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Endocrine Profile in Rats with Postgastrectomy Malabsorption: a Pilot Study

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ABSTRACT

Abnormal endocrine profile, especially in the enteropancreatic axis, was described in rats with malnutrition caused by malabsorption after total gastrectomy. Insulin, substance P and motilin concentrations at the fasting condition were significantly elevated in malnutritious rats after total gastrectomy when compared to those in control rats. A significant elevation of pancreatic glucagon and motilin was noted after intraduodenal fat administration in malnutritious rats. These data suggest that these peptides of many humoral factors may thus cause abnormal enteropancreatic axis and consequent malnutrition.

Posttotalgastrectomy malnutrition has been widely discussed in man and animals from the standpoints of morphology, biochemistry, physiology and pathophysiology[3-6,11,12,14-18,20,22]. Endocrine profile, especially based on enteropancreatic axis[21], however, has not been adequately discussed in malnutritious animals after total gastrectomy. Some brain-gut peptides may play some role in humoral control of gastrointestinal function and it is, therefore, expected that some of these peptides may change in level in the blood before and after administration of test meal in total gastrectomized and malnutritious animals. In the present study, the authors attempted to determine such changes in gut peptides and in enteropancreatic axis before and after fat meal in rats with malnutrition (malabsorption) induced by total gastrectomy.

MATERIALS AND METHODS

Male Wistar rats, weighing 180 g, were anesthetized with Nembutal and their abdomen was opened. Total gastrectomy (esophagoduodenostomy) was performed on 18 rats and laparotomy alone was done on 10 rats as controls. The rats of these two groups were fed in the usual manner for 8 months after the operation. All the rats were weighed at the end of 8 months before sacrifice. Eight of 18 rats with postgastrectomy weighed 210 ± 20 g and the remaining 10 rats weighed 300 ± 30 g, while the 10 control rats weighed 450 ± 10 g (Table 1). The eight rats having a mean weight of 210 g were used in the study as malnutritious (malabsorption) rats (experimental group), but the remaining postgastrectomized rats were excluded from the experiment, they being not markedly malnutritious.

Four rats of the experimental group were sacrificed by decapitation without any treatment and the remaining four rats were killed at 30 min after fat administration. Five of the 10 rats belonging to control group were killed by decapitation before and 30 min after fat load. Fat (2 ml of corn oil) infusion was done by the mode of tubing into the duodenum.

Blood was drawn for laboratory evaluation of hematocrit, total protein, total cholesterol and sugar, whose levels were determined by an autoanalyzer except for blood hematocrit.

Hematocrit was determined by on routine procedure. For evaluation of hormones such as insulin, pancreatic glucagon, substance P and motilin, blood was drawn in vacuum tubes containing a small amount (about 0.3 ml) of EDTA-trasyrol. The levels of these hormones were determined by a radioimmunoassay method.

Table 1. Laboratory findings. Total gastrectomized rats are under marked malnutrition.

	Control	Experimental
B.W.(g)	450 ± 10	210 ± 20
T.P.(g/dl)	7.0 ± 1.2	4.5 ± 0.6
CHL(mg/dl)	69.2 ± 12.5	45.8 ± 8.9
BS (mg/dl)	81.5 ± 8.8	68.0 ± 18.5
Ht. (%)	45 ± 2.5	15.2 ± 21.2

B.W.: Body weight
T.P.: Total protein
CHL: Cholesterol
BS: Blood sugar
Ht.: Hematocrit

EXPERIMENTAL RESULTS

The body weights of these rats were significantly lower than those of control rats (Table 1). The levels of total protein and cholesterol in the serum were significantly lower in rats of the experimental group than those in rats of the control group (Table 1).

The rats in the experimental group, thus, were under malnutrition. The blood sugar level at fasting, however, was within normal limits in these malnutritious rats. Marked hypochromic anemia was also observed in malnutritious rats (Table 1).

Immunoreactive insulin levels were 37.8 ± 17.4 μU/ml in the malnutritious rats and 7.82 ± 1.4 μU/ml in the control rats. The statistical analysis showed a significant difference ($p<0.001$) between the experimental and the control groups. The levels of immunoreactive pancreatic glucagon which were 42.5 ± 31.8 pg/ml in the malnutritious rats and 53.5 ± 16.9 pg/ml in the control rats, however, did not differ between the experimental and the control groups. No significant difference was demonstrated in the level of immunoreactive substance P between the experimental (170.1 ± 61.4

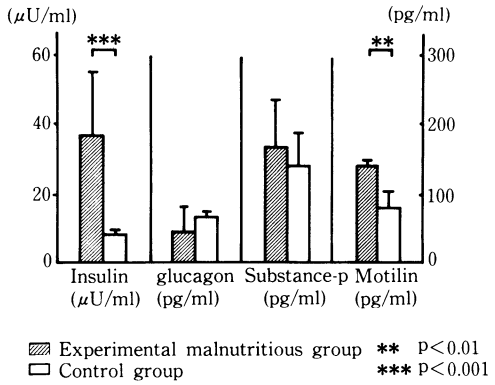

Fig. 1. Changes in levels of insulin, glucagon, substance P, and motilin in malnutritious rats with total gastrectomy.

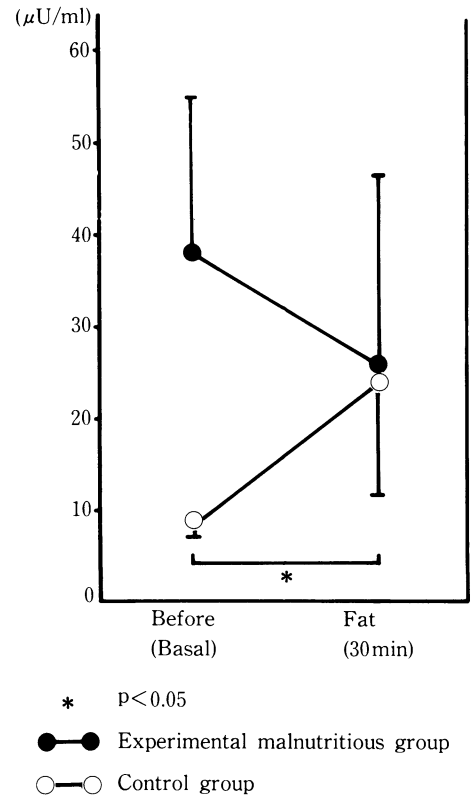

Fig. 2. Insulin did not respond to intraduodenal fat administration in malnutritious rats.

pg/ml) and the control groups (148.6 ± 43.8 pg/ml). The levels of immunoreactive motilin were 146.7 ± 7.6 pg/ml in the malnutritious rats and 80.1 ± 22.9 pg/ml in the control rats, showing a statistically significant difference ($p<0.01$). These hormone levels are shown in Fig. 1.

All the experimental malnutritious rats showed steatorrhea 30 min after fat administration in the duodenum. The levels of immunoreactive insulin in the control rats were increased to 24.5 ± 12.1 μU/ml 30 min after intraduodenal fat administration, which was significantly different ($p<0.05$) from those at fasting but not significantly different when compared to those after fat load in the experimental rats, while the levels of immunoreactive insulin in the experimental rats were decreased to 26.4 ± 20.9 μU/ml from 37.8 ± 17.4 μU/ml 30 min after intraduodenal fat administration, which were not significant different from each other (Fig. 2). The levels of immunoreactive pancreatic glucagon in the experimental rats were unexpectedly increased to 191.5 ± 14.8 pg/ml 30 min after intraduodenal fat administration showing from 42.5 ± 31.8 pg/ml at the basal condition, a significant difference ($p<0.001$), while the control rats did not show any marked change in the levels before and after intraduodenal fat administration (Fig. 3). The levels after fat administration in the experimental rats were significantly higher ($p<0.001$) than those in the control rats. The levels in the the control rats were 53.5 ± 16.9 pg/ml before and 50.1 ± 8.2 pg/ml 30 min after intraduodenal fat administration. The levels of immunoreactive motilin were also significantly elevated ($p<0.001$) to 528.1 ± 104.6 pg/ml at 30 min after intraduodenal fat administration from 146.7 ± 7.6 pg/ml before fat administration in the experimental rats (Fig. 4). The levels were also increased from 80.1 ± 22.9 pg/ml

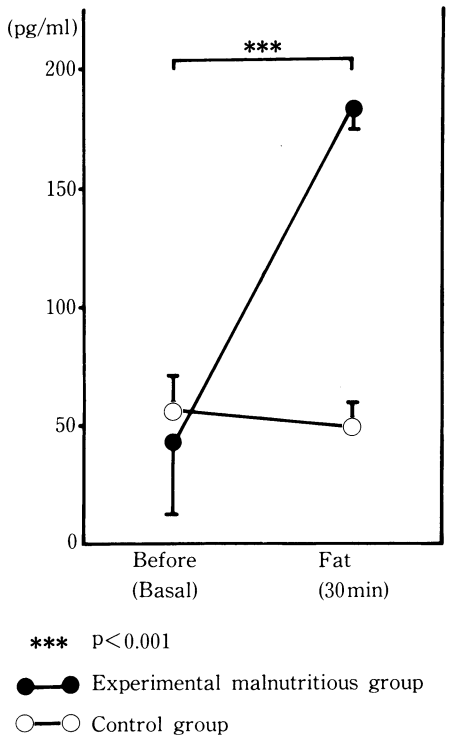

Fig. 3. Significant increase in pancreatic glucagon concentration in the blood after fat administration in malnutritious rats.

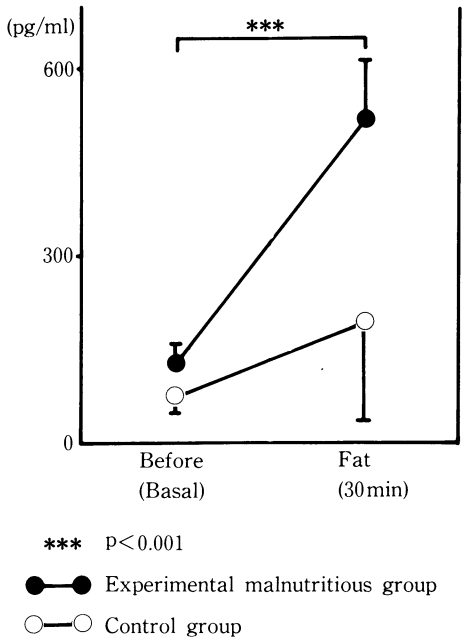

Fig. 4. Significant rise in motilin concentration in the blood after fat in malnutritious rats.

before to 199 ± 164.8 pg/ml 30 min after intraduodenal fat administration in the control rats, although the difference was not statistically significant (Fig. 4). The levels after intraduodenal fat administration were significantly different ($p<0.001$) between the experimental and control rats.

DISCUSSION

Weight loss is commonly observed after gastrectomy. In the present study, the body weight of the experimental rats was not different from that at the beginning of the experiment (at the operation). There was thus no increase in body weight of these total gastrectomized rats after 8 months. Moreover, the levels of total cholesterol and protein in the serum were both markedly low in the experimental rats. These suggest that the rats were under malnutrition, which was caused by maldigestion of protein and fat, and consequent malabsorption developed secondarily in the experimental rats after total gastrectomy. Marked steatorrhea after intraduodenal fat administration was found in the rats, indicating that fat malabsorption occurred in the gastrectomized rats. Blood sugar levels at fasting, however, were within normal limits, suggesting that carbohydrate absorption may be normal in gastrectomized rats. It is well accepted that total gastrectomy may cause malabsorption of nutrients in men and animals and some explanations of the mechanism have been given in the literatures[5,10,14,17]. Our interest was provoked to examine hormonal changes in enteropancreatic axis of malnutritious rats with malabsorption of fat and further we considered in noteworthy to study the pathogenesis of postgastrectomy syndrome in man. Enteropancreatic axis is originally known as enteroinsular axis[21], which denotes insulin release from β-cells in pancreatic islets under the presence of intraduodenal glucose. We, however, studied enteropancreatic axis with emphasis on the changes in levels of insulin, pancreatic glucagon and motilin before and after intraduodenal fat administration because of the presence of marked fat malabsorption in malnutritious rats.

A significant increase in the levels of pancreatic glucagon occurred after fat administration in rats with fat malabsorption, while no meaningful changes in its levels were observed in the control rats, suggesting that enteropancreatic axis of fat exists in malnutritious rats. This indicates that a mediator or modulator may exist to release pancreatic glucagon from α cells in islets after fat administration in the small intestine. Glucose dependent insulin releasing peptide (GIP) is a most possible mediator on the axis. Ingestion of triglyceride does not bring rise to changes in the concentrations of insulin or pancreatic glucagon in the blood in normal man. In dogs, however, ingestion of triglyceride leads to a rise of pancreatic glucagon in the blood which cannot be reproduced by intraveous infusion of chylomicrons[2]. There is no detectable change of insulin in the blood in man or dogs in response to oral fat intake, although there is a large rise in the concentration of GIP in the blood in both species[7]. The lack of effect of endogenous GIP on insulin release under those conditions is in accordance with the absence of insulinotropic actions of the peptide when it is infused in physiological doses in fasting dogs or man[1,8,9]. In the present study, no meaningful insulin response was observed to intraduodenal fat administration in malnutritious rats with marked steatorrhea. The lack of insulinotropic action of endogenous GIP possibly released under the presence of fat in the doudenum of the rats, although the levels of GIP were not determined in the present study, was understood because of the lack of glucose in the duodenum in the rats. It may be considered that the significant and probably abnormal rise in pancreatic glucagon after intraduodenal fat administration was caused by the potential glucagonotropic action of endogenous GIP in overresponse to fat in the duodenum of malnutritious rats with fat malabsorption. Fat malabsorption may be one of causes in abnormal glucagon response to fat observed in malnutritious rats with total gastrectomy.

The mechanism why endogenous motilin released largely after fat intake remains to be clarified. It is, however, doubtless that total gastrectomy and consequent malabsorption may be its main factors of the mechanism. The rise of peptide may cause steatorrhea after intraduodenal fat administration by the action on the gastrointestinal motility[13,23].

Insulin, substance P and motilin concentration were elevated before fat administration (at fast-

ing). We can not understand at the present time why the high concentrations of these peptides occurred after total gastrectomy (consequent vagotomy). Elevation of insulin and substance P levels at fasting has not been reported in malnutritious rats after total gastrectomy. These peptides may play some role on the pathogenesis of postgastrectomy malnutrition. Elevated levels of motilin have previously reported after gastrectomy in man by one of the authors[19].

Malnutritious rats had severe diarrhea which might have occurred at fasting by the action of motilin. This should be clarified in the near future.

Truncal vagotomy or selective gastric vagotomy lowers glucagon concentrations during hypoglycemia. Pancreatic glucagon concentration at fasting, however, was not influenced by total gastrectomy.

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