Effect of pancreatic atrophy and hypertrophy on the small intestine

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SUMMARY   Intestinal enzyme activities were investigated in mice with spontaneously occurring exocrine pancreatic insufficiency (EPI), in rats after induction of pancreatic insufficiency by intraductal injection of oleic acid, and in rats after feeding a proteinase inhibitor (Camostate) which induced a marked pancreatic hypertrophy. An increase in saccharase activity and *in vitro* uptake of L-phenylalanine was found in EPI mice, while activities of alkaline phosphatase and lactase were not altered. In oleic acid induced pancreatic insufficiency and in pancreatic hypertrophy no alterations in enzyme activities were observed. Morphometric analysis revealed no alterations in mucosal surface of EPI mice. It was suggested that the small intestine adapts functionally to severe and long lasting pancreatic insufficiency, but not to pancreatic hypertrophy.

In exocrine pancreatic insufficiency an increase in intestinal enzyme activities of disaccharidases have been described in man and in animals.[1-4] It was suggested that the loss of pancreatic enzymes decreased the turnover of brush border enzymes.[5] On the other side, after ligation of the pancreatic duct, exocrine insufficiency was paralleled by a decrease of the absorbing area of the intestine.[6] The aim of the present study was to analyse whether changes in intestinal enzyme activities were correlated with alterations in intestinal cell mass and transport function. Additionally we investigated whether intestinal adaptive changes depend on the severity of pancreatic insufficiency, and occur in pancreatic hypertrophy.

Methods

ANIMALS

In 12 CBA/J mice the spontaneously occurring exocrine pancreatic insufficiency syndrome (EPI) was diagnosed on the basis of rapid weight loss and fatty yellow stools four weeks before the intestinal studies.[7] Twelve healthy adult CBA/J mice served as controls.

In 18 rats pancreatic insufficiency was induced by a single injection of 50 μl oleic acid into the pancreatic duct.[8] Intestinal studies were done after six weeks.

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Saline injected animals and untreated rats served as controls. Hypertrophy of rat pancreas was induced by daily feeding the proteinase inhibitor Camostate (400 mg/kg).[9] After five, 10, and 15 days of feeding intestinal studies were undertaken. Animals were killed under ether anaesthesia. Small intestines were removed, rinsed in cold, 0·9% saline, measured, and weighed. From a 10 cm segment which started 20 cm distal the pylorus, the mucosa was scraped off and homogenised. DNA, protein, saccharase, lactase, and alkaline phosphatase were measured according to standard procedures.[10-13] In EPI mice a jejunal segment (100 mg) was removed to investigate the *in vitro* uptake of ^{14}C-L-phenylalanine according to Robinson *et al*.[14] Morphometric analysis of villus height and width, and crypt length of the jejunum was carried out on HE-stained sections.

RESULTS

In mice with severe exocrine pancreatic insufficiency (EPI) a marked increase in jejunal activity of saccharase was found, while the activities of alkaline phosphatase and lactase were not different from healthy CBA/J mice (Fig. 1). In oleic acid induced pancreatic insufficiency in rats the jejunal enzyme activities of lactase, saccharase, and alkaline phosphatase were the same as from saline treated and untreated rats (Table 1). Morphometric analysis of the jejunum in EPI mice revealed a significant decrease in villus height, and an increase in villus width, while
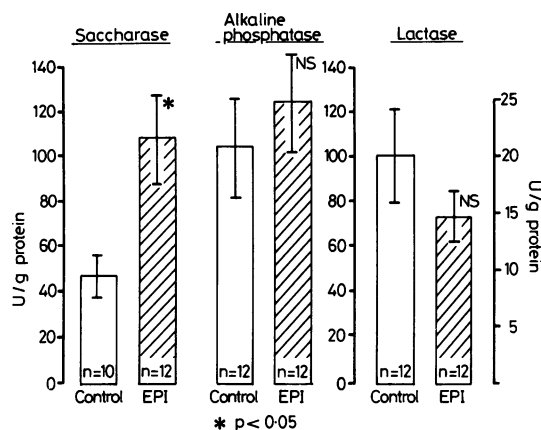
Fig. 1   *Intestinal enzyme activities in mice with exocrine pancreatic insufficiency (EPI) compared with healthy CBA/J mice. Values are means ± SEM.*

Table 1   *Intestinal enzyme activities after oleic acid-induced pancreatic insufficiency in rats.*

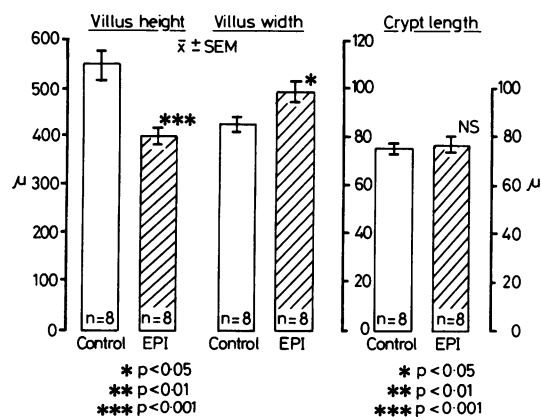| Enzyme (U/g protein)	Oleic acid	Saline	Untreated controls
Saccharase	141 ± 66	145 ± 38	172 ± 43
Lactase	17 ± 7	13 ± 6	17 ± 4
Alkaline phosphatase	256 ± 172	262 ± 157	398 ± 161

Values are means ± SD

Fig. 2   *Morphometric analysis of jejunal mucosa in mice with exocrine pancreatic insufficiency (EPI) compared with healthy CBA/J mice. Values are means + SEM.*

crypt length was not altered (Fig. 2). In rats with oleic acid induced pancreatic insufficiency no differences in jejunal morphology were found when compared with controls (data not shown). *In vitro* uptake of ^{14}C-L-phenylalanine was increased in EPI mice compared
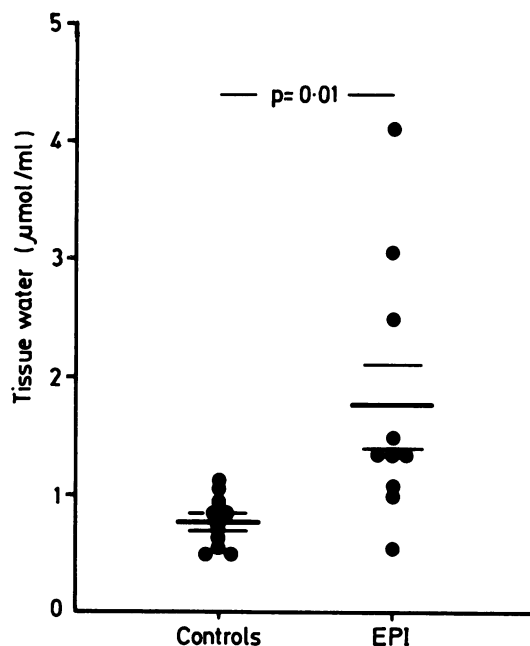

Fig. 3   *In vitro uptake of ^{14}C-L-phenylalanine in EPI mice compared with healthy CBA/J mice.*

Table 2   *Intestinal enzyme activities in rats after feeding the proteinase inhibitor Camostate.*

Enzyme (U/g protein)	Days of feeding	Camostate	Controls
Saccharase	5	172 ± 32	96 ± 28
	10	103 ± 30	134 ± 34
	15	125 ± 27	189 ± 23
Lactase	5	15 ± 3	16 ± 5
	10	13 ± 4	20 ± 6
	15	14 ± 3	17 ± 4
Alkaline phosphatase	5	268 ± 55	179 ± 53
	10	170 ± 46	251 ± 66
	15	280 ± 61	183 ± 38

Values are means ± SD

with healthy CBA/J mice (Fig. 3). Pancreatic hypertrophy by feeding a proteinase inhibitor had no effect on length, wet weight, DNA, and protein content of the small intestine (data not shown). No significant differences in enzymatic activity of saccharase, lactase, and alkaline phosphatase in jejunum were observed after feeding the inhibitor for five, 10, and 15 days (Table 2). Morphometric analysis of villi and crypts gave similar results when compared with controls.

DISCUSSION

In the present study intestinal adaptation to pancreatic insufficiency was seen in severely diseased EPI

mice only. The EPI mice presented with weight loss, steatorrhea, and destroyed pancreas which was replaced by adipose tissue. They could only survive when they ingested the pancreatic enzyme containing faeces of healthy mice.[7] In oleic acid induced pancreatic insufficiency the functional impairment was only moderate, as the rats still gained weight and did not show deficiency syndromes, although 97% of the exocrine pancreas was destructed.[8] In this model of pancreatic insufficiency no changes in intestinal enzyme content and morphology were observed. We therefore concluded that severity and duration of pancreatic insufficiency are important factors in intestinal adaptation. A similar conclusion was drawn from studies in patients with pancreatic insufficiency.[2] Patients with steatorrhea had higher maltase and sucrase activities than those without steatorrhea. At variance with these studies is the observation of Creutzfeldt et al that in rats with pancreatic atrophy induced by feeding a copper deficient diet and penicillamine, intestinal enzyme activities were increased only in the proximal part of the small intestine.[4]

An explanation for increased activity of some intestinal enzymes in pancreatic insufficiency was given by Alpers et al.[3 5 15] Because disaccharidases and transport proteins are associated with the brush border they could preferentially be degraded by pancreatic enzymes which stick to the membrane of intestinal mucosa. As was seen in the duct ligation model of pancreatic insufficiency by Balas and coworkers, we found a significant reduction in villus height in mice with severe pancreatic insufficiency.[6] As the villi became smaller but broader, the total cell surface was not significantly altered.

A direct trophic effect of pancreatic secretions on intestinal mucosa was suggested from studies in which the duodenal papilla was transplanted to other regions of the intestine,[16] but was doubted by Ecknauer and coworkers.[17] In our study, daily feeding of a proteinase inhibitor for up to 15 days induced pancreatic hypersecretion and a strong increase in plasma CCK which had no trophic effect on the small bowel.[9] Whether CCK alone has a trophic effect on intestinal mucosa was controversely discussed in different studies.[4 18 19]

We conclude that the small intestine adapts functionally only to severe and long lasting pancreatic insufficiency, and not to pancreatic hypertrophy induced by endogenous CCK.

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