Effect of Intraduodenal Bile and Na-Taurodeoxycholate on Exocrine Pancreatic Secretion and on Plasma Levels of Secretin, Pancreatic Polypeptide, and Gastrin in Man

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The effect of intraduodenally administered cattle bile (CB) and Na-taurodeoxycholate (TDC) on basal pancreatic secretion and plasma levels of secretin, pancreatic polypeptide (PP), and gastrin were investigated on two separate days in 10 fasting volunteers. Doses of 2–6 g CB and 200–600 mg TDC were given intraduodenally at 65-min intervals. Volume, bicarbonate, lipase, trypsin, amylase, and bilirubin were measured in 10-min fractions of duodenal juice, and GI peptides determined by radioimmunoassay. CB and TDC enhanced significantly and dose-dependently volume, bicarbonate and enzyme secretion, and plasma secretin and PP levels. In contrast, plasma gastrin showed only a marginal increase. We conclude that the hydrokinetic effect of intraduodenal CB and TDC is at least partially mediated by secretin. Gastrin could be ruled out as a mediator of the ecbolic effect, whereas other GI peptides, primarily CCK, and/or neural mechanisms must be considered possible mediators. Both pathways may also play a role in the PP release observed.

Key words: Bile; bile salts; gastrin; GI peptides; Na-taurodeoxycholate; pancreatic polypeptide; pancreatic secretion; radioimmunoassay; secretin

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Conflicting reports exist on the effect of intraduodenal bile and bile salts on exocrine pancreatic secretion (1–8). We have previously shown that intraduodenal cattle bile (CB) enhanced secretin-stimulated hydrokinetic and ecbolic pancreatic secretion in man dose-dependently (9). In addition, Na-taurodeoxycholate (TDC) proved to be nearly as effective as total bile.

The mediators of bile- and bile salt-induced effects on both hydrokinetic and ecbolic pancreatic secretion are still poorly defined. Osnes et al. (10) were the first to show that intraduodenal infusion of bile in man elicited significant plasma secretin concentrations and pancreatic secretion. In other studies, however, plasma secretin was not significantly influenced by bile (11, 12). Furthermore, various bile salts were capable of increasing plasma secretin concentrations but only when applied in high doses (13).

The aim of the present study was to investigate the effect of physiologic doses of a standardized CB preparation and TDC intraduodenally on

basal pancreatic secretion and on plasma levels of secretin, gastrin, and pancreatic polypeptide (PP).

MATERIALS AND METHODS

Experimental procedure

The study was carried out on 10 fasting healthy volunteers (age, 25 ± 0.8 years; weight, 69.1 ± 3.3 kg). Under fluoroscopic control the tip of a double-lumen Dreiling tube was advanced to the ligament of Treitz, enabling continuous and separate aspiration of gastric and pancreatic juice. Details have been described earlier (9).

On one day each person received standardized dried CB (kindly supplied by Kali-Chemie, FRG) intraduodenally, dissolved in 20 ml H_2O, in doses of 2 (twice), 4, and 6 g (310, 639, and 937 mosmol/l; pH 7.45, 7.18, and 7.04, respectively), and on another day the same persons received chromatographically pure TDC (Calbiochem-Behring, FRG) intraduodenally, again dissolved in 20 ml H_2O, in doses of 200 (twice), 400, and 600 mg (19.0, 38.5, and 57.5 mmol/l; 33.0, 50.0, and 67.0 mosmol/l; pH 7.9, 8.1, and 8.1, respectively), at 65-min intervals. Aspiration of duodenal juice was interrupted for 5 min immediately after instillation to ensure sufficient contact of the stimuli with the duodenal mucosa. Thereafter, collection in 10-min fractions of duodenal juice was continued. Besides the volume and pH, the concentrations of bicarbonate, lipase, trypsin, amylase, and bilirubin were measured. The determination of bicarbonate and of pancreatic enzymes was performed in accordance with the recommendation of the Multi Centre Study of the European Pancreatic Club (14). Blood samples for radioimmunologic determination of secretin, PP, and gastrin were withdrawn in ice-chilled 10-ml syringes (containing 37.1 μmol K_2-ethylenediaminetetraacetic acid (EDTA) and 5000 KIU aprotinin) before, at, and 5, 10, 15, 25, 45, and 65 min after intraduodenal stimulation. The samples were left on ice until centrifugation at 4°C, and the plasma was immediately frozen in 1.5-ml aliquots.

The first stimulus in each series—2 g CB and 200 mg TDC, respectively—was given to 'wash out' preformed zymogens from the pancreatic ducts. The preparation of CB used in this study contained 10% TDC based on weight. Doses of TDC were therefore applied corresponding to their CB content.

Radioimmunoassay procedures

Secretin. Secretin was measured radioimmunologically in acidified plasma in accordance with Burhol & Waldum (15). The antiserum to pure porcine secretin was produced in rabbits by the method of Burhol & Waldum (16). The effective equilibrium constant (K_{eff}) was 1.6×10^{11} l/mol, and the index of heterogeneity (α) 1.0. The antiserum showed no cross-reactivity against the peptides of the secretin–glucagon family and PP.

Synthetic porcine secretin was labelled with iodine-125 by a modified chloramine-T technique (17) and subjected to gel chromatography. High specific radioactivity of approximately 42.4 MBq/nmol, as calculated by the method of Morris et al. (18), was obtained by purification on a cation exchange column. The immunoreactivity of 125-iodinated secretin was identical to that of unlabelled synthetic secretin as evaluated by Scatchard plots (19).

Incubation was performed in triplicate polystyrol tubes at 4°C. Two hundred microlitres 'secretin-free' charcoaled pool plasma, synthetic porcine secretin standards in charcoaled pool plasma, and unknown plasma samples, respectively, were preincubated with 15 μl 1 M HCl for 1 h. Afterwards, 200 μl assay buffer (0.1 M sodium acetate buffer, pH 5.0, containing 0.07 mmol/l bovine serum albumin (BSA), 3.08 mmol/l NaN_3, and 1000 KIU aprotinin/ml) and 100 μl suspension of a secretin antiserum/anti-rabbit gammaglobulin antiserum precipitate (dilution of secretin antiserum, 1:15,000, and of goat anti-rabbit gammaglobulin antiserum, 1:40; 9 μg rabbit gammaglobulin/100 μl suspension caused maximal precipitation) were added. After 72 h, 100 μl of tracer solution (≈3000 cpm) were added to each tube; after another 48 h of incubation bound and free label were separated by centrifugation at 4°C, the supernatant removed by suction, and the precipitate counted in an automatic gamma-counter. The standard curves

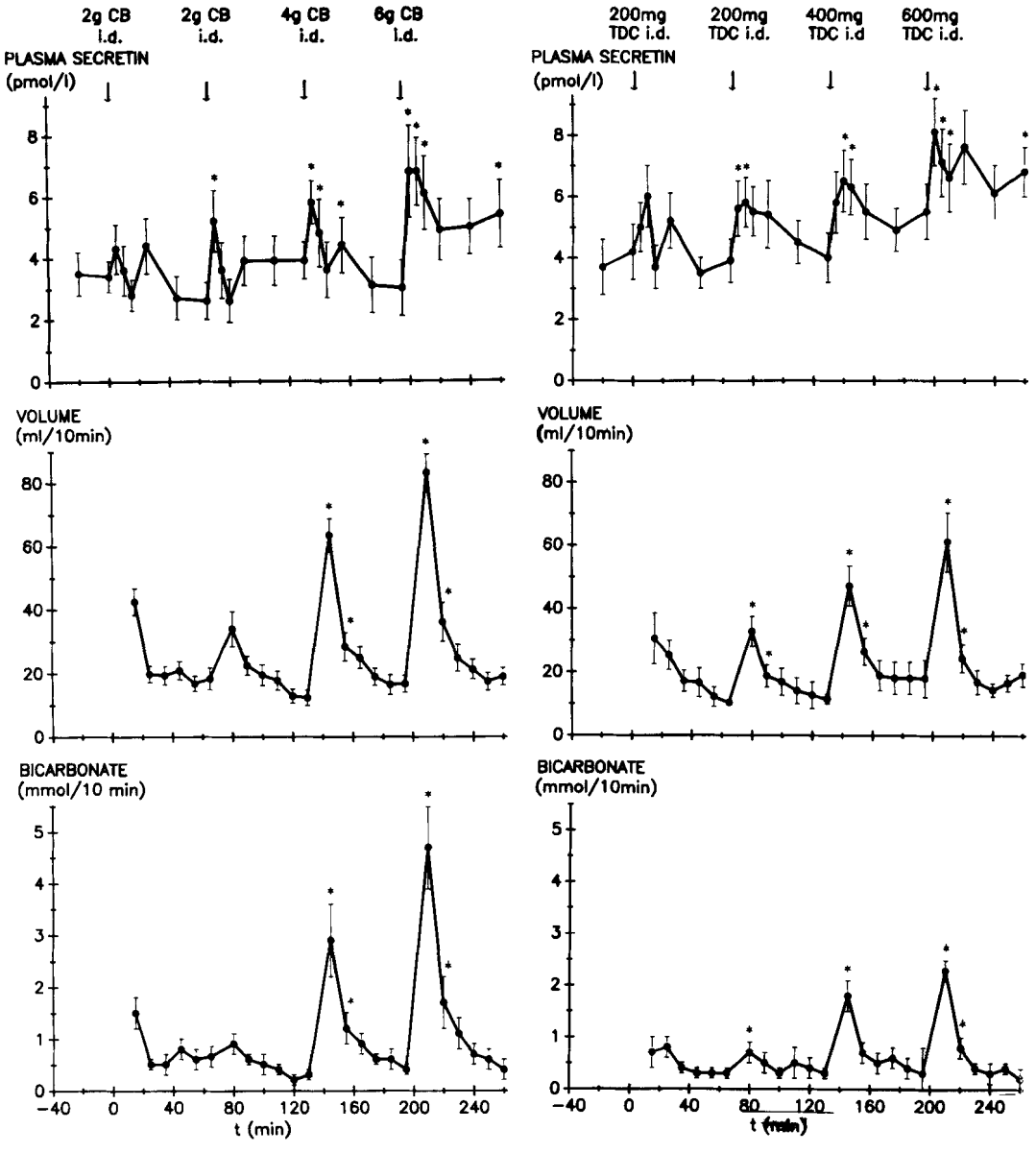

Fig. 1. Effect of 2, 2, 4, and 6 g CB intraduodenally (left) and of 200, 200, 400, and 600 mg TDC intraduodenally (right) on plasma secretin concentrations and on pancreatic volume and bicarbonate secretion ($n = 10$). Asterisks indicate significant difference from 'basal' values (also in all subsequent figures).

were calculated by a computerized 'spline function' algorithm (RiaCalc LM, LKB-Pharmacia).

The detection limit of the assay was 1 pmol/l with 95% confidence limit. Recovery of known amounts of porcine secretin (5.6 and 11.2 pmol/l) added to human charcoaled plasma was 106%, respectively. Mean plasma secretin concentration of 22 fasting subjects was 3.5 ± 0.3 pmol/l. The coefficient of variation for the within-assay precision was 13.4% and 4.6% at 7.7 pmol/l and 29.6 pmol/l, respectively, and for the between-

assay precision 12.7%, 6.7%, and 9.9% at 3.9, 11.6, and 28.1 pmol/l secretin, respectively. Furthermore, gel chromatography studies showed that human secretin stimulated by 4 mmol HCl intraduodenally, pure porcine secretin in human charcoaled plasma, and ^{125}I-labelled porcine secretin in assay buffer were eluted at identical positions.

Plasma PP. Plasma PP concentrations were determined by radioimmunoassay (RIA) using an anti-porcine PP antiserum (K 5418, cross-reactivity with human PP >95%) and ^{125}I-labelled porcine PP (specific radioactivity, 54 MBq/nmol), supplied by the Novo Research Institute, Copenhagen, Denmark. The antibody showed no cross-reactivity against neuropeptide Y, peptide YY, peptides of the secretin-glucagon family, somatostatin-14, cholecystokinin-39 (CCK-39), gastrin-17, and insulin. Incubations were performed in a 0.05 M sodium phosphate buffer, pH 7.4, containing 0.07 mmol/l BSA, 3.08 mmol/l NaN_3, and 1000 KIU aprotinin/ml for 96 h at 4°C. One hundred microlitres of plasma sample or of human PP standard (Sigma Chemie) dissolved in 'PP-free' charcoaled plasma, 200 µl suspension of an anti-porcine PP antiserum/anti-rabbit gammaglobulin antiserum precipitate (dilution of PP antiserum, 1:900,000, and of goat anti-rabbit gammaglobulin antiserum, 1:90; 4.2 µg rabbit gammaglobulin/100 µl suspension caused maximal precipitation), and 100 µl of ^{125}I-labelled PP (≈3000 cpm) were mixed together. Antibody-bound radioactivity was separated, and the standard curves were calculated as described for secretin. The detection limit for human PP (95% confidence level) was 3.7 ± 0.3 pmol/l; the intra- and inter-assay coefficients of variation for triplicates were 11.1% at 12.9 pmol/l (n = 8) and 13.1% at 14.3 pmol/l (n = 17), respectively. Fasting EDTA plasma of 30 subjects contained 15.5 ± 5.8 pmol/l PP.

Gastrin. Gastrin was measured in EDTA plasma by a commercially available radioimmunoassay kit (GASK-PR, Isotopen Diagnostik CIS, Dreieich, FRG) with a detection limit of 10 pg/ml, an intra-assay variation of 8.9% at 45.8 pg/ml, and an interassay variation of 9.9% at 53.9 pg/ml. On a molar basis the antibody shows 100% cross-reactivity with human gastrin-17, 72% with human gastrin-34, and 1% with cholecystokinin-33.

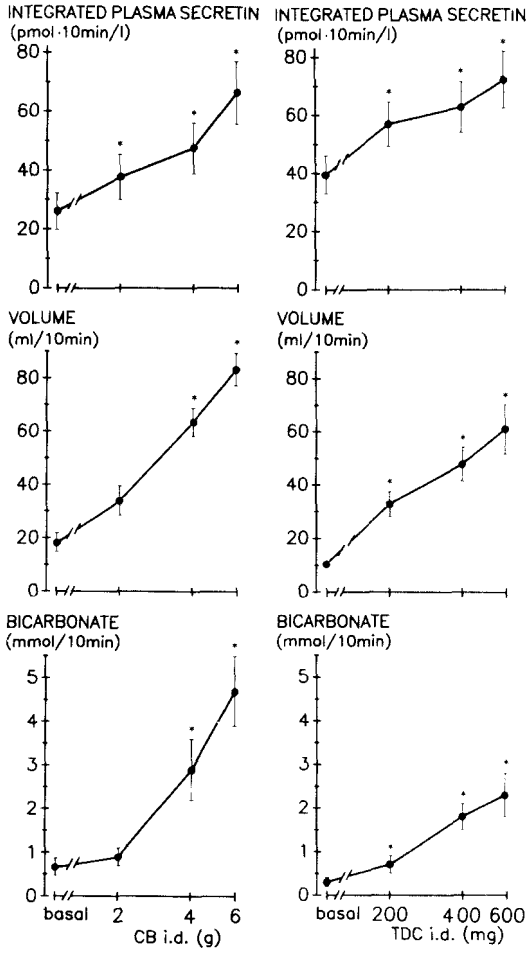

Fig. 2. Dose-response curves of intraduodenal CB (left) and of intraduodenal TDC (right) on integrated plasma secretin and on pancreatic volume and bicarbonate output (n = 10) (semilogarithmic plot).

Statistical methods

Changes in concentrations and outputs were evaluated by the Friedman two-way analysis of variance. The level of statistical significance was $p < 0.05$. In all figures values are presented as $\bar{x}$ ± SEM. Integrated GI peptide values were calculated as the areas under the concentration

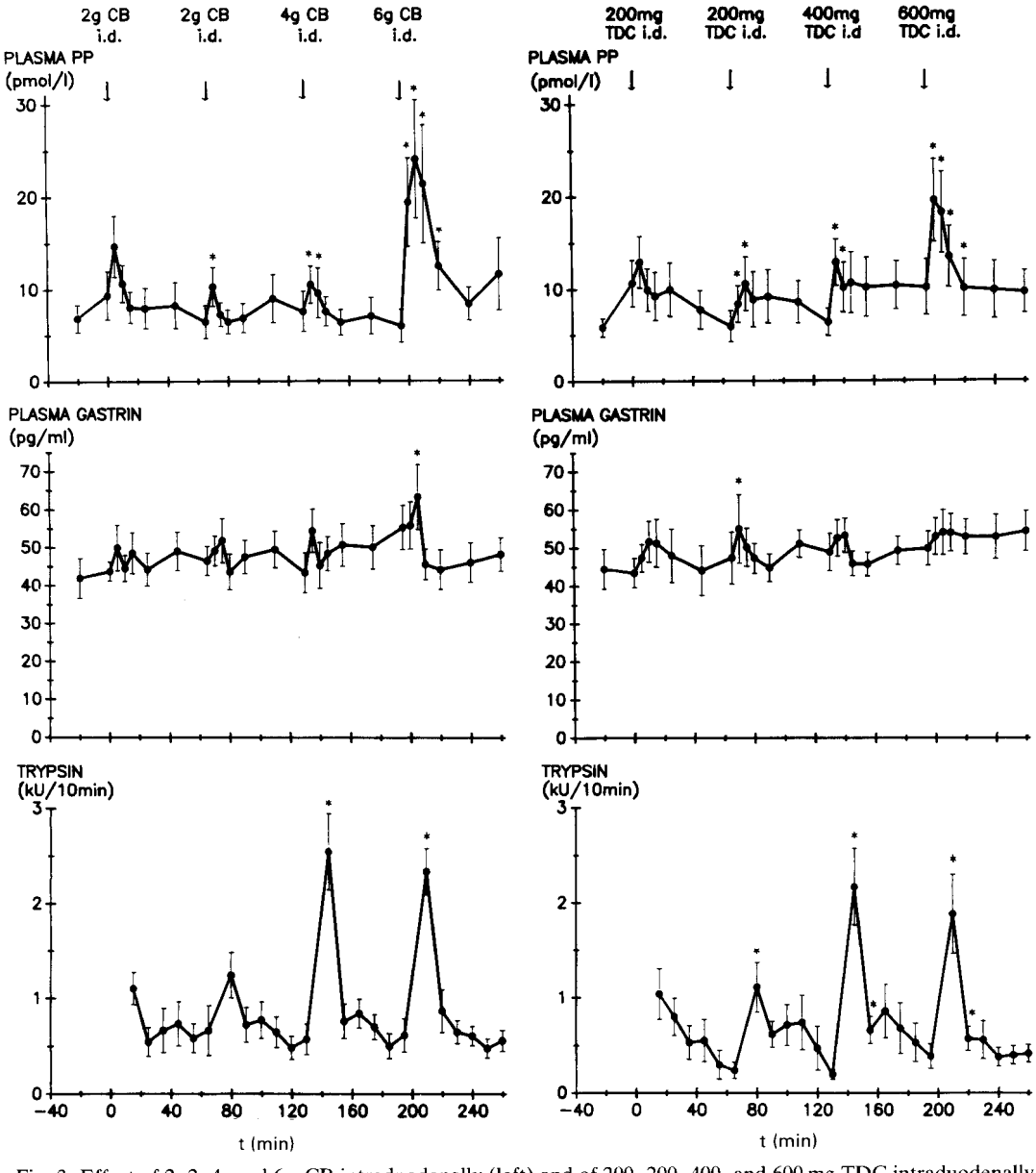

Fig. 3. Effect of 2, 2, 4, and 6 g CB intraduodenally (left) and of 200, 200, 400, and 600 mg TDC intraduodenally (right), respectively, on plasma concentrations of PP and gastrin and on pancreatic trypsin secretion ($n = 10$). Trypsin is representative for all enzymes measured.

curves for 10 min after the application of each intraduodenal stimulus. The Wilcoxon test for paired data was used to examine corresponding values after intraduodenal CB and TDC, respectively, for significant difference.

RESULTS

Four and 6 g CB intraduodenally caused a significant increase of plasma secretin concentrations and of pancreatic volume and bicarbonate secretion rate within 10 min. Plasma secretin rose

significantly also after 2 g CB, but there was only a non-significant effect on volume and bicarbonate secretion. TDC intraduodenally enhanced significantly plasma secretin concentrations and volume and bicarbonate secretion rate within 10 min at all given doses (Fig. 1). Integrated plasma secretin secretion and volume and bicarbonate output also showed a significant and dose-dependent increase after all doses of CB and TDC, except for volume and bicarbonate output after 2 g CB (Fig. 2).

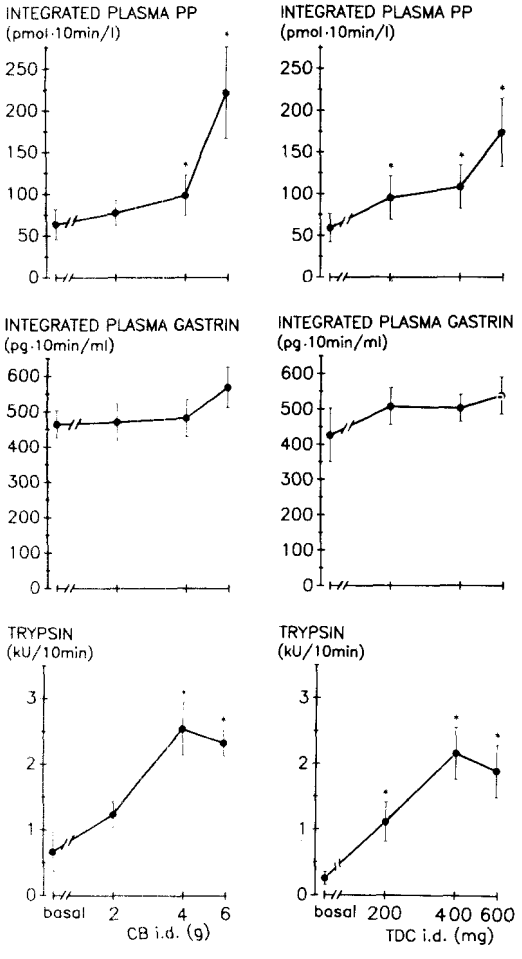

Fig. 4. Dose-response curves of intraduodenal CB (left) and of intraduodenal TDC (right) on integrated plasma PP and gastrin and on pancreatic trypsin output (n = 10). Trypsin is representative of all enzymes measured (semilogarithmic plot).

Trypsin secretion rate—representative of all pancreatic enzymes measured—rose significantly after 4 and 6 g CB intraduodenally and also after all doses of TDC intraduodenally (Fig. 3). Trypsin output showed a dose-dependent increase after 2 and 4 g CB and after 200 and 400 mg TDC. However, there was no further augmentation after the highest dose of both stimuli (Fig. 4).

Plasma PP concentrations were significantly raised by all doses of CB and TDC, especially after the highest doses (Fig. 3). Integrated plasma PP secretion rose significantly and dose-dependently after intraduodenal application of 4 and 6 g CB and also after all doses of TDC (Fig. 4).

In contrast, plasma gastrin concentrations rose but unessentially, and integrated plasma gastrin secretion did not change significantly at all given doses of CB and TDC (Figs. 3 and 4).

When the stimulatory potencies of CB and TDC were compared, a significant difference was only found for bicarbonate output after the respective highest dose.

DISCUSSION

The present study shows a dose-dependent hydrokinetic and ecbolic effect of intraduodenal CB and TDC on basal pancreatic secretion in man. The results confirm our previous findings during a constant infusion of secretin (9).

Instead of human bile a standardized CB preparation was used in our studies to establish a dose-response relationship. The contents of total bile salts in human gallbladder bile and in our CB preparation are comparable (20). The proportion of chenodeoxycholate and its conjugates in CB, however, was lower in favour of cholate and its conjugates.

In pure pancreatic juice obtained by endoscopic retrograde pancreatography Osnes et al. (21) observed an increase of volume, bicarbonate, and amylase secretion and of plasma secretin concentration after repeated intraduodenal instillation of 6 g CB. Trypsin and lipase output, however, was enhanced significantly only after the first stimulus. Therefore, the influence of intraduodenal CB on ecbolic secretion was ascribed to a 'washing out' effect by secretin. These contra-

dictory results may be attributed to the rapid follow-up study of the intraduodenal stimuli without reaspiration of bile. Therefore, peripapillary cholinergic receptors might have been blocked (21, 22).

In accordance with other investigators (3, 8, 23), our previous studies show (2, 9) that bile salts are the effective constituents of bile. Their stimulatory effect seems to be independent of their action as detergents (24). However, only some bile salts, such as TDC, act as specific intraduodenal stimulants of pancreatic secretion (9). TDC represents approximately 8 mol % of the total bile salts in human bile and approximately 10 mol % of the bile salts in the CB preparation used. The amounts of TDC applied in our study are in the physiologic range and comparable with those contained in CB. The concentrations of TDC used (20–60 mM) are above the critical micellar concentration and similar to those found in human gallbladder bile (20, 25). Postprandial intraduodenal bile salt concentrations are lower (up to 20 mM), but the TDC solutions applied have also been diluted intraduodenally by pancreatic and duodenal juice.

TDC is almost as potent as total bile both on secretin-stimulated (9) and on basal pancreatic secretion. CB exerted a significantly higher effect only on bicarbonate output after the highest dose given. It is noteworthy that the doses of TDC given alone corresponded to those applied with total bile.

In contrast, Na-taurocholate (TC) was only a weak and dose-independent stimulus of secretin-induced hydrokinetic secretion without provoking a significant ecbolic effect in man (9). These results are consistent with those of Björnsson et al. (26), who also found a significant increase of caerulein- and secretin-induced bicarbonate secretion but not of trypsin secretion by intraduodenal perfusion of TC in man. On basal pancreatic secretion, however, TC did not exert a hydrokinetic effect. On the other hand, duodenal perfusion of TC provoked a marked hydrokinetic and a sparse ecbolic secretion under basal conditions in the anaesthetized cat (27). Species differences may account for this discrepancy. Other studies in man showed no influence or even an inhibiting effect of TC, when pancreatic secretion was stimulated by duodenal perfusion with essential amino acids and monoolein, respectively (4, 6). In lower concentrations bile acids have also been reported to diminish, but in higher concentrations to enhance the stimulatory effect of fatty acids on pancreatic secretion (28). These discrepancies may partially be explained by species differences and differences in experimental design—bolus versus continuous perfusion technique—or by the load of bile salts applied. Moreover, the interactions of digestive products and bile salts remain to be clarified by using a very potent bile salt like TDC.

Osnes et al. (10, 21) were the first to describe the release of plasma secretin with a subsequent increase of pancreatic secretion induced by intraduodenal CB in man, but only doses of 6 g CB were applied. The secretin release caused by bile, by TC, and by a mixture of bile salts has been confirmed by other studies (3, 13, 27). However, Burhol et al. (11) were not able to demonstrate a significant increase of plasma secretin by bile. In our study the kinetics of plasma secretin concentration was correlated to that of volume and bicarbonate secretion rate after each dose of CB and TDC. Moreover, integrated plasma secretin showed a dose-dependent increase after all doses of CB and TDC. Since the effect of CB and TDC is dose-dependent and the applied doses are within the physiologic range, a specific effect of these intraduodenal stimuli on secretin release has to be assumed. The pH of the instilled solutions cannot have influenced secretin levels, since secretin release in man occurs below a threshold of pH 3 (29). Furthermore, it is unlikely that the secretin increase observed is secondary to an acid release into the duodenum, since gastric juice was removed continuously by suction, and the pH of the duodenal aspirate was permanently within the neutral range. Thus, our data strongly support the hypothesis that secretin acts as a major mediator of pancreatic hydrokinetic secretion induced by intraduodenal CB and TDC in man.

Cholinergic mechanisms and/or a release of cholecystokinin have been discussed as mediators of the ecbolic effect of bile and bile salts (30, 31). Forell (30) could show that propantheline, an

anticholinergic drug, caused a marked inhibition of the ecbolic effect of intraduodenal CB but did not influence the hydrokinetic action. Davies et al. (31), however, found a postprandial decrease of plasma CCK concentrations and trypsin output after diversion of bile from the duodenum in dogs. Both pathways are also capable of eliciting PP from the pancreas (32, 33). Therefore, plasma PP concentrations may serve as an indirect marker of the involvement of cholinergic mechanisms and/or cholecystokinin release. Indeed, plasma PP concentrations rose significantly after each dose of CB and TDC, and the kinetics was correlated to that of trypsin secretion rate. Moreover, the dose-dependent increase of integrated plasma PP after CB and TDC intraduodenally supports the hypothesis that the observed augmentation of pancreatic enzyme output is a true ecbolic effect and not a 'washing out' phenomenon (21). It is unlikely that the increase in PP observed is due to distension of the duodenum, since the instilled volumes were identical. It is also possible that the increase of PP is secondary to a release of other GI peptides like secretin, VIP, and GIP, but so far this has been reported only for pharmacologic doses (34–36). The release of PP by these peptides is noteworthy because not only an increase of secretin but also of VIP and GIP has been observed after intraduodenal CB (11, 37). PP for its part inhibits CCK-mediated gallbladder contraction and enzyme secretion of the pancreas in man (38). Therefore, the unequivocal PP release after the highest doses of CB and TDC may explain the lack of any further increase in trypsin secretion after these doses.

Gastrin as a hormonal mediator of intraduodenal CB- and TDC-induced increase of ecbolic pancreatic secretion does not seem to play any role in this effect. We observed only a marginal and no dose-dependent augmentation of plasma gastrin concentrations after both CB and TDC. Our results are in accordance with Londong et al. (39), who also found only a slight increase of gastrin after 6 g CB. Nor does plasma gastrin in physiologic concentrations stimulate exocrine pancreatic secretion (40, 41).

In conclusion, intraduodenal CB and TDC induce a dose-dependent increase of pancreatic hydrokinetic secretion which seems to be mainly mediated by secretin. Cholinergic reflexes and a CCK release must be considered as mediators of CB- and TDC-induced enzyme secretion and of the concomitant PP release observed. On the other hand, gastrin seems to be of no importance.

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