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Pancreatic Lysosomal Enzyme Secretion Via Gut-Hormone-Regulated Pathway in Rats

Tetsuya Hirano, Tadao Manabe, Takahisa Kyogoku,
Katsuhiro Ando and Takayoshi Tobe

First Department of Surgery, Faculty of Medicine, Kyoto University, Kyoto 606, Japan
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Abstract

To explore the secretory profiles of lysosomal enzyme in pancreatic juice, we stimulated the secretion of lysosomal enzyme by intravenous pancreatic secretagogues and intraduodenal instillation of liquid meals in rats. Lysosomal hydrolases, such as cathepsin B, are secreted from the apices of pancreatic acinar cells via a hormone-regulated pathway, as in the secretion of pancreatic digestive enzymes. The intravenous infusion of the cholecystokinin analogue caerulein, or the intraduodenal administration of nutrients results in a closely related secretion of both amylase and cathepsin B from the apices of acinar cells, suggesting that they are discharged from the same presecretory compartment (zymogen granules). Lysosomal enzymes appear to enter into the secretory compartment as a result of malsorting, but the cause of this anomaly is not known.

We found small amounts of lysosomal enzymes colocalized with digestive enzymes within zymogen granules in normal acinar cells and in normal pancreatic juice, suggesting some physiological roles of lysosomal enzymes in pancreatic ducts. Furthermore, lysosomal enzymes appear to play important roles in the pathogenesis of pancreatic disease, such as pancreatitis, from both inside and outside the pancreas, since cathepsin B can probably activate trypsinogen.

Introduction

There have been many reports on the secretory profiles of lysosomal enzymes in many cell lines[3,5,10,20,24], and some physiological roles of lysosomal enzymes in biological fluids have been suggested[14]. Recently there have been histochemical reports about the colocalization of lysosomal enzyme with digestive enzymes in normal acinar cells[15,18,25]

These reports suggest that the molecular sorting of lysosomal enzymes at the exist side of the Golgi complex is incomplete under normal condition in rat acinar cells and also suggest the possible secretion of lysosomal enzymes stimulated by gut hormone such as cholecystokinin (CCK) together with pancreatic digestive enzymes, into pancreatic juice.

Moreover, recent our study showed the secretion of lysosomal enzymes into gastric, duodenal and pancreatic juice stimulated by gut hormones such as CCK analogue, caerulein, pentagastrin, or

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索引語：膵液，カテプシンB，ライソゾーム酵素.
Present address: First Department of Surgery, Faculty of Medicine, Kyoto University, 54 Shogoin-Kawaracho, Sakyoku, Kyoto 606, Japan

VIP in rat and rabbit[7,8,9]. However, little is known about the mechanisms of lysosomal enzyme secretion in normal physiological state such as food intake. Most of the studies evaluating this phenomenon have used nonpolarized cell types and have shown that under most conditions lysosomal enzymes are secreted in a constitutive pathway[2,11].

Lysosomal enzymes are synthesized in the endoplasmic reticulum and, along with other newly synthesized proteins including structural proteins and secretory digestive enzymes, transported to the Golgi complex. During transit through the Golgi, lysosomal hydrolases are glycosylated, 6-mannose phosphorylated, and bound to 6-mannose phosphate-specific receptors[12,13,22,23]. As a result, lysosomal hydrolases are diverted towards lysosomal compartment and separate from the pathway by which secretory proteins such as digestive enzymes are secreted from the acinar cell.

In this communication, we reported the results of studies on lysosomal enzyme secretion in the hormone-regulated pathway towards the lumen from the exocrine pancreas. Pancreatic acinar cells are believed to secrete digestive enzymes exclusively from the apical surface of the cell, via well-characterized hormone-regulated pathway[19]. We observed that a small amount of lysosomal enzymes was secreted from the apical surface of acinar cells under resting conditions, and that cholecystokinin analogue caerulein or the intraduodenal instillation of nutrients stimulated the amount of lysosomal enzyme secretion from acinar cells. This increased output of lysosomal enzyme stimulated by caerulein or food administration also showed the significant correlationships to the output of pancreatic digestive enzyme.

These observations suggest that secretion of lysosomal enzyme into pancreatic juice from the acinar cells occurs primarily via the hormone-regulated rather than via the constitutive pathway.

Since the lysosomal enzyme cathepsin B can activate trypsinogen[4,6,21], and trypsin can activate many other digestive enzymes, the colocalized secretion of lysosomal enzymes and digestive enzymes as well as the colocalization in acinar cells suggest some important roles of lysosomal enzymes in the pancreatic ductal system both in normal physiological states and in pathological states such as pancreatitis.

Materials and Methods

Materials Male Wistar rats weighing 325–350 g were obtained from Shizuoka Experimental Animal Supply (Shizuoka, Japan). They were housed in light-dark cycle regulated (light, 5:00–17:00), air-conditioned (23±3°C) animal quarters, given free access to diet (Purina Rodent Chow, Purina Mills Inc., St. Louis MO, U.S.A.) and tap water, and allowed 4 days to become acclimated to standard laboratory conditions. The rats were maintained throughout the study in accordance with the guidelines of the Committee on Animal Care of Kyoto University, Kyoto, Japan. Caerulein and secretin were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.) Isocal meal (15.3% protein, 19.7% fat, 59.7% carbohydrates) was purchased from Mead Johnson (Evansville, IN, U.S.A.). CBZ-arginyl-arginine-β-naphthylamide was from Bachem Biosciences (Philadelphia, PA, U.S.A.) and β-naphthylamide from Sigma Chemical. All other reagents were of the highest purity commercially available.

Animal preparation After a 16-hour fast, rats were anesthetized with intraperitoneal sodium pentobarbital (25 mg/kg intially, supplemented by periodic doses of 10 mg/kg intravenously as needed), and a cannula (V-3, Insul-Tab. Inc., Woburn, MA, U.S.A.) was introduced into the superior vena cava via the right external jugular vein. After midline abdominal laparotomy, the pylorus was

ligated and a gastrostomy cannula (PE 20, Clay Adams, Parsippany, NJ, U.S.A.) was placed for drainage. The pancreatico-biliary duct was catheterized (PE 50) extraduodenally, adjacent to the duodenum and another catheter (PE 10) was placed in the common hepatic duct as an external biliary fistula. An infusion cannula (V-3) was placed in the descending portion of the duodenum just below the pylorus for administration of liquid meals. After the placement and exteriorization of the various catheters, the abdominal wound was closed. The core temperature of the animals was maintained with a heating pad (American Medical Systems, Cincinnati, OH, U.S.A.) and overhead lamps.

Secretion of digestive and lysosomal enzymes stimulated by secretin and caerulein. After 30 minutes for stablization, secretin was infused for one hour through the venous catheter at a rate calculated to deliver 0.2 CU/kg · hr to wash out the bile from the pancreatico-biliary duct and to maintain the flow of pancreatic juice. For the next 2 hours, to stimulate the secretion of digestive enzymes, caerulein was infused at 5 different rates calculated to deliver from 0.1 to 1.5 μg/kg · hr (0.1, 0.2, 0.5, 1.0 and 1.5) at an infusion speed of 0.58 ml/hr in heparinized (30 U/ml) 150 mM NaCl solution (heparinized saline) with an infusion pump (Harvard Apparatus, South Natick, MA, U.S.A.). The pancreatic juice was collected each hour in preweighed ice-chilled Eppendorf tubes (secretin fraction, S; caerulein fractions, C_1 and C_2). For each dose of caerulein 4 animals were used and 3 pancreatic juice fractions were obtained from each animal. Amylase and cathepsin B activity output were measured in each fraction and expressed as U/kg · hr. The volume of pancreatic juice was calculated from its specific gravity taken as 1.0 g/ml by direct weighing. All the experiments were begun at 8:00 AM to rule out the effect of circadian rhythm on the rat exocrine pancreas.

Secretion of digestive and lysosomal enzymes stimulated by intraduodenal liquid meal. Six other rats were used in this experiment. After 30 minutes for stabilization, pancreatic juice was collected for one hour base-line values (B), and a liquid meal (Isocal®; 3 g/kg · body weight in 2.0 ml of water) was instilled into the duodenum through the duodenostomy catheter for 15 minutes with an infusion pump. Three more samples of pancreatic juice (D_1, D_2 and D_3) were obtained at 1-hour intervals and the cathepsin B activity was measured. Protein, amylase and cathepsin B outputs were expressed as mg or U/kg · hr. During this experiment, heparinized saline was infused at a speed of 0.58 ml/hr.

Assays. Amylase was measured by the method of Bernfeld[1] with soluble starch as the substrate. One unit of activity is defined as that which liberates 1 mg of maltose per minute at 30°C. Cathepsin B was measured as described by McDonald and Ellis with CBZ-arginyl-arginine-β-naphthylamide as the substrate[17] One unit of activity is defined as that which liberates 1 nanomole of β-naphthylamine per minute at 37°C. Protein was determined by the method of Lowry et al[16] with bovine serum albumin as the standard.

The results reported in this communication represent the mean ± SEM values of n determinations in each animal. The significance of differences was eveluated by ANOVA with the Tukey method. A p value of <0.05 was considered to be significant.

Results

Secretion of amylase and cathepsin B into rat pancreatic juice stimulated by secretion and caerulein. The volume of each pancreatic juice fraction is listed in Table 1. In the secretin fraction (S), there was little change in volume, but stimulation with caerulein caused a marked increase in the

volume. These results indicate that caerulein can stimulate pancreatic juice secretion in the rat. With higher doses of caerulein, however, (1.0 μg/kg・hr and 1.5 μg/kg・hr), the volume was less than with doses of 0.2 and 0.5 μg/kg・hr. Maximum flow was observed at a dose of 0.2 and 0.5 μg/kg・hr. The infusion of secretion (0.2 CU/kg・hr) alone raised the rates of amylase (1560±281 U/kg・hr) and cathepsin B (3±1 U/kg・hr) secretion into the pancreatic juice only slightly. Caerulein, infusion, on the contrary, resulted in a dose-dependent stimulation of both amylase and cathepsin B output (Figs. 1a and b): with 0.1 μg/kg・hr of caerulein, cathepsin B was 10±1 U/kg・hr and amylase 4996±235 U/kg・hr; with 0.2 μg/kg・hr of caerulein, cathepsin B was 18±2 U/kg・hr and amylase 7457±195 U/kg・hr; with 0.5 μg/kg・hr of caerulein, cathepsin B was 33±2 U/kg・hr and amylase 9042±556 U/kg・hr). At higher doses of caerulein enzyme output was lower; with 1.0 μg/kg・hr cathepsin B was 20±2 U/kg・hr and amylase 6249±192 U/kg・hr and

Table 1 Changes in the pancreatic juice volume stimulated by 5 different doses of caerulein (0.1, 0.2, 0.5, 1.0 and 1.5 μg/kg・hr) and by secretin (0.2 CU/kg・hr)

Group	n	Pancreatic juice volume (ml/kg・hr) Pancreatic juice fraction		
		S	C_1	C_2
0.1	4	0.23±0.03	0.85±0.07	0.96±0.08
0.2	4	0.28±0.05	1.04±0.09	1.12±0.06
0.5	4	0.25±0.03	1.26±0.11	1.33±0.09
1.0	4	0.29±0.04	1.13±0.12	0.95±0.10
1.5	4	0.21±0.03	0.74±0.08*	0.64±0.12**

The values are expressed as mean±SEM and as ml/kg・hr.
(S, secretin fraction (0.2 CU/kg・hr); C_1 and C_2, caerulein fractions by hours; *, $p<0.05$ compared with 0.2, 0.5 and 1.0; **, $p<0.05$ compared with 0.2 and 0.5)

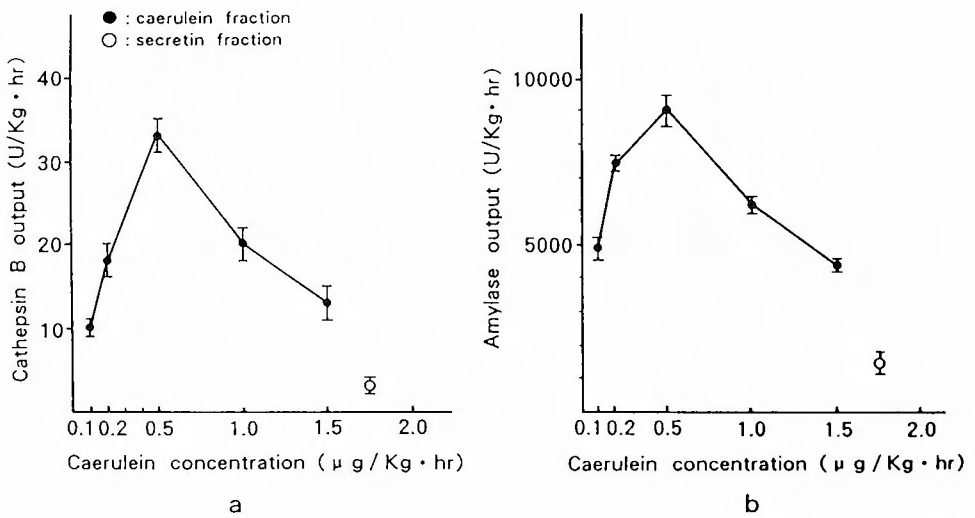

Fig. 1 Secretion of cathepsin B (a) and amylase (b) into rat pancreatic juice stimulated by secretin (0.2 CU/kg・hr) and 5 different doses of caerulein (0.1, 0.2, 0.5, 1.0 and 1.5 μg/kg・hr). Four rats were injected with each caerulein dose and from each animal, 1 secretin fraction and 2 caerulein fractions were obtained. Amylase and cathepsin B outputs were expressed in U/kg・hr. (●, caerulein fraction; ○, secretin fraction)

with 1.5 μg/kg · hr of caerulein, cathepsin B was 13±2 U/kg · hr and amylase 4484±146 U/kg · hr. There was a close correlation ($p<0.001$) between the outputs of amylase and cathepsin B at all doses of caerulein tested (0.1–1.5 μg/kg · hr) (Fig. 2).

Secretion of amylase and cathepsin B into pancreatic juice stimulated by intraduodenal liquid meal instillation. Intraduodenal infusion of a liquid meal increased the volume of pancreatic juice to 3–4 times the base-line for almost 2 hours in anesthetized rats (Table 2). It also stimulated cathepsin B, amylase, and protein secretion (Figs. 3a, b and c).

Cathepsin B outputs were 3±1 U/kg · hr (B), 15±2 U/kg · hr (D_1), 11±1 U/kg · hr (D_2), and 4±1 U/kg · hr (D_3). Amylase outputs were 1070±131 U/kg · hr (B), 5389±341 U/kg · hr (D_1),

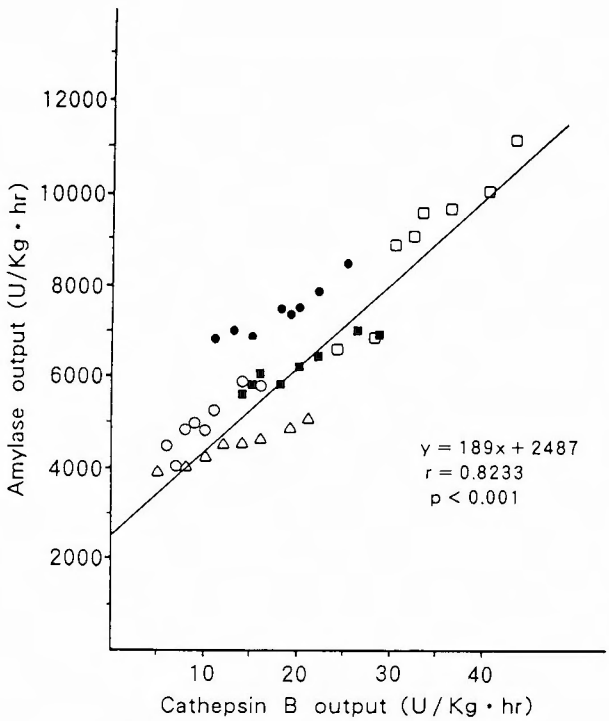

Fig. 2 Correlation between amylase and cathepsin B outputs stimulated by 5 different doses of caerulein (0.1, 0.2, 0.5, 1.0 and 1.5 μg/kg · hr). Four animals were used for each concentration and from each animal 2, caerulein fraction were obtained. (○, 0.1 μg/kg · hr; ●, 0.2 μg/kg · hr; □, 0.5 μg/kg · hr; ■, 1.0 μg/kg · hr; △, 1.5 μg/kr · hr $r=0.8233$; $p<0.001$)

Table 2 Changes in pancreatic juice volume stimulated by intraduodenal instillation of liquid meal

Group	n	Pancreatic juice volume (ml/kg · hr) Pancreatic juice fraction			
		B	D_1	D_2	D_3
Intraduodenal infusion of liquid meal	6	0.17±0.02	0.72±0.07*	0.45±0.08**	0.20±0.05

The values are expressed as mean±SEM and ml/kg·hr.
(B, Base-line fraction; D_1, D_2 and D_3 fractions, 1, 2, and 3 hours after food stimulation, *, $P<0.01$ compared with B, D3, and $p<0.05$ compared D2; **, $p<0.02$ compared with B and $p<0.05$ compared with D_3)

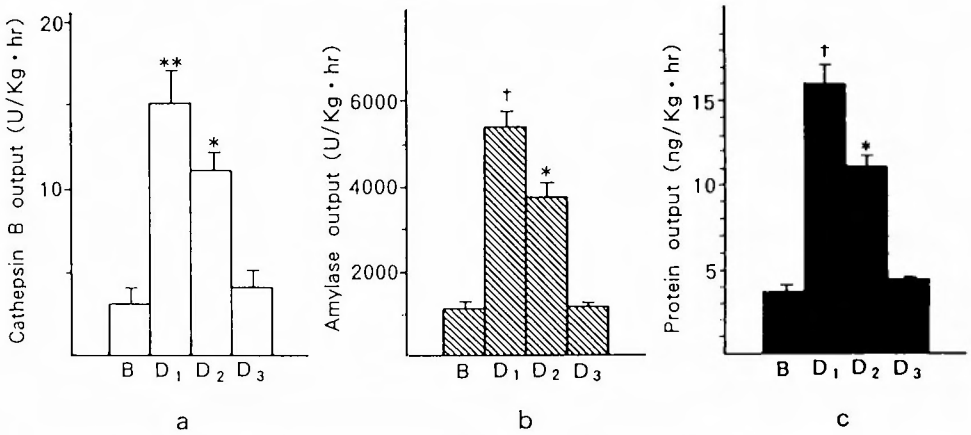

Fig. 3 Secretion of cathepsin B (a), amylase (b), and protein (c) into rat pancreatic juice stimulated by intraduodenal instillation of a liquid meal. Six animals were used in this experimental and from each animal, 1 base-line fraction (B), and three post-stimulation fractions at hourly intervals (D_1, D_2, and D_3) were obtained. (*, $p<0.01$ compared with B and D_3; **, $p<0.001$ compared with B and D_3; +, $p<0.001$ compared with B and D_3, and $p<0.05$ compared with D_2)

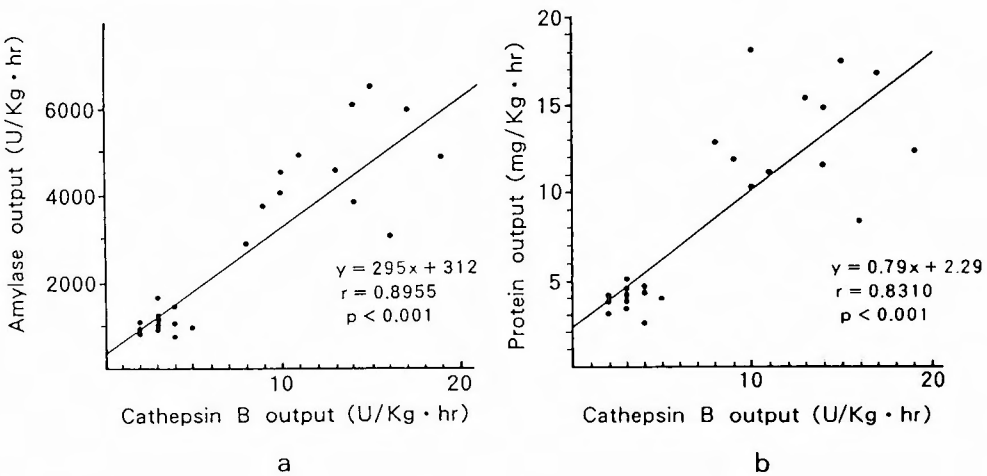

Fig. 4 Correlation between cathepsin B and amylase output (a), and protein output (b) into rat pancreatic juice stimulated by intraduodenal instillation of liquid meal. The animals were the same as in Fig. 3. ((a) $r=0.8955$ ($p<0.001$), (b) $r=0.8310$ ($p<0.001$))

3729±297 U/kg・hr (D_2), and 1093±68 U/kg・hr (D_3). Protein output were 3.6±0.3 mg/kg・hr (B), 15.9±0.9 mg/kg・hr (D_1), 11.0±0.6 mg/kg・hr (D_2), and 4.3±0.2 mg/kg・hr (D_3). All three were significantly above the base-line values for 2 hours after food instillation into the duodenum, but by 3 hours after food stimulation, all three values had returned to the pre-stimulation levels. As noted in Figs. 4a and b, the meal-stimulated secretion of cathepsin B was closely correlated with the meal-stimulated secretion of amylase ($r=0.8955$, $p<0.001$) and of protein ($r=0.8310$, $p<0.001$).

Discussion

Pancreatic acinar cells are believed to secrete mainly pancreatic digestive enzymes through the hormone-regulated, well-characterized pathway via the complex intracellular process[19], and its main secretory pathway is believed to be from the apical surface of the acinar cells towards the luminal direction-into the pancreatic ductal system.

In contrast to this hormone-regulated pathway of pancreatic digestive enzymes, lysosomal hydrolases have been reported to be secreted via the constitutive pathway like as the structural protein such as the plasma membrane or basement membrane proteins[2,11].

Both these two types of enzymes-digestive enzymes and lysosomal hydrolases-are synthesized on the membrane-bound polysomes in the rough endoplasmic reticulum and transported to the Golgi complex, and during a passage through the Golgi complex, lysosomal hydrolases are glycosylated, 6-mannose phosphorylated and bound by 6-mannose phosphate-specific receptors. With this 6-mannose phosphate-specific receptor, lysosomal hydrolases are transported towards lysosomal compartment, separately from the pathway of digestive enzymes. In this way, the lysosomal enzymes are segregated from the proteins that are destined for secretion and theoretically, there seems to be no chance for the colocalization of these two types of enzymes in the same subcellular compartment after the Golgi complex. In this study, we report the results of studies which characterized the lysosomal enzyme secretion into the pancreatic juice, and show that CCK analogue caerulein can stimulate the apical secretion of lysosomal enzyme into the pancreatic juice like as in the digestive enzyme, in a dose-dependent manner, where in the higher dose of caerulein, the secretion of lysosomal enzyme can be inhibited. Only negligible amount of cathepsin B was observed under the stimulation of secretion or in the basal phase.

Furthermore, intraduodenal instillation of liquid nutrient also showed the increased output of the lysosomal enzyme into the pancreatic juice like as in the digestive enzymes, and both in the infusion of caerulein and intraduodenal instillation of nutrient, there were highly significant positive correlationships between the output of lysosomal enzymes and digestive enzyme.

There seems to be two hypotheses for the explanation of this lysosomal enzyme secretion into pancreatic juice from the apical surface of the acinar cells

1. In the normal pancreatic acinar cells a small amount of lysosomal enzymes are colocalized with pancreatic enzymes in the secretory compartment, zymogen granules.

2. A small amount of lysosomal enzymes near the apical surface of acinar cells are secreted by the direct stimulation of caerulein separately from the pathway of digestive enzymes from the different secretory compartment.

In either case, it is clear that a small amount of lysosomal enzymes can be secreted via well-characterized hormone-regulated pathway into the pancreatic juice from rat pancreatic acinar cells.

But when thinking about the reports about the colocalization of lysosomal hydrolases with digestive enzymes in the zymogen granules in the normal pancreatic acinar cells[15,18,25], and as in our study, the close correlationships between the output of lysosomal enzyme and digestive enzyme, the first hypothesis-normally colocalized lysosomal enzymes with digestive enzymes in the zymogen granules-seems to be plausible and possible explanation.

We can not explain clearly how this colocalization occurs in the zymogen granules, but there seems to be several possible mechanisms; trapping of lysosomal enzymes by the bulk flow of secretory digestive proteins, or lack of mannose-6-phosphate receptors to lysosome enzymes containing

organelles.

In all there mechanisms, these seems to be incompleteness of separation of both two types of enzymes in the molecular sorting, near the Golgi complex, and it is concluded that segregation of lysosomal and digestive enzymes is incomplete in normal acinar cells resulting in the colocalization in the zymogen granules and this colocalization phenomenon seems to reflect the physiological conditions rather than pathologicaly missorting. Since lysosomal enzymes and secretory proteins share the mechanism for membrane translocation, they are mixed together in the lumen of the rough endoplasmic reticulum.

For clarifying these issues, further sophisticated techniques such as immunolocalization will be needed in the future study.

Since the lysosomal hydrolase cathepsin B can activate trypsinogen[4,6,21], and trypsin can activate many other digestive enzymes, this colocalization of lysosomal enzyme and digestive enzyme in the normal zymogen granules and also in the normal pancreatic juice, might shed light on the pathophysiology of the pancreatic diseases such as pancreatitis, and also indicate the potential danger of the exocrine pancreas in the pathogenesis of pancreatitis, from the inside and outside the acinar cells.

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和文抄録

消化管ホルモンの刺激による膵ライソゾーム酵素の膵液中への分泌

京都大学医学部第一外科学教室
平野　鉄也，真辺　忠夫，京極　高久
安東　勝宏，戸部　隆吉

この研究では，膵外分泌刺激ホルモンの投与および十二指腸内食餌負荷によるラット膵液中へのライソゾーム酵素の分泌動態を検討した．ライソゾーム酵素であるカテプシン B が膵消化酵素と同様に，膵外分泌刺激ホルモンの投与により膵液中へ分泌されることが判明し，セルレイン刺激下，および十二指腸内食餌負荷におけるカテプシン B とアミラーゼ分泌量の間には有意の正の相関関係が観察された．これらの結果は，正常膵腺房細胞内でのライソゾーム酵素と膵消化酵素の同一細胞内分（チモーゲン顆粒）内での共存を示唆させるとともに，膵管系でのライソゾーム酵素の何らかの生理学的役割をも示唆させた．さらに，カテプシン B がトリプシノーゲンを活性化し得ることにより，これらの膵腺房細胞内外での共存が，膵炎といった膵の病態生理にて重要な役割を果している可能性も示唆された．