
	Atropine (−)	Atropine (+)	Atropine (−)	Atropine (+)
0	0.92±0.07	0.96±0.08	1.80±0.12	1.67±0.12
1	1.01±0.15	0.97±0.09	1.91±0.12	1.83±0.15
3	1.09±0.11	1.07±0.10	2.05±0.09	2.11±0.17*
9	1.41±0.10*	1.43±0.14*	2.40±0.14*	2.35±0.18*

*: vs. 0 mmol/hr. $P<0.05$

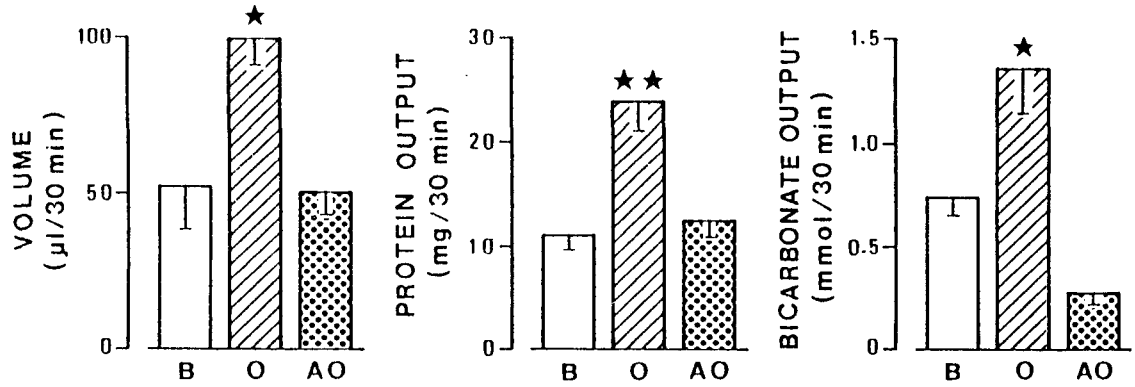

Fig. 2. Effect of sodium oleate (O) on pancreatic exocrine secretion in six anesthetized dogs. Atropine sulfate given intravenously (50 μg/kg followed by 50 μg/kg/hr) significantly inhibited pancreatic secretion induced by 30-min intraduodenal perfusion of sodium oleate at a dose of 9 mmol/hr (AO) (volume: $P<0.05$; protien ouput: $P<0.01$; bicarbonate ouput: $P<0.05$). The basal pancreatic secretion (B) was collected for 30 min during which the duodenum was perfused with 0.15 M NaCl solution. Star represents significant difference from basal value (0 mmol/hr of sodium oleate).
★: $P<0.05$ ★★: $P<0.01$

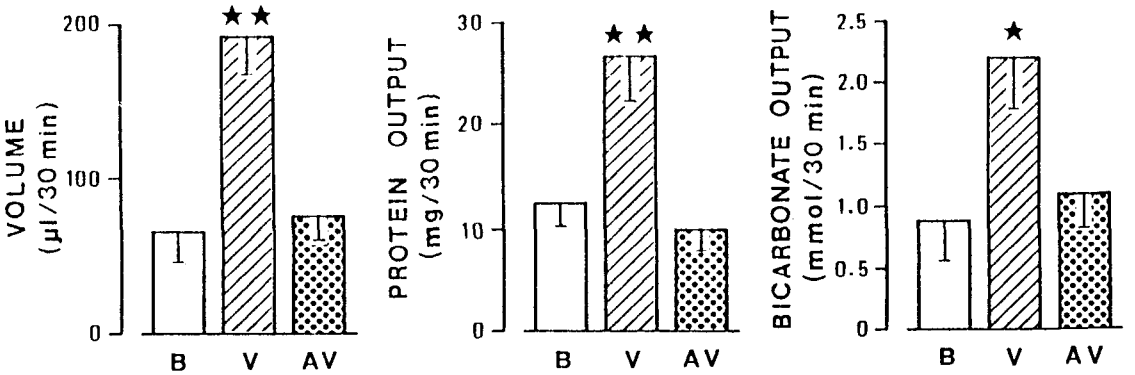

Fig. 3. Effect of 10-min electrical vagal stimulation (V) on 30-min pancreatic exocrine secretion in six anesthetized dogs. The electrical stimulation of both bagi increased pancreatic secretion in volume, protien output and bicarbonate output ($P<0.01$, $P<0.01$ and $P<0.05$, respectively). Atropine (50 μg/kg followed by 50 μg/kg/hr) inhibited the vagally stimulated pancreatic secretion in volume, protein output and bicarbonate output (AV) ($P<0.01$, $P<0.01$ and $P<0.05$, respectively). The basal pancreatic secretion (B) was collected for 30 min before the electrical stimulation of both vagi. Star represents significant difference from basal value. ★: $P<0.05$ ★★: $P<0.01$

Effects of the electrical vagal stimulation on pancreatic exocrine secretion and on plasma CCK and secretin levels

As shown in Fig. 3, electrical stimulation of both vagus nerves increased pancreatic volume, protein output and bicarbonate output from the basal values. The amounts of pancreatic secretion induced by vagal stimulation were larger than those induced by intraduo-

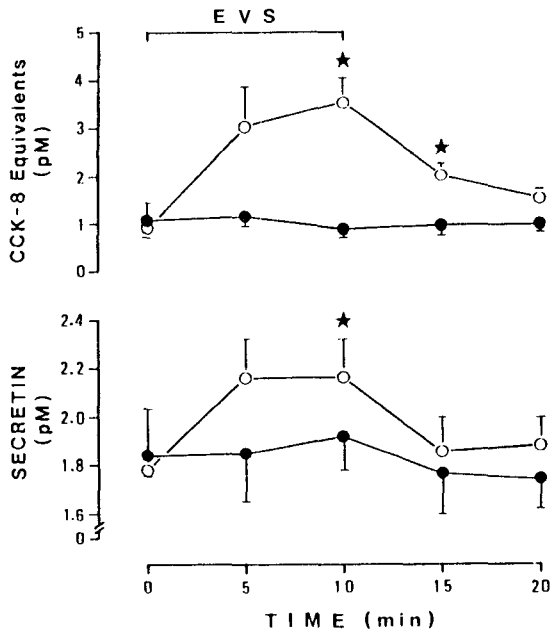

Fig. 4. Time courses of changes in portal plasma concentrations of bioactive cholecystokinin (upper) and immunoreactive secretin (lower) in response to 10-min electrical vagal stimulation (EVS). The vagal stimulation increased significantly both plasma cholecystokinin bioactivity ($P<0.01$) and secretin concentration ($P<0.01$) (○-○). When atropine was given intravenously, the increased release of two hormones was not notified (●-●). Star represents significant difference from 0 min. ★: $P<0.05$

denal sodium oleate (9 mmol/hr). Atropine administration totally abolished the increases of pancreatic volume, protein output and bicarbonate output, which were not different from the basal values. Plasma levels of CCK sampled from the portal vein were significantly elevated from a basal value of 0.99 ± 0.16 pM to a peak value of 3.51 ± 0.54 pM 10 min after electrical stimulation of both vagus nerves (Fig. 4). The plasma concentration of secretin was also increased from a basal value of 1.84 ± 0.20 pM to a peak value of 2.17 ± 0.13 pM. These increases were inhibited significantly by systemic administration of atropine.

DISCUSSION

The involvement of cholinergic and hormonal mechanisms in pancreatic response to intraduodenal fat perfusion was studied in anesthetized dogs. In the present study we have confirmed previous observations (Faichney et al, 1981; Watanabe et al, 1986; Jo et al, 1987; Watanabe et al, 1988) that intraduodenal fat stimulates pancreatic exocrine secretion. The increased pancreatic secretion in response to intestinal fat was known to be associated with increased release of two major pancreatic hormones, secretin and CCK. It has long been argued about neural control of pancreatic hormone release during intestinal phase of pancreatic secretion (Konturek et al, 1974; Guzman et al, 1979; Niebel et al, 1983; Jo et al, 1987). The results of our study clearly show that there is no cholinergic facilitation of releasing above two hormones during intestinal phase. These findings are in agreement with the observations of Niebel et al (1983) and Jo et al (1987). The finding that atropine did not alter release of pancreatic hormones in response to intestinal fat implies that the possible mechanisms by which atropine inhibits the pancreatic secretory response may be direct inhibition of cholinergic influence of the exocrine pancreas. Solomon and Grossman (1979) also hypothesized already that the release of humoral pancreatic excitants, presumably secretin and CCK in response to intestinal stimulants was neither mediated nor modulated by vagal cholinergic mechanism.

The neural components contributing to the basal cholinergic activity of the pancreas are considered to be present in the vagus, splanchnic nerves and intrinsic cholinergic nerves in intact dog (Singer et al, 1986; Hüchtebrock et al, 1991). With our results, it is difficult to elucidate which one is blocked by atropine among the above nervous system. Based on

the study of Singer et al (1986), intrinsic cholinergic nervous system might be one of the neural components blocked by atropine. In their study, the pancreatic bicarbonate secretion induced by secretin was significantly inhibited by atropine even after total extrinsic denervation of the pancreas by truncal vagotomy, and celiac and superior mesenteric ganglionectomy. Another plausible action of atropine on nervous system of the pancreas is interrupting vagal cholinergic enteropancreatic reflex initiated by intestinal stimulants. Although the existence of such a local enteropancreatic reflex has been suggested and demonstrated functionally during the past years (Modlin et al, 1979; Singer et al, 1980), the neural pathway of the reflex needs to be confirmed with anatomic study. Because the splanchnic nerves are generally inhibitory for pancreatic exocrine secretion (Holst, 1986), the inhibition of pancreatic secretion by atropine may result from the blocking actions of either intrinsic cholinergic nervous system, vagus nerve or both.

In a subsequent study, humoral contribution to vagally stimulated pancreatic secretion was studied. Electrical vagal stimulation elicited a significant increase in volume, bicarbonate and protein secretion, although the effect of electrical vagal stimulation of pancreatic exocrine secretion has been known to be smaller in dogs than in other species such as pigs (Hickson, 1970). Furthermore, bioactive CCK activity in portal blood was also increased concomitantly. This observation is in agreement with the recent finding of Kim et al (1989) that CCK in plasma, measured by both radioimmunoassay and bioassay, was increased by vagal stimulation in dogs. The interesting finding of the present study is that secretin was also released significantly into the plasma by electrical vagal stimulation. This result is in conflict with others (Lee et al, 1978). The discrepancy cannot be explained now. Since Konturek et al (1974) found that vagotomy in dogs reduced the pancreatic secretory response to intraduodenal acidification but not to exogenous secretin, it is assumed that vagal innervation plays a permissive role in the release of secretin. The failure of other study in anesthetized dogs (Guzman et al, 1979) to demonstrate an increase in plasma CCK levels by vagal stimulation was probably due to the relative insensitivity of earlier CCK radioimmunoassay system. Furthermore, they infused very large amount of secretin (0.25 CU/kg/hr) as background to maintain continuous flow of pancreatic secretion, therefore the small increase in plasma secretin level might be impossible to be detected. The present finding that vagal stimulation-induced CCK and secretin release was abolished by atropinization indicates that the release of these hormones is under cholinergic influence. Thus, it is concluded that the releasing mechanism of endogenous CCK and secretin might not be sole, but at least two, one is atropine-resistant and another atropine-sensitive. At present, the origin of these pancreatic hormones released by vagal stimulation is obscure, whereas the endogenous CCK and secretin released in response to various luminal stimulants are confined to the foregut in dogs (Konturek et al, 1986a, 1986b). It is also unknown whether CCK and secretin released by electrical vagal stimulation are responsible for the increased pancreatic secretion. According to Kim et al (1989), CCK receptor antagonist given intravenously markedly suppressed pancreatic secretion resulting from vagal stimulation. Therefore CCK released by vagal stimulation appears to be active in stimulating exocrine pancreas. However, the role of plasma secretin released by vagal stimulation remains to be verified. These findings do not exclude the feasibility of a direct inhibitory action of atropine on pancreatic tissue in vagally stimulated dogs. Despite of the fact that the cholinergic nerves are essential in pancreatic exocrine secretion, to what extent cholinergic neural component participates during intestinal phase of the pancreatic secretion is not known yet.

REFERENCES

Brugge WR, Burke CA, Izzo RS & Praissman M (1987) Role of cholecystokinin in intestinal phase of human pancreatic secretion. *Dig Dis Sci* **32,** 155-163

Chang T-M & Chey WY (1980) Radioimmunoassay of secretin, a critical review and current state. *Dig Dis Sci* **25,** 529-552

Chariot J, Nagain C, Hugonet F, Tsocas A & RozÉ C (1990) Control of interdigestive and intraduodenal meal-stimulated pancreatic secretion in rats. *Am J Physiol* **259,** G198-G204

Chey WY, Kim MS & Lee KY (1979) Influence of the vagus nerve on release and action of secretin in dog. *J Physiol (London)* **293,** 435-446

Faichney A, Chey WY, Kim YC, Lee KY, Kim MS & Chang T-M (1981) Effect of sodium oleate on plasma secretin concentration and pancreatic secretion in dog. *Gastroenterology* **81,** 458-462

Guzman S, Chayvialle JA, Banks WA, Rayford PL & Thompson JC (1979) Effect of vagal stimulation on pancreatic secretion and on blood levels of gastrin, cholecystokinin, secretin, vasoactive intestinal peptide, and somatostatin. *Surgery* **86,** 329-335

Hickson JCD (1970) The secretion of pancreatic juice in response to stimulation of the vagus nerves in the pig. *J Physiol (London)* **206,** 275-297

Hüchtebrock H-J, Niebel W, Singer MV & Forssmann WG (1991) Intrinsic pancreatic nerves after mechanical denervation of the extrinsic pancreatic nerves in dogs. *Pancreas* **6,** 1-8

Holst JJ (1986) Neural regulation of pancreatic exocrine function. In: Go VLW, Gardner JD, Brooks FP, Lebenthal E, Dimagno E & Scheel GA (ed) *The exocrine pancreas.* Chapter 20. Raven Press, New York, p 287-300

Hotz J, Zwicker M, Minne H & Ziegler R (1975) Pancreatic enzyme secretion in the conscious rat. Method and application. *PflÜgers Arch* **353,** 171-189

Jo YH, Lee KY & Chey WY (1987) Cholinergic dependence of pancreatic secretion stimulated by sodium oleate in dogs. *Gastroenterology* **92,** 1455 (Abstract)

Kim CK, Lee KY, Wang T, Sun G, Chang T-M & Chey WY (1989) Role of endogenous cholecystokinin on vagally stimulated pancreatic secretion in dogs. *Am J Physiol* **257,** G944-G949

Kim JR & Kim CC (1989) The role of β-adrenergic receptor in regulating amylase release in isolated rat pancreatic acini. *J Cath Med Coll (Seoul)* **42,** 865-873

Konturek SJ, Becker HD & Thompson JC (1974) Effect of vagotomy on hormones stimulating pancreatic secretion. *Arch Surg* **108,** 704-708

Konturek SJ, Tasler J, Bilski J, de Jong AJ, Jansen JBMJ & Lamers CB (1986a) Physiological role and localization of cholecystokinin release in dogs. *Am J Physiol* **250,** G391-G397

Konturek SJ, Tasler J, Bilski J, Konturek J & Bielanski W (1986b) Study on the localization of secretin release form canine intestine. *Digestion* **34,** 207-215

Lee K, Chey W & Tai H (1978) Roles of the vagus in endogenous release of secretin and exocrine pancreatic secretion in dog. In: Grossman M, Speranza V, Basso N & Sezoch E (ed) *Gastrointestinal Hormones and Pathology of the Digestive system.* Plenum, New York, p 211-216

Liddle RA, Goldfine ID & Williams JA (1984) Bioassay of plasma cholecystokinin in rats: effects of food, trypsin inhibitor, and alcohol. *Gastroenterology* **87,** 542-549

Maton PN, Selden AC & Chadwick VS (1984) Atropine inhibits meal-stimulated release of cholecystokinin. *Scand J Gastroenterol* **19,** 831-834

Modlin IM, Hansky J, Singer M & Walsh JH (1979) Evidence that the cholinergic enteropancreatic reflex may be independent of cholecystokinin release. *Surgery* **86,** 352-361

Niebel W, Singer MV, Hanssen LE & Goebell H (1983) Effect of atropine on pancreatic bicarbonate output and plasma concentrations of immunoreactive secretin in response to intraduodenal stimulants. *Scand J Gastroenterol* **18,** 803-808

Rhie DJ & Kim MS (1991) Effects of urethane

anesthesia on pancreatic exocrine secretion in rats. *J Cath Med Coll (Seoul)* **44,** 21-28

Singer MV, Niebel W, Kniesburges S, Hoffmeister D & Goebell H (1986) Action of atropine on the pancreatic secretory response to secretin before and after cutting the extrinsic nerves of the pancreas in dogs. *Gastroenterology* **90,** 355-361

Singer MV, Solomon TE, Wood J & Grossman MI (1980) Latency of pancreatic enzyme response to intraduodenal stimulants. *Am J Physiol* **238,** G23-G29

Solomon TE & Grossman MI (1979) Effect of atropine and vagotomy on response of transplanted pancreas. *Am J Physiol* **236,** E186-E190

Valenzuela JE, Lamers CB, Modlin IM & Walsh JH (1983) Cholinergic component in the human pancreatic secretory response to intraintestinal oleate. *Gut* **24,** 807-811

Vazquez-Echarri J, Baumgärtner D & Singer MV (1986) Dose-response effects of atropine on pancreatic secretory response to intestinal tryptophan in dogs. *Am J Physiol* **251,** G847-G851

Walsh JH (1987) Gastrointestinal Hormones. In: Johnson LR (ed) *Physiology of the gastrointestinal tract.* Chapter 7. Raven Press, New York, p 181-253

Watanabe S, Chey WY, Lee KY & Chang T-M (1986) Secretin is released by digestive products of fat in dogs. *Gastroenterology* **90,** 1008-1017

Watanabe S, Lee KY, Chang T-M, Berger-Ornstein L & Chey WY (1988) Role of pancreatic enzymes on release of cholecystokinin-pancreozymin in response to fat. *Am J Physiol* **254,** G837-G842

Williams JA, Korc M & Dormer RL (1978) Action of secretagogues on a new preparation of functionally intact, isolated pancreatic acini. *Am J Physiol* **235,** E517-E524