Effect of Ileo-Jejunal Transposition on Intestinal Adaptation after Total Colectomy in Dogs

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Sasaki, I., Tuchiya, T., Naito, H., Funayama, Y., Toda, M., Suzuki, Y., Sato, T. and Ohneda, A. Effect of Ileo-Jejunal Transposition on Intestinal Adaptation after Total Colectomy in Dogs. Tohoku J. exp. Med., 1987, 151 (4), 419-428 — The effect of ileo-jejunal transposition (IJT) on the intestinal adaptation after total colectomy was investigated in 4 mongrel dogs. Hyperenteroglucagonemia was observed in the IJT with colectomy group, especially in postprandial state. Obvious hyperplastic changes were observed in all part of the small intestinal mucosa in the colectomy with IJT group. However, there were no significant differences in body weight changes between the colectomy with IJT group and the colectomy group. Postprandial plasma gastrin levels were lower in the colectomy with IJT group compared to the control. These results suggest that IJT causes hyperenteroglucagonemia and intestinal mucosal hypertrophy in colectomized dogs. Enteroglucagon may have an inhibitory effect on postprandial gastrin release. ——— ileo-jejunal transposition; intestinal mucosal hyperplasia; enteroglucagon; total colectomy

Many patients who underwent total colectomy or massive small bowel resection are suffered from troublesome problems including diarrhea and malabsorption which greatly influence the postoperative quality of life (Sasaki et al. 1986). Some of these patients may become symptom-free and in good conditions with time after surgery, but some other patients remain suffered from these problems. To reduce these problems, several surgical modifications, such as interposition of antiperistaltic intestinal segment or valve formation, have been attempted clinically in some institutes. These procedures were devised to prolong the intestinal transit time mechanically, but not to enhance functional adaptation of the intestine.

It has been suggested that a variety of factors are involved in development of intestinal mucosal hypertrophy which represents the adaptation of the small intestine (Johnson 1982). Johnson classified these factors into two general types.

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of stimulations that result in growth of gastrointestinal mucosa; one is a group of hormones other than gastro-intestinal hormones, such as growth hormone and thyroxine, and the other is the group of factors promoted by ingestion and digestion of food, such as nerve stimulation, endocrine effects, luminal nutrition and others. Recent studies have led some investigators to an assumption that enteroglucagon is one of factors possessing a trophic effect on the intestinal mucosa (Polak et al. 1982; Williamson and Malt 1982). Also, it was demonstrated that hyperenteroglucagonemia occurred after ileo-jejunal transposition in rats (Gregor et al. 1981; Polak et al. 1982).

In this study, as a preclinical study, we studied the trophic effect of ileo-jejunal transposition on the small intestine after total colectomy in dogs, and it relation to plasma levels of enteroglucagon.

**Materials and Methods**

*Animal preparation.* Four mongrel dogs, weighing 15-23 kg, underwent total colectomy with ileo-rectal anastomosis under intubated general anesthesia using intravenous administration of pentobilital sodium (25 mg/kg). In addition to total colectomy, two dogs received ileo-jejunal transposition simultaneously (colectomy with IJT group). Leaving the distal 5 cm of the ileum, its distal quarter part was isoperistaltically transposed into the jejunum located 15 cm distal from the Treitz's ligament. Fig. 1 illustrates the procedures of surgical operation and the final state of the whole intestine after the operation. The other two dogs were subjected to sham operations, in which transection and re-anastomosis of the same part of the intestine and total colectomy with ileoproctostomy was performed (colectomy group).

*Blood sample collection.* Body weight was measured every week after operation. A test meal loading was carried out three times in each dog both before surgery and at 18th week after operation. Loading of a test meal was made in conscious dogs placed in a modified Pavlov stand after at least 18 hr of fasting. For the test meal, 425 g of commercial dog food (Vita-one: protein 13.5%, fat 5.0%) were given to animals. Blood samples were obtained from the antecubital vein during the fasting period and 15, 30, 60, 90, 120, 180, 240

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**Fig. 1. Experimental models.**

Colectomy with IJT group: in addition to total colectomy with ileoproctostomy, distal quarter part of the small intestine (-----) was isoperistaltically transposed in the jejunum (A-A') 15 cm distal from the Treitz's ligament.

Colectomy group: transection and reanastomosis was performed with colectomy.
min after meal loading. Each sample was mixed with etylenediaminetetraacetic acid-2Na (EDTA, 1.25 mg/ml blood) and aprotinin (500 KIU/ml blood). Plasma was separated by centrifugation at 4°C immediately after blood collection and stored at −20°C until the hormone assays.

**Plasma hormone assays.** Plasma immunoreactive gastrin level was measured using an assay kit with a detection limit of 10 pg/ml (CEA-IRA-SORIN Association, GifSur-Yvette, France). Plasma total glucagon-like immunoreactivity (total-GLI) and plasma glucagon immunoreactivity (GI) were measured using antiserum G25, which cross-reacted with both pancreatic glucagon and gut glucagon-like immunoreactive substance (Ohneda et al. 1979), and an assay kit for GI (Daiichi Radioisotope Association, Tokyo). To examine the molecular heterogeneity of circulating plasma total GLI, gel filtration was carried out for the fasting and postprandial plasma samples. One ml of plasma was applied to a calibrated Sephadex G-50 fine column (1×60) and eluted at 4°C at a rate of 1 ml/5 min with a phosphate buffer solution. Fractions were collected and assayed with antiserum G-25.

**Histological examination.** For histological studies, intestinal segments of 3 cm long were taken from the transected part of the jejunum and ileum at the operation and 18th week after the operation. These samples were fixed in 10% formalin for 10 hr and embedded in paraffin wax. Hematoxilin-Eosin staining was carried out and mucosal height was measured microscopically. Immunostaining was carried out on paraffin section for light-microscopical analysis with a rabbit anti-porcine glicentin C-terminal fragment 49–69 serum (R-4804; Yanaihara 1980) using the peroxidase-antiperoxidase (PAP) method.

**Statistical analysis.** The observed values were expressed as mean ± S.E. and statistical analysis for significance was performed using Student's t-test. Differences with a p value of less than 0.05 were considered to be significant.

**RESULTS**

**Changes of body weight.** Percent changes in body weight of animals after the surgical operation are shown in Fig. 2. Body weight of all dogs decreased from 2 to 4th week after the operation, but it gradually regained to the levels of 88.5% and 84.5% of the preoperative state at the 18th week both in the colectomy and in the IJT group.

![Fig. 2. Changes in body weight of dogs after the surgical operation.](image)

○ --- ○, colectomy group;
- - - - - - , colectomy with IJT group.
Plasma total GLI levels. As shown in Fig. 3, the preoperative plasma level of total-GLI at fasting state was 700±40 pg/ml on the average. The level increased to reach a peak level of 1,378±132 pg/ml, at 120 min after test meal.

Fig. 3. Plasma total GLI levels after test meal in dogs. Values are given as means±s.e.
-○-, before surgery (n = 12);
- -○-, after colectomy (n = 6);
-●-, after colectomy with IJT (n = 6).
Significant differences against levels before surgery are shown by asterisks. **p<0.01.

and the colectomy with IJT groups.

Plasma total-GLI levels. As shown in Fig. 3, the preoperative plasma level of total-GLI at fasting state was 700±40 pg/ml on the average. The level increased to reach a peak level of 1,378±132 pg/ml, at 120 min after test meal.

Fig. 4. Gel-filtration patterns of fasting and postprandial plasma total-GLI from the colectomy with IJT group. (Sephadex G50. 60×1)
-○-, fasting plasma;
-●-, 60 min postprandial plasma.
There was no difference before and after the surgery in the colectomy group. On the other hand, in the colectomy with IJT group, both fasting and postprandial plasma total-GLI levels were significantly higher than the preoperative values and the values in the colectomy group. The levels at fasting state and 120 min after test meal were $1890 \pm 220$ pg/ml and $9370 \pm 431$ pg/ml, respectively.

**Heterogeneity of plasma total-GLI.** Fig. 4 shows the chromatograms of total GLI of fasting and postprandial plasma from the colectomy with IJT group. In both plasma, the peak appeared at the fraction number 26, which represents glycentin.

**Plasma GI levels.** Fig. 5 shows the postprandial plasma GI levels. The preoperative plasma GI level was $129 \pm 32$ pg/ml at fasting state and the peak level was $175 \pm 35$ pg/ml 30 min after test meal. Fasting plasma GI level in the colectomy group was $163 \pm 54$ pg/ml, and the peak level was $255 \pm 72$ pg/ml at 60 min after test meal. Fasting plasma GI level in the colectomy with IJT group was $120 \pm 36$ pg/ml, and the peak level was $261 \pm 50$ pg/ml at 90 min after test meal. Plasma GI levels in both groups were slightly higher than those in the preoperative state, but there were not significant differences.

**Plasma gastrin levels.** Fig. 6 shows the changes in plasma gastrin levels after test meal. Fasting plasma gastrin levels in the preoperative animal, the colectomy group and the colectomy with IJT group were $45 \pm 6$ pg/ml, $35 \pm 4$

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![Fig. 5. Plasma GI levels after test meal in dogs. Values are given as means±s.e.](image)

○○○, before surgery ($n=12$);
○——○, after colectomy ($n=6$);
●——●, after colectomy with IJT ($n=6$).
Fig. 6. Plasma gastrin levels after test meal. Values are given as means ± s.e.
- - - - O, before surgery (n = 12);
○ - ○, after colectomy (n = 6);
● - ●, after colectomy with IJT (n = 6).
Significant difference against levels before surgery are shown by asterisks
* p < 0.05, ** p < 0.01.

Fig. 7. The height of intestinal mucosa. Values are given as means ± s.e.
- - - - ○, control (n = 6);
○ - ○, after colectomy;
● - ●, after colectomy with IJT.
pg/ml and 41±3 pg/ml, respectively. There were no significant differences among them. Postprandial plasma gastrin levels in the colectomy group were close to the preoperative level. In contrast, plasma gastrin levels in the colectomy with IJT group were significantly lower at 60, 90, 120 min after test meal than those of the preoperative state (p <0.05).

Height of Intestinal Mucosa. Fig. 7. shows the heights of intestinal mucosa collected at the preoperative state and 18th week after the operation. Initially, intestinal mucosal heights measured in the three segments, 15 cm diatal from the Treitz’s ligament, the distal fourth of the small intestine and terminal ileum, were 2.13±0.3 mm, 1.43±0.02 mm, 0.88±0.02 mm, respectively. The mucosal height

Fig. 8. Section of the ileum of (a) control and (b) colectomy with IJT group 18 weeks after operation. ×150.
of the distal zones of the intestine tended to be lower than the proximal ones. In two dogs of the colectomy group, mucosal heights were close to those in control group. In contrast, mucosal heights in two dogs underwent the colectomy with IJT were markedly increased: 3.00 and 2.75 mm at 15 cm distal from the Treitz's ligament, 2.50 and 2.25 mm in the interposed ileal segment, 2.50 and 2.00 mm in terminal ileum, respectively. Distinct hyperplastic changes were seen in all parts of the small intestine of this group. Fig. 8 shows a section of the ileum of (a) control and (b) colectomy with IJT groups. Although in the colectomy with IJT group the levels of circulating enteroglucagon increased, the number of

Fig. 9. Enteroglucagon secreting cells in the ileum of (a) control and (b) colectomy with IJT groups at 18th week after the operation. ×150.
enteroglucagon secreting cells did not show a significant increase in comparison with the preoperative state. (Fig 9. a, b)

**DISCUSSION**

It has been reported that enteroglucagon may play an important role in adaptational changes in the intestine after intestinal resection (Bloom and Polak 1982a, b). Gleeson et al. (1971) reported a single patient who had an endocrine tumor in the kidney which appeared to produce enteroglucagon. This patient had marked intestinal mucosal hyperplasia and decreased intestinal transit time, that were all normalized after tumor resection. Bloom and Polak (1982c) demonstrated that enteroglucagon is released from endocrine cells (EG cell) not only in the distal small intestine but also in the large bowel. Ileal transposition to the upper jejunum is known to induce hypertrophic changes in the intestinal mucosa as well as an elevation of circulating enteroglucagon levels in rats (Gregor et al. 1981; Polak et al. 1982). However, there has been no report to estimate the effect of IJT on plasma levels of enteroglucagon and the intestinal adaptation after total colectomy.

In this study, morphological and hormonal parameters were investigated. Plasma levels of total GLI showed marked increases both at fasting and after test meal in colectomy coupled with the IJT group. It was suggested that such augmented level of total GLI is mostly attributable to enteroglucagon, because plasma levels of GI, which represents glucagon, were not changed both in the colectomy group and the colectomy with IJT group. And it was shown that hyperenteroglucagonemia was more manifest after test meal than at fasting. Enteroglucagon may be mainly released from the transposed ileal segment in the colectomy with IJT group, since test meal immediately contacts with EG cells in the segment. Thus, it is conceivable that hyperenteroglucagonemia is more striking after test meal than in fasting state.

Although the biological activity of the enteroglucagon has not been totally established yet, there is a suggestion that this hormone not only has inhibitory effects on gastric secretion and pancreatic exocrine function but also has a promotive effect on intestinal mucosal hypertrophy (Ghatei and Bloom 1981). It has been reported that glucagon inhibits the secretion of gastrin from G-cell (Konturek et al. 1975), but there has been no report of the effect of enteroglucagon on the gastrin release. In this study, in the colectomy with IJT group, postprandial plasma gastrin levels were significantly lower than those in the control and the colectomy group. Enteroglucagon may have an inhibitory effect on the postprandial gastrin release.

The histological studies showed that intestinal mucosal hypertrophic change occurred in the group of colectomy with IJT but not in the colectomy group. But changes in body weight after operation were not significantly different between the two groups as long as 18 weeks after operation. These results demonstrate
that IJT causes an increase of circulating enteroglucagon which may induce the mucosal hypertrophy in small bowel in colectomized dogs. Despite these positive effects regarding to intestinal adaptation, IJT did not show any physically benefical effect in the dogs as far as the change of body weight is concerned. Further investigations, such as changes of intestinal functional parameters, will be necessary before the clinical introduction of IJT in supporting intestinal adaptation in patients subjected to total colectomy.

References