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COMMEMORATIVE ESSAYS IN GASTROENTEROLOGY

ALIMENTARY TRACT

ON THE COVER

Cecal lymphoid patch of the rabbit. Double labeling of M cells by vimentin-antibody V9 (red fluorescence) together with the lectin derived from Vicia villosa *(VVA-fluorescein isothiocyanate; green fluorescence), which binds to* N*-acetylgalactosamine residues. The survey micrograph shows that on the flanks of the dome areas, approximately 30% of the epithelial cells are labeled by both vimentin antibody and VVA (yellow fluorescence results from red and green overlapping). The epithelium of the nondome region remains almost unlabeled.* *See Gebert et al. on page 1350.*

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AUTHOR INDEX TO VOLUME 105

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br—Book Reviews
cr—Case Reports
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c—Correspondence
e—Editorials
paps—Policy and Position Statement
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SUBJECT INDEX TO VOLUME 105

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Effects of Intraduodenally Applied Bile Salts on Pancreatic Secretion

Dear Sir:

We read with interest the report by Miyasaka et al.[1] on the effect of several bile salts (BS) on exocrine pancreatic secretion in conscious rats with external bile and pancreatic fistulas. Intraduodenal application of deoxycholate (DCA), taurodeoxycholate (TDCA), glycodeoxycholate (GDCA), chenodeoxycholate (CDCA), glycochenodeoxycholate (GCDC), and ursodeoxycholate (UDCA) significantly increased pancreatic volume, bicarbonate, and protein secretion. On the other hand, taurochenodeoxycholate (TCDC), tauroursodeoxycholate (TU), glycoursodeoxycholate (GU), cholate (CA), and taurocholate (TC) did not influence pancreatic secretion. The unconjugated BS DCA, CDCA, and UDCA caused a significantly higher secretion than their corresponding taurine-conjugated or glycine-conjugated derivates. The stimulatory effect of CDCA was partially inhibited by infusion of either a cholecystokinin (CCK) antagonist (CR 1409) or a secretin antiserum. In contrast to these results obtained during reinfusion of bile and pancreatic juice (BPJ) into the duodenum, TCDC, TU, GU, TC, and CA diminished pancreatic secretion and plasma CCK concentrations after exclusion of BPJ from the intestine.

Miyasaka et al. concluded that unconjugated BS increase pancreatic secretion via a release of CCK and secretin, whereas conjugated BS inhibit pancreatic secretion and CCK release. The apparently opposite effects of different BS species on pancreatic secretion were partly explained by differences in their physical-chemical properties such as pK^a values and hydrophobicities.

Our major objection is that the results obtained during reinfusion of BPJ ("return of BPJ") were mixed together with those observed after exclusion of BPJ. However, in the rat, diversion of BPJ from the proximal small bowel causes an increase of basal pancreatic secretion[2] being reversed by reinfusion of BPJ.

During reinfusion of BPJ, DCA, GDCA, TDCA, CDCA, GCDC, and UDCA infused intraduodenally stimulated volume, bicarbonate, and protein secretion, whereas TCDC, GU, TU, CA, and TC did not influence pancreatic secretion. Unconjugated BS (except CA and TC, which were ineffective) exerted a significantly stronger effect than conjugated BS, indicating that conjugation by either glycine or taurine attenuates (GDCA, TDCA, GCDC) or eliminates (TCDC, GU, TU) the stimulatory effect of the respective unconjugated BS. However, none of the BS tested caused an inhibition of pancreatic secretion during reinfusion conditions as generally stated by Miyasaka et al.

Exclusion of BPJ evoked an approximately twofold increase of pancreatic secretion. Under these conditions, TCDC, GU, TU, TC, and CA transiently decreased exocrine pancreatic secretion. It is noteworthy that these BS were ineffective during reinfusion conditions. However, the other BS with a stimulatory action (DCA, GDCA, TDCA, CDCA, GCDC, and UDCA) were not tested. With respect to the latter, Miyasaka et al. refer to an earlier study in conscious BPJ-diverted rats.[3] But in this study, only UDCA was tested, causing an increase of bicarbonate but not of protein output. It seems inappropriate to draw a conclusion from the effect of one BS to that of others because they differ in their potency to stimulate pancreatic secretion, as shown in this paper[1] and others.[4,5]

The hydrokinetic effect of several BS on basal pancreatic secretion shown in this study was referred to a secretin release. This is in accordance with results obtained in other species (human and cat).[6] However, other mediators like vasoactive intestinal polypeptide also have to be discussed because the immunoneutralization of secretin reduced pancreatic volume and bicarbonate secretion by only about 50%–60%.

The mediators of BS-induced enzyme secretion are less well defined. Besides cholinergic mechanisms, CCK seems to be involved, but a significant CCK release could be shown thus far only after TDCA in humans.[6] The strong inhibition of the ecbolic effect of CDCA by a specific CCK antagonist shown in this study[1] during reinfusion conditions also points to a role of CCK as a mediator.

In conclusion, the results of this study in rats are in accordance with the hypothesis that BS in the duodenum either stimulate or leave unchanged but do not inhibit pancreatic secretion during reinfusion conditions.[5] On the other hand, BS do inhibit pancreatic secretion during diversion of BPJ, which is thought to be a special condition in rats. During reinfusion conditions, the efficacy of BS may be attenuated or eliminated, but not reversed into an inhibitory action by conjugation. The experimental conditions (reinfusion or diversion of BPJ) are responsible for the opposite effects of BS observed in this report.

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Reply. We appreciate the interest that Drs. Riepl and Lehnert have shown in our paper, and we feel that we need to comment on the regulation of pancreatic secretion in conscious rats.

1. In conscious rats, basal secretion means nonstimulated secretion; circulating CCK does not contribute to this secretion, although basal secretion was further inhibited by administration of atropine[1] or secretin antibody.[2] Thus, if drugs or materials could not inhibit basal secretion, this does not mean that these agents do not possess inhibitory action on pancreatic secretion. For example, pancreatic polypeptide or peptide YY inhibits stimulated secretion but not basal secretion.
2. Bile salts TU, GU, TCDC, TC, CA that did not stimulate pancreatic secretion in an intact bile-pancreatic juice model showed an inhibitory effect on CCK release and pancreatic secretion produced by bile-pancreatic juice diversion. Thus, bile salts were concluded to have an inhibitory action. Our conclusion was not in accordance with the hypothesis. The evidence that these bile salts inhibited CCK release is very interesting. We reported in a recent study[3] that rat bile has two inhibitory mechanisms on pancreatic secretion, via stabilizing luminal trypsin and its direct action.
3. We did not examine the effect of DCA, TDCA, GDCA, GCDC, and CDCA on pancreatic secretion during bile-pancreatic juice diversion. To test the effect of all bile salts would be preferable; however, as we have shown in Figure 2 of reference 4, the pattern of changes of concentrations of protein and bicarbonate were similar among DCA, CDCA, and UDCA. Moreover, the potency of these three bile salts was not significantly different, although the potency of GCDC, TDCA, and GDCA was less. Therefore, we believe that the experiments to examine the effect of all bile salts during bile-pancreatic juice diversion was not mandatory. We showed the effect of CCK antagonist and secretin antibody on CDCA-stimulated secretion,[4] and we did the same treatment during UDCA-stimulated secretion,[5] although we did not test DCA-stimulated secretion.
4. CDCA, UDCA, and DCA increased bicarbonate concentration and decreased protein concentration (Figure 2[4]). These results strongly suggested the involvement of secretin because only physiological concentrations of secretin could increase bicarbonate concentration in conscious rats. To comment on the claim by Riepl and Lehnert for involvement of VIP is hardly possible because they refer to a report that is listed as being in press.
5. Administration of CCK antagonist decreased protein secretion in CDCA infusion (Table 1,[4]). It was reported[6] that CCK neuron was substantial in the pancreas, and we recently found CCK messenger RNA in the pancreas by reverse-transcriptase polymerase chain reaction methods. Therefore, the contribution of CCK is considered to be substantial, even if circulating CCK did not significantly increase.

The condition of bile and pancreatic juice diversion is indeed a special condition in conscious rats, but this condition (bile-pancreatic juice diversion) is a very good model to examine pancreatic secretion stimulated by endogenously released CCK. All animals and humans have two different conditions of pancreatic secretion, stimulated and nonstimulated. To obtain stimulated secretion in animals except for conscious rats, administration of stimulants is necessary. However, we can observe these two different conditions in conscious rats simply by return or diversion of bile-pancreatic juice with a very high reproducibility.

Thus, the conclusion proposed by Riepl and Lehnert that the experimental conditions (return or diversion of bile-pancreatic juice) are responsible for the opposite effects of bile salts is inappropriate.

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