Pancreatic size and enzyme contents after vagal deafferentation in jejunectomised pigs under free or restricted feeding

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SUMMARY A factorial experiment was designed to test under different feeding levels the effects of the surgical deprivation of sensory afferences (deafferentation) arising from the gastrointestinal tract, including the intestinal chemosensitivity, on the jejunectomised pig used as a model. Within 28 days, the limited jejunectomy failed to affect the pancreas and the enzyme activities were not affected by the feeding level (within the limit of 70% of *ad libitum*). It was shown that the deafferentation induced significant reductions in the pancreatic tissue mass and in the various enzyme activities, thus suggesting the possible importance of intestinal sensibility for the pancreas.

Recent reviews of the mechanisms responsible for intestinal and pancreatic adaptation after small intestine resection,¹⁻² have stressed the basic role of endoluminal nutrition. This was first suggested many years ago³ and since then, the suggestion has been reinforced by the effects of several manipulations such as ileal transposition, hyperphagia, fasting, small bowel bypass, and enteral v parenteral nutrition. Indeed, the presence of nutrients within the intestinal lumen may well be necessary to support epithelial cell nutrition and growth directly, in course of absorption.⁴ Luminal nutrition could also act together with bile and pancreatic secretions which were first proposed to have trophic effects, in 1970.⁵

The evidence that humoral factors are responsible for compensatory hyperplasia comes from cross circulation studies in the rat⁶⁻⁷ and pig.⁸ It includes a humoral mediation of endoluminal factors, in addition to direct local effects.⁹⁻¹¹ Enteroglucagon now seems to play a major role in intestinal adaptation.¹² Although cholecystokinin (CCK), when associated with secretin,¹³ can prevent the intestinal mucosal hypoplasia of TPN, its main trophic action is on the pancreas.¹⁴

The nervous system might also be suspected to play some direct (enteric or central reflexes), or indirect (modulation of regulatory peptides release), role.

Indeed, there are differing degrees of compensatory hypertrophy, depending on the composition of the diet¹⁵ which could be related to the highly discriminating ability of visceral sensitivity arising from the numerous vagal receptors, including a large variety of chemoreceptors.¹⁶ The importance of visceral sensitivity has been first evidenced in relation with intestinal adaptation.⁸ The modulation of its role according to the food intake level was also shown in that case.¹⁷

The aim of the present study was to investigate, using the pig as a model, the significance of vagally mediated intestinal chemosensitivity to endoluminal nutrients as regards pancreatic morphology and exocrine function, after small intestine resection and under various feeding conditions.

Methods

ANIMALS

The whole experiment, which lasted 28 days, involved 72 Large White pigs whose initial live weight was 28.6 ± 0.2 kg (mean $\pm$ SEM). Pigs were randomly allotted to the 12 combinations resulting from a factorial design including four treatments $\times$ three feeding levels $\times$ six repetitions.

The four treatments were: (1) unoperated controls (C group); (2) jejunectomy (J group); (3) jejunectomy and subtotal vagal deafferentation (J-SD group); (4) jejunectomy and total vagal deafferentation (J-TD

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group). As in previous experiments,⁸⁻¹⁷ the jejunectomy consisted of a limited, 4 m resection, ending 120 cm above the ileocaecal junction, with 68 % of the total small intestine length left *in situ* and end-to-end restoration of intestinal continuity. The vagal deafferentation selectively suppressed afferent impulses originating below the diaphragm but preserved efferent impulses from the brain stem. It was achieved by removing the left nodose ganglion, performing contralateral truncal vagotomy at the level of the diaphragm (subtotal deafferentation) and, in the case of total deafferentation,¹⁸ by additional transection of the intra-thoracic branches connecting the two vagus nerves.

The three feeding levels were respectively: (i) *ad libitum* feeding, (ii) 85 % and (iii) 70 % of the *ad libitum* level. Except for the first seven days after surgery, this was achieved within each repetition, by daily measurement of the true dry matter intake of the four *ad libitum* fed pigs, and then by calculation for a matched treatment of the quantities to be allotted to the pigs submitted to a restricted feeding. Both controls at the start of the experimental period and operated pigs underwent fasting for two days; then the hierarchy of the three feeding levels was applied according to a postsurgical feeding scale over seven days.

The feed included ground whole wheat (81.5 %), soya bean meal (12.0 %), purified wood cellulose (3.0 %), minerals and vitamins (3.5 %). It supplied 3618 kcal per kg dry matter, at a 14.3 % crude protein level.

At the end of the full 28 days period, the pigs were slaughtered under electrical narcosis. The whole pancreas was immediately removed, and deep frozen after recording its wet weight. Pancreatic tissue was then homogenised. Its dry matter content and the tissue enzyme activities of amylase, chymotrypsin, trypsin, apparent and potential lipase were determined.¹⁹

Results

FOOD INTAKE AND SOMATIC GROWTH

There were significant differences between the feeding groups as the mean daily dry matter intake recorded over the whole period confirmed the expected feeding schedule (maximum deviation: 2 %). That resulted in the same hierarchy of the mean daily live weight gains, with significant differences between feeding groups. Jejunectomy never significantly reduced the dry matter intake, however, nor the daily mean live weight gain as compared with the homologous C-pigs. Though significantly lower than in the C-pigs, the dry matter intake in J-SD and J-TD pigs was similar to that recorded in the J-pigs. Within a similar

Fig. 1 Effects of the feeding level on the pancreas: mean ($\pm$ SEM) effects independent of the surgical treatments. The values 100, 85 and 70 refer to the percentage of *ad libitum* feeding.

Fig. 2 Effects of the feeding level on total enzyme activities of pancreatic tissue: mean ($\pm$ SEM) effects independent of the surgical treatments.

feeding group, the live weight gain was similar in J, J-SD and J-TD pigs.

PANCREATIC TISSUE

The effects of the feeding level were limited. While the protein content per gram of pancreatic tissue was unaffected, only the 70 % feeding level significantly reduced the wet and dry weights and the total protein content of the pancreas (Fig. 1). But enzyme activities were not significantly affected by the feeding level (Fig. 2).

As regards the surgical treatments, independent of the feeding level, all values recorded in J pigs were similar to control values. In contrast, the wet and dry weights of the pancreas and the total pancreatic protein content were significantly reduced

Fig. 3 Effects of the surgical treatments on the pancreas: mean ($\pm$ SEM) effects independent of the feeding level. C = control pigs; J = jejunectomised pigs; J-SD = pigs submitted to jejunectomy and subtotal deafferentation; J-TD = jejunectomy and total deafferentation.

Fig. 4 Effects of the surgical treatments on total enzyme activities of pancreatic tissue: mean ($\pm$ SEM) effects independent of the feeding level. For explanations see Figure 3.

in J-SD and J-TD pigs while the protein content per gram of pancreatic tissue was not modified (Fig. 3). In addition, the total enzyme activities of trypsin, chymotrypsin, amylase and lipase were significantly depressed in J-SD and J-TD pigs (Fig. 4), as well as the corresponding specific, and per gram of tissue, enzyme activities. There was no significant interaction between the feeding level and the surgical procedures tested.

Discussion

Relatively little is known regarding the exocrine pancreas after small intestine resection, except for massive resections in the rat.²⁰⁻²¹ According to our

results, a limited distal jejunectomy does not affect the pancreas of the pig when performed alone.

As regards intestinal adaptation, despite a reduced intake after surgery, there may be a relative nutrient overload of residual segments after massive resection, able to induce compensatory hypertrophy in connection with other trigger mechanisms. Meanwhile, as the pancreas supplies the main enzymes responsible for hydrolysis of food components, pancreatic exocrine function has to be adjusted to the total intake.²² This ability seems to be preserved, even under the most severe food restriction (70% of *ad libitum*) as all enzyme activities were not significantly modified despite a reduced weight and total protein content of the pancreas. These results after a long term restriction are quite different from the effects of a short term starvation for example, as reviewed by Solomon.²² Our data however would suggest that the nervous and humoral factors triggering pancreatic exocrine function are still active even under restricted feeding.

Our experiment allowed us to test accurately the effects of vagal deafferentation on the pancreas in jejunectomised pigs as both the jejunectomy and the food intake level failed to induce any significant disorder of pancreatic function.

In contrast, the vagal deafferentation, either subtotal or total, induced both a morphological (reduced weight and total proteins) and functional (enzyme activities) lessening of the pancreatic tissue. The question arises as to whether these effects result directly from the nervous dysfunction or indirectly from a secondary humoral dysfunction, or both. Moreover, the effects recorded on the pancreas could be direct effects on this target organ as well as indirect effects resulting from the consequences of vagal deafferentation in jejunectomised pigs – that is, impaired compensatory hypertrophy.¹⁷

By analogy, let us recall that some intestinal hypoplasia has been reported after total abdominal vagotomy in dogs²³⁻²⁴ but postresectional compensatory mechanisms were still found to operate after bilateral truncal vagotomy.²⁵ Bilateral subdiaphragmatic vagotomy was shown to inhibit and delay DNA synthesis and proliferation of liver cells after partial hepatectomy.²⁶ As regards the pancreas itself, while reduced tissue weights and tissue enzyme activities were found in pigs 28 days after vagal deafferentation, a trophic effect was recently recorded²⁷ in rats three months after bilateral truncal vagotomy (increased weight by 40% and increased enzyme concentrations). Nevertheless, vagal deafferentation is very different from truncal vagotomy because one only suppresses the afferent stimuli to the central nervous system and preserves efferent impulses to the digestive tract. In addition, it should be noted that the

delayed gastric emptying induced by vagal deafferentation,²⁸ which limits food delivery to the duodenum, could be considered in some way as a food restriction. In the rat,²⁷ however, gastric stasis was also observed in most of vagotomised animals, and the trophic effect of vagotomy was the most pronounced in rats with severe stomach distension.

Another interesting hypothesis is related to the possible pancreaticotrophic function of CCK which can be suspected from the literature.² Increased concentrations of CCK and a change in the temporal pattern of the release of CCK as well as an increase in basal concentrations of pancreatic polypeptide were reported after intestinal resection in dogs.²⁹

Thus the question of the effects of vagal deafferentation on the circulating levels of certain regulatory peptides after small intestine resection arises. Although jejunectomy in itself does not affect the pancreas, it might be that a postresectional impaired CCK response was responsible for the recorded pancreatic dysfunction. Conversely it might be that the pancreatic dysfunction after vagal deafferentation was in some way the cause of the impairment of compensatory hypertrophy. Further experiments are needed therefore to elucidate the underlying mechanisms.

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