Intestinal Fat Suppresses Protein-Induced Exocrine Pancreatic Secretion in Chronically Bile-Pancreatic Juice-Diverted Rats (44491)

HIROSHI HARA,[1] CHINATSU SAUCHI, TAKASHI NISHI, AND TAKANORI KASAI

Division of Applied Bioscience, Graduate School of Agriculture, Hokkaido University, Sapporo 060–8589, Japan

Abstract. **Previously, we showed that the increase in pancreatic enzyme secretion was lower after feeding a casein diet containing fat than that after feeding a fat-free casein diet in chronically bile-pancreatic juice (BPJ)-diverted rats. In the present study, we determined whether the suppressive effects of fats on flow volume of BPJ and pancreatic enzyme secretion depend on delaying gastric emptying and examined the characteristics of the suppression with intraduodenal instillation of soybean oil or lecithin in BPJ-diverted rats. The study was conducted as three separate experiments using conscious rats with chronic BPJ diversion by means of a common bile-pancreatic duct catheter. The flow volume of BPJ and the secretion of pancreatic amylase and trypsin were determined after intraduodenal instillation of the test solution. Exocrine pancreatic secretion was strongly stimulated by administration of guanidinated casein hydrolysate (HGC, 150 mg/ml) in chronic BPJ-diverted rats. However, pancreatic secretion after administration of an emulsion containing HGC with either soybean oil (100 mg/ml) or mixed fat (50 mg/ml soybean oil + 50 mg/ml lecithin) was much lower than that after administration of HGC alone. In contrast, administration of the soybean oil emulsion without HGC resulted in a small, but significant increase in the volume of BPJ. The suppressive effects of soybean oil (100 mg/ml) on the increases in the BPJ flow and enzyme secretion were similar to those of sodium taurocholate (10 mg/ml), and there was no additive effect of soybean oil on taurocholate suppression. In conclusion, duodenally instilled soybean oil suppressed increases in flow volume of BPJ and pancreatic enzyme secretion induced by HGC in chronic BPJ-diverted rats, showing that the suppressive effect of the fat does not depend on delaying gastric emptying.** [P.S.E.B.M. 2000, Vol 223]

Dietary fat affects various digestive functions, such as suppressing gastric emptying and enhancing exocrine pancreatic secretion. Long-chain fatty acids are known to increase exocrine pancreatic secretion (1–3). We have developed a test system to examine BPJ-independent control of the exocrine pancreas using rats whose bile-pancreatic juice (BPJ) was chronically diverted from the proximal small intestine (4). In the BPJ-diverted rats, dietary protein increases enzyme output from the pancreas independent of BPJ (5, 6). However, dietary fat suppresses the BPJ-independent increase in pancreatic enzyme secretion induced by dietary protein (5). The mechanisms responsible for these observations are not known. It is possible that the suppressive effect of dietary fat results from delayed gastric emptying (7, 8), i.e., the delayed transit of ingested protein attenuates the pancreatic enzyme secretion.

Here, we investigated the effect of intraduodenally instilled dietary triglycerides and lecithin on the flow volume of BPJ and pancreatic enzyme secretion enhanced by guanidinated casein in BPJ-diverted rats to determine whether the suppressive effects of dietary fat depend on delayed gastric emptying. Guanidinated casein was used in these studies since the modified protein stimulates pancreatic en-

[1]To whom requests for reprints should be addressed at Division of Applied Bioscience, School of Agriculture, Hokkaido University, Kita-9, Nishi-9, Kita-ku, Sapporo 060–8589, Japan. E-mail: hara@chem.agr.hokudai.ac.jp

Received May 3, 1999. [P.S.E.B.M. 2000, Vol 223]
Accepted October 8, 1999.

0037-9727/00/2233-0276$15.00/0

zyme secretion to a much higher degree than intact casein in the BPJ-diverted rats (9). We also examined the effects of these fats on basal secretion of the exocrine pancreas (secretion in the fasting state), in chronically BPJ-diverted rats. Additionally, we compared the suppressive effect of the triglyceride with that of the bile acid taurocholate, known to inhibit pancreatic enzyme secretion enhanced by BPJ diversion (10–12).

Materials and Methods

Animals and Diets. Male Sprague-Dawley rats (Japan SLC Inc., Hamamatsu, Japan) were fed a semipurified sucrose-based diet containing casein (250 g/kg diet), corn oil(50 g/kg diet) and sufficient amounts of other nutrients [AIN-76 based vitamin mixture (13) and the mineral mixture described by Reeves (14)] for 5 days. After a 24- hr fast, cannula were implanted into the common bile-pancreatic duct and the small intestine of the rats (≈ 250 g) under pentobarbital anesthesia (sodium pentobarbital, 40 mg/kg body weight; Abbott Co., North Chicago, IL), as previously described (15, 16). Briefly, the small tip of a polyethylene catheter (SP 28; I.D. 0.4 mm, O.D. 0.8 mm; Natsume Seisakusyo, Tokyo, Japan) was inserted into the common bile-pancreatic duct. The other end of the catheter was connected to silicone tubing (Silascon No.00, I.D. 0.5 mm, O.D. 1.0 mm; Dow Corning Co., Kanagawa, Japan), and the silicone tubing was led subcutaneously behind the neck. A silicone catheter (Silascon No.00) for BPJ returning to the intestinal lumen was placed through a fistula 45 cm distal from the ligament of Treitz. The intestinal catheter was connected to the bile-pancreatic duct catheter behind the neck to maintain the flow of BPJ. Another silicone catheter (Silascon No.00) for instillation of the test solution was inserted into the duodenal lumen through a gastric fistula. In the BPJ-diverted rats, BPJ flow bypassed the proximal small intestine through the catheters. The rats were allowed to recover for 6 days with free access to the semipurified diet described above. The common bile-pancreatic duct was examined after experiments, and rats with a swollen duct due to occlusion of the catheters were excluded from the analysis.

The present study was conducted as three separate experiments. The BPJ-diverted rats were divided into three groups (Experiments 1 and 3) or two groups (Experiment 2) on the basis of body weight after a 6-day recovery period and a 24-hr fast. Test solution or emulsion was administered into the duodenum through the catheter by a bolus injection (1 ml for 1 min) after sampling the BPJ twice in a fasting state. For BPJ sampling, a polyethylene tube (SP 28; Natsume Seisakusyo) was connected to the bile-pancreatic duct catheter, and BPJ was drawn out through the polyethylene tube under a head placed 5 cm from the bottom of the cage. Bile-pancreatic juice was collected for 3 min at each of the times shown in Figures 1, 2, and 3. Bile-pancreatic juice was recirculated continuously into the ileum through the intestinal catheter except during the 3-min sampling peri-

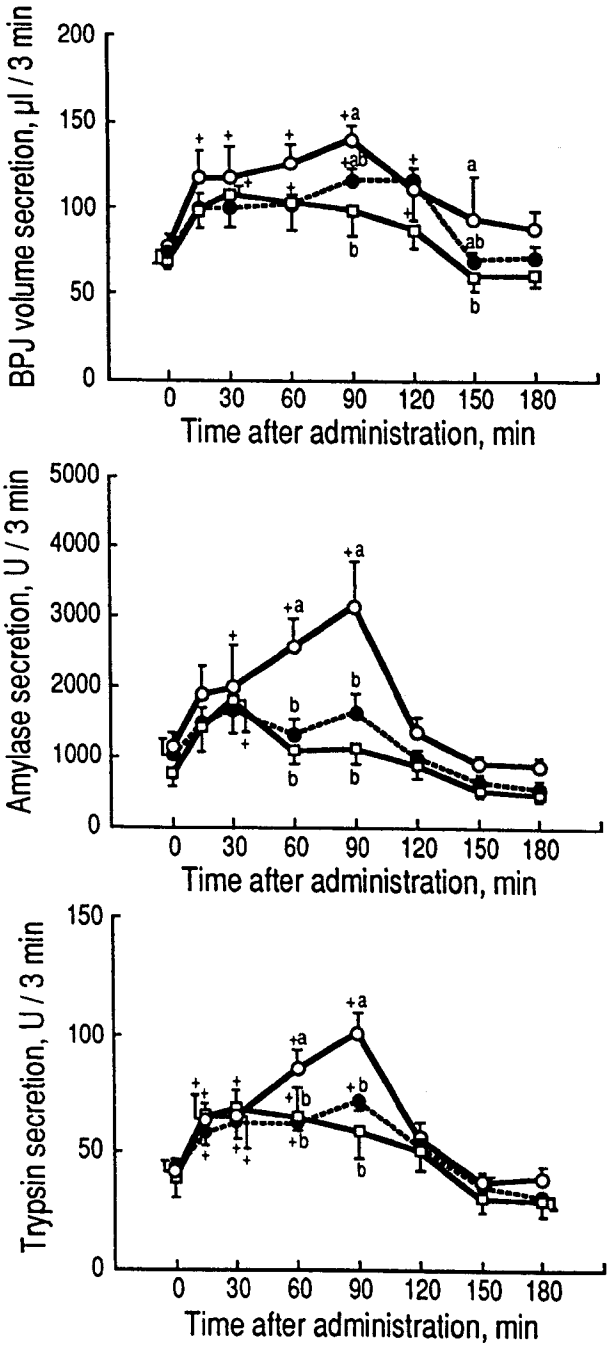
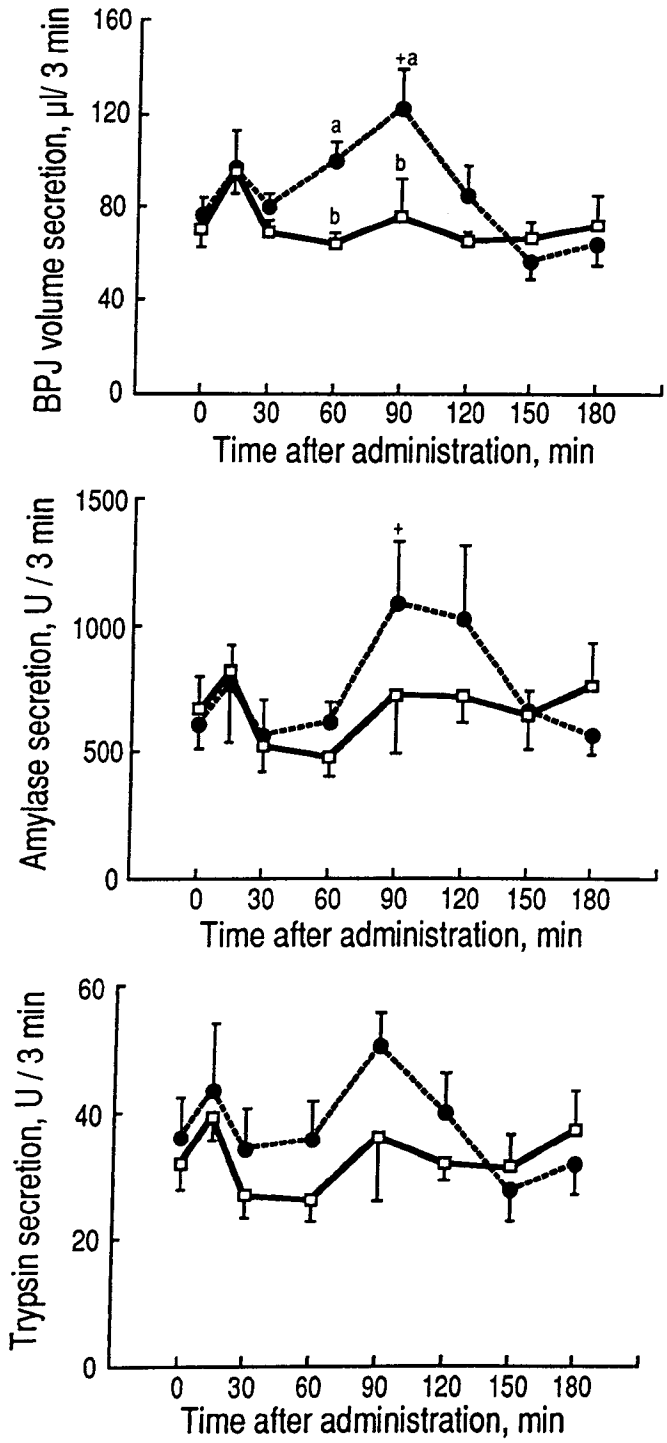


Figure 1. Suppressive effects of fats on enhanced pancreatic secretion by guanidinated casein hydrolysate in chronically bile-pancreatic juice (BPJ)-diverted rats. BPJ volume and amylase and trypsin secretion were monitored at indicated times after intraduodenal instillation of 1 ml containing either 150 mg guanidinated casein hydrolysate (HGC) with 10 mg sodium caseinate solution (open circle, $n = 7$), HGC + 100 mg soybean oil as an emulsion (closed circle, $n = 8$), or HGC + 50 mg soybean oil and 50 mg lecithin as an emulsion (square, $n = 7$). The value at each time represents the volume of BPJ or the level of amylase or trypsin activity in BPJ secreted for 3 min from the time shown on the graph. The values for 0 min (fasting state) are the average for two sampling times before administration. Additional details are described in Materials and Methods. *P*-values of BPJ volume, amylase, and trypsin secretion were < 0.001, < 0.001, and 0.004 for administration (A), all < 0.001 for time (T), and 0.934, 0.203, and 0.173 for A × T, respectively. A mean with a plus sign differs significantly from the value at 0 min in each group ($P < 0.05$). Mean values at the same time postadministration not sharing the same letter differ significantly ($P < 0.05$).



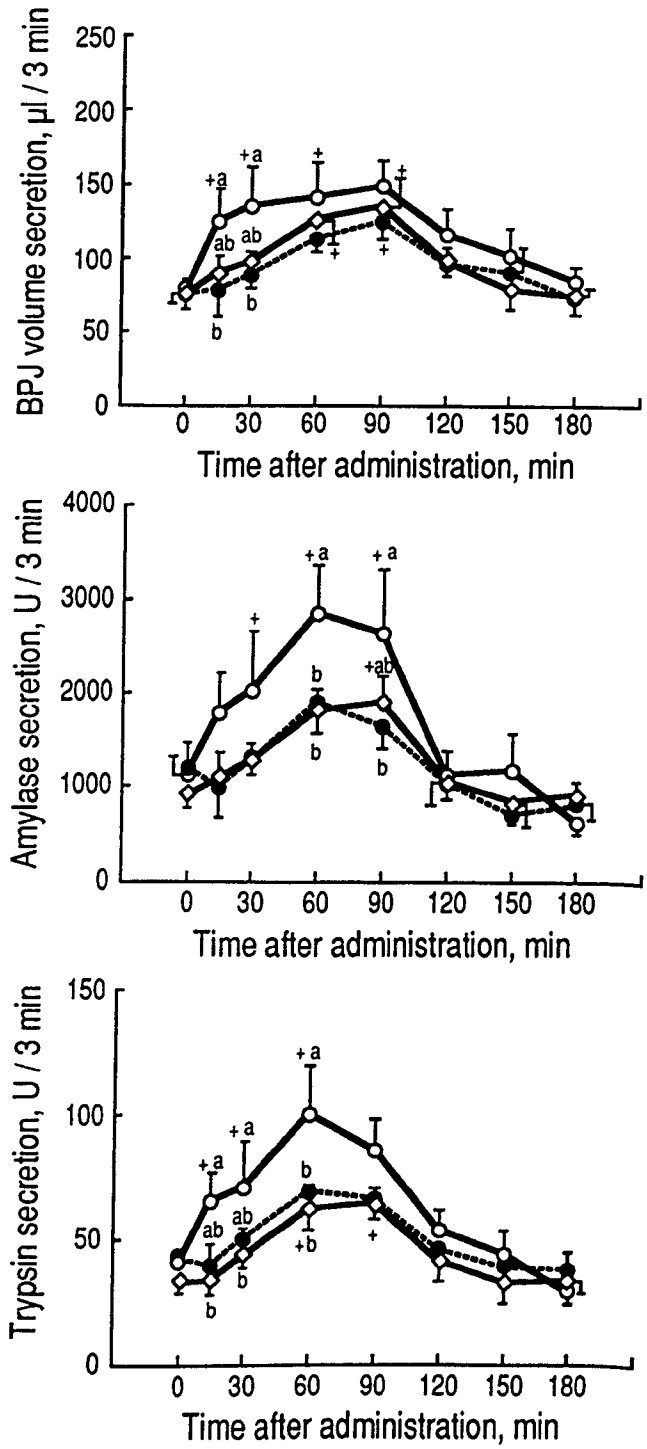


Figure 2. Effects of fats on basal pancreatic secretion in chronically bile-pancreatic juice (BPJ)-diverted rats. Levels of BPJ volume, amylase, and trypsin secretion after intraduodenal instillation of 1 ml containing either 100 mg soybean oil emulsified with 10 mg sodium caseinate (closed circle, $n = 6$) or 50 mg soybean oil and 50 mg lecithin emulsified with 10 mg sodium caseinate (square, $n = 8$) are shown. Other details were the same as for Figure 1. *P*-values of BPJ volume, amylase, and trypsin secretion were 0.013, 0.350, and 0.096 for administration (A), 0.004, 0.126, and 0.166 for time (T), and 0.072, 0.636, and 0.721 for A x T, respectively. A mean with a plus sign differed significantly from the value at 0 min in each group ($P < 0.05$). Mean values not sharing a letter at the same time postadministration are significantly different ($P < 0.05$).

Figure 3. Comparison of the suppressive effects of fats and sodium taurocholate on pancreatic secretion enhanced by guanidinated casein hydrolysate in chronically bile-pancreatic juice (BPJ)-diverted rats. Output of BPJ, amylase, and trypsin after intraduodenal instillation of 1 ml of either 150 mg guanidinated casein hydrolysate solution (HGC, open circle, $n = 8$), HGC + 100 mg soybean oil emulsified with 10 mg sodium taurocholate (closed circle, $n = 6$), or HGC + 10 mg sodium taurocholate (diamond, $n = 7$) is shown. Other details were the same as in Figure 1. *P*-values of BPJ volume, amylase, and trypsin secretion were 0.004, 0.006, and < 0.001 for administration (A), all < 0.001 for time (T), and 0.994, 0.814, and 0.645 for A x T, respectively. A mean with a plus sign is significantly different from the value at 0 min in each group ($P < 0.05$). Mean values not sharing a letter significantly differ at the same time postadministration ($P < 0.05$).

ods. Rats moved freely in the cages throughout the experimental period. The experiments were performed in a room controlled at 23 ± 2°C, with a 12:12-hr light:dark cycle (8:00–20:00, light period).

The study was approved by the Hokkaido University Animal Committee, and the animals were maintained in accordance with the guidelines for the care and use of laboratory animals of Hokkaido University.

In Experiment 1, we investigated the suppressive effects of intraduodenally administered soybean oil and lecithin on guanidinated casein hydrolysate (HGC)–induced BPJ volume and secretion of pancreatic amylase and trypsin in chronically BPJ-diverted rats. Cannulated rats were duodenally instilled with either HGC (150 mg/ml) containing 10 mg/ml sodium caseinate solution (HGC1; $n = 7$), HGC1 and soybean oil (100 mg/ml) emulsified with 10 mg/ml sodium caseinate ($n = 8$), or HGC1 with soybean oil (50 mg/ml) and lecithin (50 mg/ml, 92% phosphatidylcholine, Epikuron 200, Lucas Meyer, Hamburg, Germany) emulsified with 10 mg/ml sodium caseinate (mixed fat; $n = 7$).

In Experiment 2, we examined the effects of intraduodenally administered soybean oil (100 mg/ml) emulsified with 10 mg/ml sodium caseinate ($n = 6$) or soybean oil (50 mg/ml) and lecithin (50 mg/ml) emulsified with 10 mg/ml sodium caseinate (mixed fat; $n = 8$) on basal BPJ and enzyme secretion.

In Experiment 3, we compared the suppressive effects of intraduodenally administered taurocholate and soybean oil on BPJ and enzyme secretion. Rats received either HGC (150 mg/ml) solution (HGC2; $n = 8$), HGC2 and soybean oil (100 mg/ml) emulsified with 10 mg/ml sodium taurocholate (soybean oil; $n = 6$), or HGC2 with 10 mg/ml sodium taurocholate ($n = 7$).

Guanidinated casein was prepared by a previously described method (9). The conversion rate of lysyl residues to homoarginine was 96%. Guanidinated casein (55 g/l) was hydrolyzed with pepsin (0.55 g/l; Sigma Chemical Co., St. Louis, MO) at pH 1.8 for 1 hr at 37°C, and the hydrolysate was neutralized and desalted (guanidinated casein hydrolysate: HGC).

Analyses. BPJ volume was measured gravimetrically (100 μl = 100 mg). Trypsinogen in BPJ was activated by treatment with enterokinase (Sigma Chemical Co.) at 30°C for 20 min in 15 m*M* Tris buffer (pH 8.1). Trypsin activity was estimated photometrically using a synthetic substrate, Nα-*P*-toluenesulfonyl-L-arginine methyl ester (TAME) (17). Amylase activity in BPJ was measured using procion yellow starch as the substrate (18).

Calculations and Statistical Analyses. Values for the fasting state (0 min in Figs. 1–3) were calculated as the average of two sampling times before intraduodenal administration. Trypsin and amylase secretion were expressed as activities of these enzymes in BPJ secreted for 3 min (U/3 min). One unit of trypsin activity was defined as the amount of activity resulting in hydrolysis of 1 μmole of substrate per min at 30°C. Procion yellow starch, the substrate for the amylase assay, was calibrated using a purified α-amylase from porcine pancreas (Type 1A, Sigma Chemical Co.) at 37°C. The influence of administration and time on the secretion profiles was determined by two-way analysis of variance (ANOVA). The significance of differences among means was determined by least significant difference ($P < 0.05$).

Results

Body weight gain of rats after the operation was similar in all experiments, and averaged 4.6 g/day. Diarrhea was not evident in any BPJ-diverted rats. The volume of BPJ and amylase and trypsin output in chronically BPJ-diverted rats increased immediately after intraduodenal administration of HGC solution and reached peak values at 90 min postadministration (Fig. 1). Intraduodenal administration of HGC with emulsified soybean oil increased the exocrine pancreatic secretion similarly to HGC at 30 min. However, the volume of BPJ and the amounts of secreted enzymes were lower in rats that received HGC with soybean oil than in rats administered HGC alone at 60 and 90 min postadministration. BPJ secretion 60 and 90 min after the administration in rats administered the emulsion with half of the soybean oil replaced by lecithin (mixed fat) also were lower than those in rats administered HGC alone. BPJ volume in rats administered HGC with soybean oil tended to be higher than that for the mixed fat group 90 and 120 min after administration.

BPJ secretion and the levels of amylase and trypsin output after administration of soybean oil and mixed fat emulsion without HGC are shown in Figure 2. The BPJ flow was increased 90 min after administration of soybean oil emulsion and was significantly higher in the soybean oil group than in the mixed fat group at 60 and 90 min postadministration. Amylase and trypsin secretion tended to be increased as a result of administration of soybean oil although the changes were not statistically significant.

Amylase and trypsin output in BPJ-diverted rats were lower 60 min after administration of taurocholate with HGC as compared with the levels after administration of HGC alone (Fig. 3). The output of these enzymes increased immediately after administration of HGC alone, whereas their secretion was not increased until 60 min after administration of HGC solution with taurocholate. The secretion after administration of HGC solution together with taurocholate and soybean oil was similar to those after administration of HGC solution with only taurocholate.

Discussion

Intraduodenally instilled triglycerides (soybean oil) inhibited increases in the flow volume of BPJ and the secretion of pancreatic amylase and trypsin induced by guanidinated casein in chronically BPJ diverted rats (Fig. 1). This result demonstrated that delaying gastric emptying is not responsible for the inhibition with soybean oil and that soybean oil suppresses the pancreatic secretion when it reaches the small intestine. This suppressive effect on the exocrine

pancreas appears to represent a novel action of dietary triglycerides.

The inhibition by intraduodenally instilled soybean oil appeared 60 min after administration but was not evident at earlier times (Fig. 1). This finding suggests that the intraduodenally instilled soybean oil inhibits flow volume of BPJ and pancreatic enzyme secretion in the ileal lumen, not in the upper small intestine. BPJ flowed directly into the ileum in the BPJ-diverted rats and although soybean oil was delivered into the duodenum, it was likely not digested until arrival in the ileum in this animal model. Possibly, released fatty acids and monoacylglycerol stimulated the ileal mucosa, thereby suppressing BPJ volume and pancreatic enzyme secretion. Peptide YY producing cells are mainly located in the ileal and colonic mucosa (19). The digestive products of dietary fats stimulate peptide YY secretion (20, 21), and this hormone inhibits exocrine pancreatic secretion evoked by CCK (22–24). We previously demonstrated that CCK was involved in the increase in pancreatic enzyme secretion that occurs upon administration of HGC to BPJ-diverted rats (16), and we also showed that HGC stimulated the release of CCK from isolated jejunal mucosal cells (25).

Basal flow of BPJ and pancreatic enzyme output (secretion in the fasting state) in the BPJ-diverted rats was not suppressed upon administration of either soybean oil or mixed fat (Fig. 2). Moreover, the flow volume of BPJ was significantly increased 90 min after administration of soybean oil. These findings suggest that the intestinal fats can act as both an inhibitor and a stimulator of pancreatic secretion. In Figure 1, the effect as a stimulator is obscured by the large increase in the secretion induced by HGC. The results also suggest that the signaling pathway for the increment of the BPJ flow volume induced by administration of soybean oil differs from that induced by HGC.

Administration of the soybean oil emulsion with lecithin did not increase the flow volume of BPJ, whereas administration of the soybean oil alone increased the secretion as shown in Figure 2. In general, dietary fat stimulates exocrine pancreatic secretion, and fatty acids released as a product of fat digestion are involved in this response (26–28). The increased flow volume of BPJ observed in the present study may be caused by fatty acids liberated in the ileum from soybean oil, and the release of a pancreatic secretagogue in the lower part of the intestine. This stimulatory effect may be abolished in the mixed fat group by the lowering of the luminal fatty acid concentration by increasing the rate of fatty acid absorption, rather than by decreasing fat digestion. Indeed, we have observed a greater increase in serum triglyceride concentration after administration of mixed fat than after administration of emulsified soybean oil (unpublished data). Thus, the threshold of fatty acid concentration for stimulation of exocrine pancreatic secretion may be higher than that for inhibition.

The present study also shows that sodium taurocholate suppresses HGC-stimulated pancreatic secretion (Fig. 3). The suppression with taurocholate appeared earlier than that observed with soybean oil (Fig. 1). The suppressive effect of taurocholate may be evoked in upper parts of the small intestine. Bile acids including taurocholate are known to inhibit enhanced exocrine pancreatic secretion that results from BPJ diversion (10–12). Intraduodenally instilled soybean oil showed no additive effect on taurocholate suppression, suggesting that there is a common pathway for inhibition of the flow volume of BPJ and pancreatic enzyme secretion by soybean oil and taurocholate. We speculate that release of CCK or CCK action is suppressed by both taurocholate and soybean oil with direct suppression by taurocholate in the proximal small intestine and the products of triglyceride hydrolysis indirectly attenuating the CCK-mediated processes *via* enhanced secretion of peptide YY in the distal small intestine.

In conclusion, dietary soybean oil suppresses flow volume of BPJ and pancreatic enzyme secretion in the small intestine in chronically BPJ-diverted rats. This effect is independent of gastric emptying rate. Our results suggest that digestive products of dietary fats in the distal small intestine reduce the exocrine pancreatic secretion. High amounts of fatty acids in the lower intestine may be toxic, and the suppression of digestive enzyme secretion could be a beneficial response for the BPJ-diverted rats. The possible clinical implication of the suppressive action of dietary fat merits further investigation.

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