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## Research Article

Interactions between bile acids (taurocholate, TC; taurochenodeoxycholate, TCDC; or taurodeoxycholate, TDC) and digestive products (essential amino acids, EAA or monoolein, MO) in the lumen of the proximal small bowel, affecting pancreatic enzyme secretion and gallbladder contraction, were studied in 77 healthy volunteers by a perfusion method. Perfusion of EAA or MO caused significant increases in pancreatic enzyme output together with gallbladder contraction; MO was more potent and induced enzyme outputs comparable to the maximal response attained with intravenous cholecystokinin-pancreozymin (CCK-PZ). Perfusion of TC alone had no effect, but addition of 10 mM of either TC, TCDC, or TDC to perfusates containing EAA, or 10 mM TC to MO, or both significantly reduced pancreatic enzyme output and prevented gallbladder contraction. A lower concentration of TC (5 mM) added to EAA also produced a significant inhibitory effect. Inhibition of the stimulatory action of digestive products occurred in the jejunum as well as in the duodenum. The inhibitory action of bile acid was considered to be intraluminal since (*a*) bile acid did not modify the effects of CCK-PZ given intravenously; and (*b*) the stimulatory effect of digestive products perfused in the duodenum on pancreatic and gallbladder function was not influenced by simultaneous perfusion of bile acid in the jejunum.

It is proposed that this inhibitory effect of bile acid is mediated through inhibition [...]



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# Interactions between Intraluminal Bile Acids and Digestive Products on Pancreatic and Gallbladder Function

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ABSTRACT Interactions between bile acids (taurocholate, TC; taurochenodeoxycholate, TCDC; or taurodeoxycholate, TDC) and digestive products (essential amino acids, EAA or monoolein, MO) in the lumen of the proximal small bowel, affecting pancreatic enzyme secretion and gallbladder contraction, were studied in 77 healthy volunteers by a perfusion method. Perfusion of EAA or MO caused significant increases in pancreatic enzyme output together with gallbladder contraction; MO was more potent and induced enzyme outputs comparable to the maximal response attained with intravenous cholecystokinin-pancreozymin (CCK-PZ). Perfusion of TC alone had no effect, but addition of 10 mM of either TC, TCDC, or TDC to perfusates containing EAA, or 10 mM TC to MO, or both significantly reduced pancreatic enzyme output and prevented gallbladder contraction. A lower concentration of TC (5 mM) added to EAA also produced a significant inhibitory effect. Inhibition of the stimulatory action of digestive products occurred in the jejunum as well as in the duodenum. The inhibitory action of bile acid was considered to be intraluminal since (a) bile acid did not modify the effects of CCK-PZ given intravenously; and (b) the stimulatory effect of digestive products perfused in the duodenum on pancreatic and gallbladder function was not influenced by simultaneous perfusion of bile acid in the jejunum.

It is proposed that this inhibitory effect of bile acid is mediated through inhibition of CCK-PZ secretion by high intraluminal concentrations of bile acid. Inhibition of CCK-PZ secretion by bile acid may contribute to the regulation of pancreatic and gallbladder function during digestion by reducing pancreatic enzyme secretion and permitting the gallbladder to refill after evacuation of its contents.

#### INTRODUCTION

Certain products of digestive hydrolysis of nutrients in the lumen of the proximal small bowel provide the major stimulus for secretion of pancreatic enzymes and gallbladder contraction (1), thought to be mediated by release of cholecystokinin-pancreozymin (CCK-PZ)<sup>1</sup> from the mucosa of the upper small intestine. The potency of various amino acids, micellar fatty acids, and dextrose for stimulation of pancreatic and biliary function differ in man (2). In animals, fatty acids also stimulate pancreatic enzyme secretion and gallbladder contraction (3). The effects of combinations of these compounds, normally present together with secretions in the small intestine after meals, have not been investigated. The present study, employing a perfusion technique for measuring total pancreatic enzyme and biliary outputs in response to duodenal perfusion of different stimuli (2, 4), has three major aims. First, to compare the effects of essential amino acids (EAA) and monoolein (MO) separately and together on pancreatic enzyme output and gallbladder emptying. Second, to determine the intraluminal role of bile acids alone or in combination with EAA or MO or both on pancreatic secretion and gallbladder contraction. And, third, to define certain characteristics of the actions of bile acids on the response to EAA or MO.

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<sup>&</sup>lt;sup>1</sup> Abbreviations used in this paper: CCK-PZ, cholecystokinin-pancreozymin; EAA, essential amino acids; ME, emulsified monoolein; MO, monoolein; PEG, polyethylene glycol; TC, taurocholate: TCDC, taurochenodeoxycholate; TDC, taurodeoxycholate.

			Enzyme output (mean±SE)		
Perfusate	Amount	Perfusions	Trypsin	Lipase	Bilirubin output (mean $\pm$ SE)
	mM	number	kU/h		mg/h
Normal saline (control)	150	8	$5.7 \pm 1.6$	$26.8 \pm 4.2$	$5.5 \pm 1.1$
Sodium TC	10	5	$7.3 \pm 0.3$	$28.9 \pm 3.8$	$1.3 \pm 0.8$
EAA	78				
Alone In combination with		18	$22.3 \pm 2.1$	98.1±12.3	$24.3 \pm 2.3$
TC	5	5	$13.3 \pm 1.7$	$72.8 \pm 8.6$	$5.5 \pm 1.6$
TC	10	10	$6.9 \pm 0.8$	$38.6 \pm 7.2$	$2.4 \pm 1.9$
Sodium TDC	10	4	$11.6 \pm 1.9$	$54.1 \pm 13.2$	$6.4 \pm 1.3$
Sodium TCDC	10	5	$10.8 \pm 2.7$	$56.7 \pm 11.4$	$4.8 \pm 2.0$
МО	10				
Stabilized with 1 mM TC (ME) In combination with		5	$38.2 \pm 3.6$	179.4±16.7	$28.6 \pm 5.5$
TC	10	8	$10.6 \pm 0.6$	$48.7 \pm 2.7$	$6.7 \pm 1.4$
EAA		4	$40.1 \pm 4.3$	$216.5 \pm 28.2$	
EAA + TC (10 mM)		5	$12.3 \pm 3.7$	$58.3 \pm 16.1$	
CCK-PZ (i.v.)					
With normal saline (control) In combination with EAA $+$ MO $+$ TC		5	41.3±1.8	$205.9 \pm 32.0$	
(10 mM)		5	$39.9 \pm 4.4$	$152.0 \pm 30.6$	$37.6 \pm 8.2$
Intrajejunal EAA	78				
Alone		8	$17.1 \pm 2.8$	$89.4 \pm 21.8$	$33.0 \pm 9.7$
With TC	10	4	$4.7 \pm 0.8$	$32.4 \pm 6.9$	$4.0\pm0.4$

 TABLE I

 Composition of the Perfusates and Outputs of Pancreatic Enzymes and Bilirubin

## METHODS

77 healthy male volunteers (aged 21-52) participated in the studies. After an overnight fast, a two-lumen polyethylene tube was placed intraduodenally under fluoroscopic control. Isotonic saline or test solutions containing a nonabsorbable marker polyethylene glycol (PEG) 5 g/liter were infused into the second part of the duodenum at a constant rate (10 ml/min). Specimens of duodenal contents during steady-state conditions were drained by siphonage from the area of the ligament of Treitz, 20 cm distal to the infusion site. Perfusates were collected over ice and pooled at 20-min intervals. Gastric juice was continuously aspirated from the antrum by an additional tube. In each study, isotonic saline was perfused initially for cleansing for 60 min and was followed by perfusion for 100 min of either a control (isotonic saline) or test solution containing EAA or MO alone or in combination with different bile acids, comprising sodium taurocholate (TC), sodium taurochenodeoxycholate (TCDC), or sodium taurodeoxycholate (TDC) (Table I).

Volume, pH and PEG concentrations (5) were measured in gastric and duodenal aspirates. Duodenal trypsin, lipase, bilirubin, and bile acid concentrations were also determined by methods previously described (4, 6) and outputs of these substances were calculated from their concentrations in duodenal samples relative to PEG. Since perfusion of digestive products causes an initial, but nonspecific, higher output of pancreatic enzymes consistent with a "washout effect" (2), only aspirates collected after the first 40 min of perfusion were considered representative of the effect of luminal stimuli on pancreatic enzyme output (Table I). Luminal bile acid concentrations (quoted in the text) are those found during this period. By contrast, gallbladder contraction generally occurred during the first few minutes of perfusion of a stimulus and was determined from "peak" bilirubin output per hour. This value was derived from the highest bilirubin output in any 20-min period added to the bilirubin outputs in the two adjacent 20-min periods (Table I).

The composition of the perfusates is tabulated (Table I). Essential amino acids (2) were obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis. Sodium TC, sodium TCDC, and sodium TDC were synthesized from taurine (Eastman Organic Chemicals Div. Eastman Kodak Co., Rochester, N. Y.) and cholic acid, chenodeoxycholic acid, and deoxycholic acid, respectively (Matheson Coleman, & Bell, East Rutherford, N. J.) as described by Hofmann (7). The products migrated as single spots on thin-layer chromatography. Emulsified monoolein (ME) consisted of 10 mM of 1-monoolein (Eastman Organic Chemicals Div.) in dilute 1 mM sodium TC. This solution was sonicated for 60 min using a Biosonik (Will Scientific, Inc., Rochester, N. Y.) to emulsify the MO into solution. The preparation was found



FIGURE 1 Trypsin and bilirubin outputs during continuous intraduodenal perfusion of EAA (four studies).

to be greater than 95% monoglyceride by thin-layer chromatography and recoveries from the perfusates showed that the monoglyceride had been more than 90% hydrolyzed to fatty acid during the study. When EAA, MO, or bile acids were combined in test solutions, the original molar concentrations were preserved. All perfusates were prepared immediately before use, made isotonic with sodium chloride, adjusted to pH 6.3 and warmed to  $37^{\circ}$ C.

The effects of the various test solutions on pancreatic enzyme secretion and gallbladder contraction were compared with those obtained with intravenous CCK-PZ (Batch #22927, supplied by Professor E. Jorpes, Karolinska Institutet, Stockholm, Sweden) given to 10 subjects for 60 min at a dose of 0.250 Crick Harper Raper U/kg/min during intraduodenal perfusion of isotonic saline (five studies) or the combination of EAA, MO, and TC (five studies). This dose of i.v. CCK-PZ produced "maximal" pancreatic enzyme output of a similar magnitude to those reported here (8). CCK-PZ given at this high dose quickly produces a steady pancreatic enzyme output which makes it unnecessary



FIGURE 2 Trypsin and bilirubin output during continuous intraduodenal perfusion of EAA during and after addition of 10 mM sodium TC (four studies).

to risk side effects by prolonging the infusion for more than  $60 \text{ min.}^2$ 

To characterize the effect of TC on pancreatic and biliary responses to EAA, we performed additional studies. Each was carried out on different volunteers and consisted of one or several sequential perfusions: (a) to establish the profile of pancreatic and biliary secretory responses to prolonged stimulation with EAA, EAA was perfused intraduodenally over a period of 5 h (four studies) after the initial 1-h perfusion of isotonic saline (Fig. 1); (b) to determine the reversibility of the effect of TC on the response to EAA, 10 mM TC was added during the first 100 min (Fig. 2) or during the second 100 min (Fig. 3) of a 5-h EAA perfusion study (four studies each); (c) to determine the effect of TC on the response to EAA in the jejunum, EAA alone (eight studies) or EAA plus TC (four studies) was perfused for 100 min, 30 cm distal to the ligament of Treitz, while normal saline was perfused in the duodenum; and finally, (d) to further establish whether the site of action of TC was local or systemic, EAA was perfused alone intraduodenally for 100 min and then combined with TC for an additional 100 min. During the third 100-min period, TC was substituted for the saline perfusion 30 cm beyond the ligament of Treitz (four studies). Phenol red was added to all jejunal perfusates as a marker to monitor proximal reflux into the duodenal segment, but none occurred.

The validity and reproducibility of the perfusion technique, coefficients of variation of the chemical determinations, and calibration of measurements of enzyme activity have been detailed elsewhere (2, 4). Pancreatic enzyme secretion was expressed in kilo units (International Units  $\times 10^3$ ). Essential preliminary in vitro studies showed that bile acids added to intestinal juice do not modify pancreatic enzyme activity.<sup>2</sup>

#### RESULTS

Effects of bile acids and digestive products on pancreatic enzyme and bilirubin outputs (Table I). A significant increase in pancreatic trypsin and lipase outputs over basal values occurred during perfusions with EAA (P < 0.01), ME (P < 0.01) or i.v. CCK-PZ (P < 0.01). ME was more potent (P < 0.01) than EAA, and induced outputs comparable to the maximal response attained with intravenous CCK-PZ. When EAA was combined with MO, there was no further augmentation of the response already attained by ME.

TC alone had no effect on basal pancreatic enzyme output. The significant increase in pancreatic trypsin and lipase outputs over basal levels evoked by EAA or MO was inhibited when either or both of these substances were given together with 10 mM TC (P <0.01). A significant inhibition (P < 0.01) was also observed when TDC or TCDC were added to EAA, although the reduction in enzyme output caused by these dihydroxy bile acids was not as pronounced as with 10 mM TC (P < 0.05). A lower concentration of TC, 5 mM, added to EAA also produced a significant inhibi-

<sup>a</sup> Unpublished observations of the authors.

tory effect (P < 0.01), although less marked than with 10 mM TC (P < 0.05).

Gallbladder contraction, as reflected by peak bilirubin output, was evoked by EAA, ME, and intravenous CCK-PZ, all of which yielded significantly greater outputs (P < 0.01) than normal saline. By contrast, TC alone did not produce gallbladder contraction. Moreover, gallbladder contraction induced by EAA or MO did not occur when either of these substances was given together with TC, nor when TCDC or TDC were added to EAA. Thus, the presence of bile acids in the perfusate at 10 mM concentrations prevented gallbladder contraction and reduced pancreatic enzyme outputs which would otherwise occur in response to EAA or MO. Similarly, the gallbladder did not contract when 5 mM TC was added to EAA.

Characterization of inhibition of pancreatic and biliary response to EAA by 10 mM TC (Table I and Figs. 1-4). When EAA was perfused for 5 h, there was an immediate increase in trypsin output maintained throughout the period; gallbladder contraction took place immediately and bilirubin outputs remained low thereafter (Fig. 1). By contrast (Fig. 2), when perfusion was commenced with both TC and EAA, gallbladder contraction did not occur and pancreatic enzyme secretion remained at basal levels for 100 min. However, soon after TC was withdrawn from the perfusate, the gallbladder contracted and pancreatic enzyme output increased significantly. Furthermore, during continuous intraduodenal EAA perfusion for 5 h, the temporary addition of TC for 100 min at the midpoint caused reduction of pancreatic enzyme output; the output quickly rose to earlier levels and the gallbladder promptly contracted when TC was withdrawn. Bilirubin output after gallbladder contraction induced by EAA was higher (P < 0.05) than when TC and EAA were perfused together (Fig. 1 vs. Fig. 3).

When perfused in the jejunum, EAA was more potent than EAA plus TC (P < 0.01), showing that the inhibitory action of TC occurred in the jejunum as well as in the duodenum. However, when EAA alone was perfused in the duodenum, but TC was perfused distally in the jejunum, no inhibitory action of TC was found (Fig. 4). Furthermore, the inhibitory effect of TC on pancreatic enzyme secretion and gallbladder contraction evoked by MO and EAA was not evident when these functions were stimulated by the intravenous administration of CCK-PZ (Table I).

Intraluminal bile acid concentrations related to pancreatic enzyme and bilirubin outputs (Table I). During perfusions with EAA or ME, which stimulated pancreatic enzyme secretion and gallbladder contraction, steady-state total bile acid concentrations ( $\pm$ SEM) in the duodenum after gallbladder contraction was com-



FIGURE 3 Trypsin and bilirubin outputs during continuous intraduodenal perfusion of EAA before, during, and after addition of sodium TC (four studies).

pleted (at 40 min) were  $2.6\pm0.4$  mM and  $3.8\pm0.4$  mM, respectively. These bile acid concentrations were higher (P < 0.02) than during control periods ( $1.3\pm0.4$  mM) when saline was perfused. The total intraluminal bile acid concentrations during perfusion of EAA plus TC (5 mM) or EAA plus TC (10 mM), which produced a lower enzyme response and failed to stimulate gall-bladder contraction, were  $5.3\pm0.2$  mM and  $9.7\pm0.4$  mM, respectively, and therefore higher than those obtained by perfusion of EAA alone (P < 0.05).

Intraluminal bile acid concentrations during perfusion of either EAA plus TCDC  $(8.0\pm0.1 \text{ mM})$  or EAA plus TDC  $(8.1\pm0.7 \text{ mM})$  were significantly lower than those found with EAA plus TC, 10 mM (P < 0.05). However, the steady-state PEG concentrations during



FIGURE 4 Trypsin and bilirubin outputs during continuous intraduodenal perfusion of EAA; effects of adding 10 mM sodium TC to the duodenal perfusate (d) or jejunal perfusate (j) (four studies).

perfusion of EAA plus TCDC ( $4.54\pm0.08$  g/liter) or EAA plus TDC ( $4.19\pm0.22$  g/liter) were also significantly lower than with EAA plus TC, 10 mM ( $5.28\pm0.12$ g/liter) (P < 0.01), reflecting a greater dilution of intraluminal contents during perfusion of the dihydroxy bile acids, attributable to their inhibitory effect on water and electrolyte absorption in the gut (9).

#### DISCUSSION

Since CCK-PZ released from the mucosa of the proximal small bowel by digestive products is accepted as the major stimulus for pancreatic enzyme secretion and gallbladder contraction (1), we believe that pancreatic and biliary responses to perfusion of amino acids or MO in our model were mainly determined by secretion of CCK-PZ (2). However, although we use the term "CCK-PZ secretion," the possible participation of other hormones and neural influences cannot be fully excluded by currently available techniques.

Recently we reported that intraduodenal EAA provided a more potent stimulus to CCK-PZ secretion and pancreatic enzyme output in man than micellar lipid (MO and bile acids) and that dextrose had no measurable action (2). Others and ourselves also showed that EAA caused gallbladder contraction (10, 11). Now we have found that a bile-stabilized ME is even more potent than EAA and that ME, like EAA, causes gallbladder contraction as well as secretion of pancreatic enzymes in man. Responses to ME were comparable with those to a maximal intravenous CCK-PZ stimulus (8). Our original belief that EAA provided a stimulus as potent as i.v. CCK-PZ was erroneous because of the relatively weak batch of CCK-PZ used in our earlier studies. The greater potency of ME than of EAA may be due to concomitant release of secretin (12, 13), which thus potentiates the effect of CCK-PZ (13), or to the more rapid absorption of EAA (14) in comparison with emulsified fatty acids, dispersed over a larger area of mucosa containing CCK-PZ (15).

TC alone failed to stimulate pancreatic enzyme secretion or gallbladder contraction. Lagerlöf (16) earlier found that intraduodenal bile acids had no effect on pancreatic enzyme secretion in the dog, although others (17, 18) recently reported that, under different experimental conditions, bile acids stimulated pancreatic enzyme secretion. When TC, TCDC, or TDC was given with EAA or MO or both, pancreatic enzyme output normally evoked by these compounds in the duodenum was reduced and gallbladder contraction was prevented. The inhibitory effect of TC on the response to EAA also occurred in the jejunum, thus excluding the possibility that spasm of the sphincter of Oddi was induced by a local action of TC. Thomas and Crider (19) reported that in the dog, bile inhibits pancreatic secretion stimulated by an intraluminal infusion of peptone, whereas others have shown that exclusion of bile from the rat duodenum stimulates pancreatic secretion (20).

The effect of bile acids is interpreted as due to inhibition of CCK-PZ secretion at higher intraluminal concentrations of bile acid. Such inhibition was shown, at least for TC, to be rapid and reversible. The inhibitory effect of TC commenced at perfusate concentrations of 5 mM and was enhanced by raising the concentration to 10 mM. Under both circumstances, there were corresponding increases in the concentration of bile acids in the lumen. TCDC or TDC perfused at 10 mM concentrations also inhibited the response to EAA, although their action was not as pronounced as that obtained by 10 mM TC. It seems likely that the lesser effects obtained with TCDC or TDC reflected the significantly lower intraluminal bile acid concentrations reached during perfusion of the dihydroxy bile acids. By concentration relative to PEG, bowel contents were more diluted by dihydroxy bile acids, and this is attributed to their inhibitory effects on water and electrolyte absorption (9).

The inhibitory effect of TC was localized to areas of small intestine exposed to the stimulus of EAA, since CCK-PZ activity evoked by EAA in the duodenum was not affected when TC was perfused distally. No evidence of a systemic inhibitory action by TC on the target organs was found; pancreatic enzyme output and gallbladder contraction induced by intravenous CCK-PZ were not influenced by the intraduodenal perfusion of TC together with digestive products at concentrations otherwise inhibitory to local CCK-PZ secretion.

The perfusion flow rates used by us (10 ml/min) approach or exceed peak flow rates in the upper small intestine in normal individuals after hypertonic test meals (21). Endogenous bile acid concentrations in the lumen during EAA or ME perfusion therefore never exceeded 4 mM; consequently, no spontaneous inhibition of pancreatic and biliary secretion occurred. Inhibition occurred with the addition of exogenous bile acid, resulting in luminal concentrations above 5 mM, and increased when concentrations rose above 9 mM. With normal mean postprandial intestinal flow rates of approximately 2-5 ml/min (22, 23), endogenous secretion of bile acids is sufficient to bring luminal concentrations to levels that can temporarily inhibit CCK-PZ release, since bile acid concentrations in the proximal small bowel after a test meal approach or exceed 9 mM after gallbladder contraction (11, 21, 24, 25).

From our findings, we postulate that CCK-PZ secretion in response to MO or amino acids during digestion may be inhibited by bile acids after contraction of the gallbladder. This previously neglected function of bile acids depends on their concentration in the small intestine. The mechanism appears to be localized in the small intestine and may regulate pancreatic enzyme secretion and permit filling of the gallbladder during meals.

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