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Trophic Response of Gut and Pancreas After Ileojejunal Transposition

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Objective

The authors determined whether ileojejunal transposition (IJT) stimulates the growth of the pancreas or the nontransposed segment of small intestine, and ascertained whether this trophic effect is altered by the location of transposed gut segment.

Summary Background Data

Transposition of the ileum to the proximal small intestine stimulates a marked mucosal growth of the transposed ileal segment; the cellular mechanisms responsible for this adaptive hyperplasia are not known.

Methods

The distal quarter of the small intestine (distal ileum) was transposed into the proximal (Type I), middle (Type II), or distal (Type III) portions of the remaining small intestine. On postoperative day 28, the pancreas and scraped mucosa from the segments of transposed ileum, proximal ileum, and duodenum were obtained, weighed, and examined for DNA and protein content.

Results

All types of IJT increased mucosal weight and DNA content of the transposed ileum. Types I and II IJT produced a significant proliferation of the pancreas and mucosa of the duodenum and proximal ileum. The magnitude of proliferative increases was greatest in Type I IJT.

Conclusions

Ileojejunal transposition appears to be an excellent model to examine the mechanisms by which intestinal epithelial cells proliferate in response to luminal nutrients or humoral factors.

The mucosa of the gastrointestinal tract is known to have a high rate of proliferation and differentiation in its normal physiologic state. There is an exquisite balance between production of epithelial cells in the crypt compartment and loss of terminally differentiated cells at the villus tip; thus, a fine homeostasis is maintained in the intestinal epithelial cell mass.[1]

Partial small bowel resection changes this homeostasis, and the residual small intestine undergoes "adaptive hyperplasia." [2-6] Many studies have revealed the structural and functional adaptation,[2-14] but the mechanism of these changes is not completely known. Some studies indicate luminal nutrition is essential in maintaining intestinal mucosal mass in both normal and altered physiologic conditions.[15-19] In the small intestine, villus height decreases gradually from the upper duodenum to the terminal ileum.[20-21] Rats given total parenteral nutrition without food by mouth lose this normal gradient of intestinal mass.[20-24]

Although intraluminal nutrition is significant in maintaining normal physiologic mucosal mass in the small intestine and is significant in adaptive proliferation, it appears not to be the sole factor in the regulation of intestinal epithelial proliferation. Various humoral factors have been implicated in the adaptive response after massive small bowel resection in rats.[25-31] Plasma concentrations of gastrin,[25,26] enteroglucagon,[26,27] and cholecystokinin[25] are known to be increased after massive small bowel resection. Taylor and colleagues[28,29] have shown that both enteroglucagon and cholecystokinin messenger levels of remnant small bowel increase after massive small bowel resection. Evers and colleagues[30] in our laboratory have shown that neurotensin mRNA in ileal mucosa significantly increases after 70% proximal small bowel resection, and they implicated neurotensin as a candidate gastrointestinal peptide for the regulation of the intestinal mucosal growth. Lund and colleagues[31] also have shown increased levels of insulin-like growth factor-I mRNAs in the remnant of intestine after bowel resection.[31] Rapid advances in molecular biology of gastrointestinal peptides, growth factors, and their receptors have made it possible to examine humoral factors in depth, but to define which peptides or factors play an important role in this adaptive response, we believe that it is essential to characterize this trophic response. In analogy, to find the right key we need to know the type of key hole we are working on.

To examine the effect of luminal nutrition on proliferation of small intestinal epithelial cells, Dowling and colleagues[3,32] exchanged the position of ileum and jejunum, transposing the ileum between duodenum and jejunum. This procedure significantly stimulated mucosal growth of the transposed ileal segment. Altmann and Leblond[20] showed that the villus of the transposed ileal segment in the jejunum had enlarged to the size of local jejunal villus, and the villus of jejunal segment transposed into the ileum decreased almost to the size of the local ileal villus, thus maintaining its intestinal mucosal mass gradient from proximal to distal gut. Ulshen and Herbst[33] transposed 30 cm of distal ileum to duodenojejunal junction and showed significant mucosal growth in the transposed ileum.

Ileojejunal transposition (IJT) is a model in which significant adaptive small bowel proliferation is observed at the transposed segment. Although several groups of investigators have used this model to examine the mucosal proliferation at the transposed segment, the proliferative response at the nontransposed segments of small bowel after IJT still is controversial. Moreover, the effect of altered supply of luminal nutrition on the trophic response evoked by IJT is not clear, and it is not known whether humoral factors are involved in gut proliferation after IJT. Therefore, the purpose of this study was threefold: 1) to examine the effect of IJT on nontransposed segments of small bowel (duodenum and ileum) and pancreas; 2) to determine whether the altered supply of luminal nutrition (by changing location of transposition)—exposed to transposed segment—changes the trophic response evoked by IJT; and 3) to examine plasma levels of trophic peptides, gastrin, and neurotensin after IJT.

METHODS

Experiments described were performed separately by two investigators for the following two reasons: 1) to establish the technique of IJT and confirm the resulting proliferative response, and 2) to examine the proliferative response at different time points after IJT. Rats were killed at postoperative days 21 or 28.

Experimental Design

For each experiment, 20 4-month-old male Fisher 344 rats were obtained from the National Institute of Aging (Bethesda, MD) and were acclimated for 1 week before beginning the experiment in an environment of controlled temperature (22 C) and humidity with 12-hour

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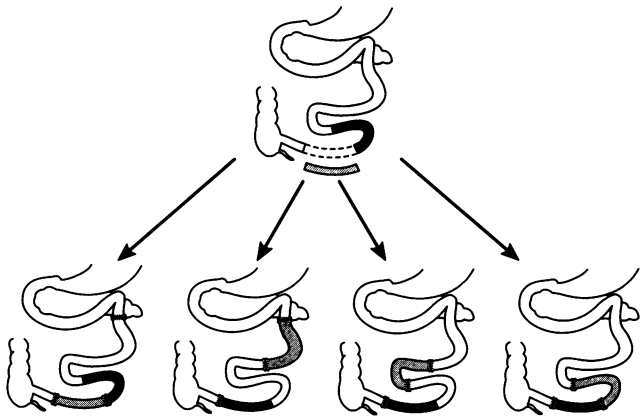

Figure 1. Schematic diagram of three types of ileal-jejunal transposition and sham operations. The distal quarter of the small intestine, shown by hatched lines, was transposed into proximal (Type I), middle (Type II), and distal (Type III) portion of remaining small intestine isoperistaltically. Proximal ileum is shown by dark area.

light/dark cycles. During the acclimation and the experimental period, all rats were fed standard laboratory chow (Ralston Purina, St. Louis, MO; 60% carbohydrate, 23% protein, 6.5% fat, 4% crude fiber, 2.5% minerals supplemented with vitamins) *ad libitum*. After an overnight fast with free access to water, rats were randomized into one of four groups. Three groups underwent different types of ileal transposition into the upper part of the small intestine, whereas the fourth group underwent a sham operation. Food intake was measured three times during the second postoperative week in experiment 1 and during the second and third postoperative weeks in experiment 2, using individual wire-bottom cages.

Ileojejunal Transposition

Rats were anesthetized with ether, and the abdominal cavity was entered through a midline incision. In the sham-operated control group, the small intestine was transected just below the ligament of Treitz, 1 cm proximal to the ileocecal valve and ¼ proximal to the ileocecal valve, and re-anastomosed without transposition, using interrupted 6-0 silk sutures (Fig. 1). In three other experimental groups, the small intestine was measured carefully from the ligament of Treitz to the ileocecal valve, and the ileum was cut 1 cm proximal to the ileocecal valve, creating a distal ileal segment that was ¼ the length of the small intestine, leaving the neurovascular supply intact. The isolated ileal segment was transposed into the proximal (just beyond the ligament of Treitz; Type I), middle (Type II), and distal portions (Type III) of the remaining small intestine isoperistaltically (Fig. 1). Intestinal continuity was restored by end-to-end anastomosis, again using interrupted 6-0 silk sutures. The midline abdominal wound was closed in two layers with 3-0 silk sutures. Postoperatively, all rats received lactated Ringer's solution with 5% dextrose (50 mL/kg body weight) subcutaneously and were fasted on the operative day. Free access to water was allowed from the first postoperative day, and free access to standard laboratory chow was allowed from the second postoperative day.

Sample Collection

Rats were decapitated without fasting on the 21st postoperative day for experiment 1 or 28th postoperative day for experiment 2. In experiment 1, the abdomen was opened and the transposed ileum and the proximal ileum (the most distal part of the small intestine after IJT; Fig. 1) were removed. The transposed ileum and proximal ileum were suspended vertically with a 10-g weight, and each 20-cm segment of the middle portion was taken for the study. The bowel was opened longitudinally, rinsed in ice-cold saline, and blotted dry. The mucosa was scraped from the muscularis by means of glass slides on an ice-cold plate. Scraped mucosa was weighed, immediately frozen, and stored at −70 C until assayed. In experiment 2, the pancreas and duodenal mucosa also were removed, weighed, immediately frozen, and stored at −70 C until assayed.

DNA and Protein Determination

Samples were homogenized by Polytron (Brinkman Instruments Inc., Westbury, NY) and analyzed for DNA content by the Burton[34] modification of the diphenylamine procedure, with calf thymus DNA as the standard. Protein content was measured by the Lowry[35] method, with bovine serum albumin (BSA) as the standard.

Radioimmunoassay for Gastrin and Neurotensin

The plasma samples from rats that underwent sham operation (control) and most proximal or Type I IJT were collected at postoperative day 21 in fed state and frozen at −20 C until gastrin and neurotensin radioimmunoassay. Plasma gastrin was measured by a double-antibody radioimmunoassay developed in our laboratory.[36] For neurotensin, plasma was first extracted with a SEP-PAK C_{18} Partridge (Water Associates, Milford, MA); the extracted solution was blown out with nitrogen gas and reconstituted with neurotensin buffer. Neurotensin levels were measured subsequently with a double-an-

Table 1. DAILY FOOD INTAKES (DFI) AFTER OPERATION

		Ileojejunal Transposition		
Experiment 1	Control (5)	Type I (5)	Type II (4)	Type III (5)
DFI: second week (g)	15.5 ± 0.4	15.8 ± 0.6	15.6 ± 0.6	15.1 ± 0.4
Experiment 2	Control (5)	Type I (5)	Type II (5)	Type III (5)
DFI: second week (g)	15.9 ± 0.5	16.5 ± 0.7	16.6 ± 0.6	16.8 ± 0.3
DFI: third week (g)	18.3 ± 0.7	19.1 ± 0.6	18.7 ± 0.5	19.0 ± 0.6

Values are expressed as mean ± SEM. The number of animals in each group is given in parentheses.

tibody radioimmunoassay developed in our laboratory.[37]

Statistics

Three measurements—mucosal (or organ weight), DNA content, and protein content—were expressed as a fraction to total body weight. The effect of IJT (Type I, II, and III) and control were assessed using a one-way classification analysis of variance procedure separately for each of the three measurements. Duncan's multiple-range test was employed for multiple comparisons. Because the protein/DNA ratio was assumed to have a skewed distribution, findings concerning the protein/DNA ratio were analyzed using the Kruskal-Wallis test. Effects of transposition types were assessed at 0.05 level of significance.

When comparing the two experiments, the findings were analyzed as a two-factor experiment, and the factors were defined as which type of surgery (IJT I, II, and III and sham-operated) and which experiment (weeks 3 or 4). Multiple comparisons were conducted using Fisher's least significant difference, with Bonferoni's adjustment for number of comparisons. All tests, effects, and interactions were assessed at the 0.05 level of significance. Values were expressed as mean ± SEM.

RESULTS

Rats tolerated the IJT and sham operation. Only one rat with Type II IJT died from anesthesia during the operation in experiment 1.

Food Intake

The average daily food intake during the second week in experiment 1, and second and third weeks in experiment 2, were not different between any types of transposition groups and the control group (Table 1).

Mucosal Weight, DNA, and Protein Content

Transposed Ileum (Fig. 2)

Three weeks after IJT, the mucosal weight of the transposed ileum increased significantly by 178% in Type I, 96% in Type II, and 66% in Type III, compared with the corresponding control ileum. After 4 weeks the mucosal weight increased by 251% in Type I, 194% in

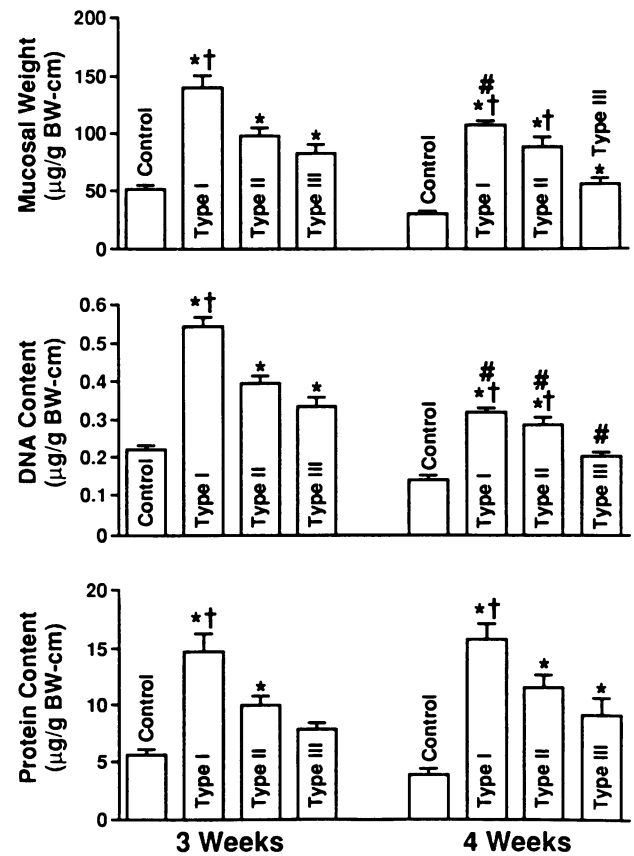

Figure 2. Mucosal weight, DNA, and protein content of the transposed ileum corrected over body weight (n = 4 in Type II IJT at week 3, others n = 5; mean ± SEM, * $p < 0.05$ *vs.* control, † $p < 0.05$ *vs.* Type III, # $p < 0.05$ *vs.* same group of 3 weeks).

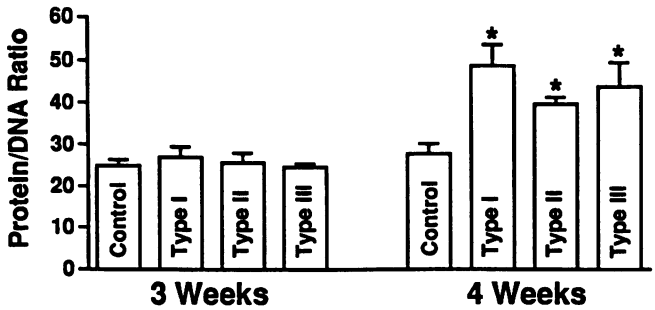

Figure 3. Protein/DNA ratio of the transposed ileum (n = 4 in Type II IJT at week 3, others n = 5; mean ± SEM, * $p < 0.05$ *vs.* control).

Type II, and 93% in Type III. The mucosal weight of Type I at week 4 was significantly lower compared with that of week 3. Similarly, the DNA content increased by 148% in Type I, 80% in Type II, and 54% in Type III after 3 weeks, with increases of 127% in Type I and 100% in Type II after 4 weeks. The DNA content in all types of IJT at week 4 were significantly lower compared with that of week 3. After 3 weeks, the protein content increased only in Type I (168%) and Type II (82%); however, after 4 weeks, there was a significant increase in all transposition groups (303% in Type I, 198% in Type II, and 140% in Type III). The protein contents were not different at week 4 compared with week 3 in all groups. The protein/DNA ratio was significantly increased only after 4 weeks (Fig. 3).

Proximal Ileum (Fig. 4)

The proximal ileal segment (named according to its original position) was displaced to the most distal part of the small intestine after IJT. After 3 weeks, mucosal weight increased in Type I (68%) and Type II (36%) compared with that of the control proximal ileum. After 4 weeks, a significant increase was again observed in Type I (38%) and Type II (35%). The mucosal weight of Type I at week 4 was significantly lower compared with that of week 3. DNA content was significantly increased by 64% in Type I and 31% in Type II after 3 weeks, and by 35% in Type I, 39% in Type II, and 35% in Type III after 4 weeks. At week 4, the DNA content of Type I and II, along with the control group, was decreased compared with that of week 3. The protein content increased in Type I (77%) after 3 weeks and in Type I (68%) and Type II (68%) after 4 weeks. The protein content was not different at week 4 compared with week 3. Protein/DNA ratio also did not change at week 3 and 4.

Duodenum (Fig. 5)

After 4 weeks, mucosal weight and DNA content significantly increased in Type I and II compared with the control duodenum; however, no significant increase was observed in Type III. The percent increase in mucosal weight was 59% in Type I and 43% in Type II. The percent increase in DNA content was 34% in Type I and 29% in Type II. Moreover, the mucosal weight of Type I was significantly increased from that of Type III, and DNA content of Type I and II were significantly increased from that of Type III. The protein content did not change after IJT. Protein/DNA ratio of duodenum also did not change after IJT.

Pancreas (Fig. 6)

Four weeks after the operation, pancreatic weight significantly increased by 26% in Type I and 15% in Type II; however, DNA content only increased in Type I by 52%. Both pancreatic weight and DNA content of Type I also were significantly greater compared with Type III. The protein content and protein/DNA ratio did not change after IJT.

Gastrin and Neurotension Plasma Level (Fig. 7)

Fed neurotensin levels were significantly increased after IJT; however, the gastrin levels were not changed 3 weeks after IJT.

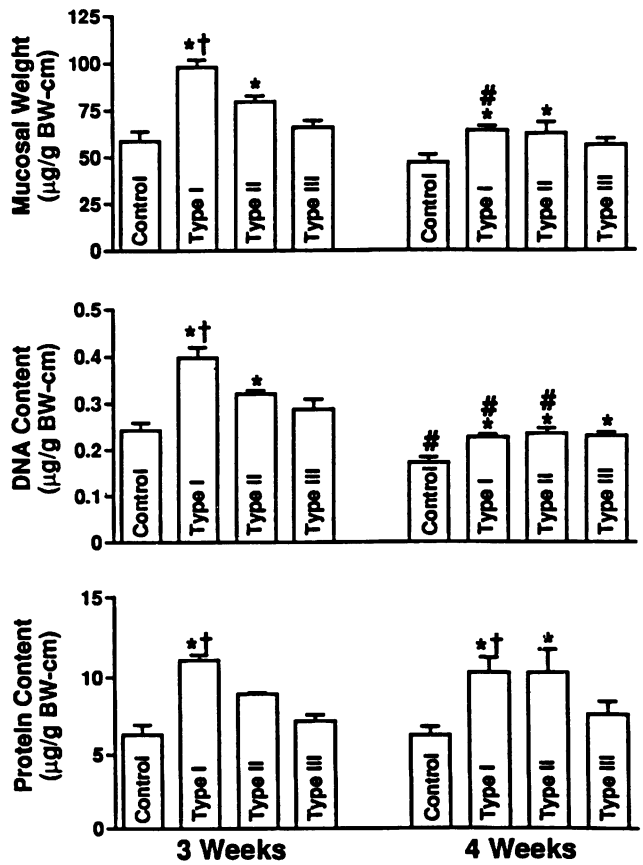

Figure 4. Mucosal weight, DNA, and protein content of the proximal ileum corrected over body weight (n = 4 in Type II IJT at week 3, others n = 5; mean ± SEM, * $p < 0.05$ *vs.* control, † $p < 0.05$ *vs.* Type III, # $p < 0.05$ *vs.* same group of 3 weeks).

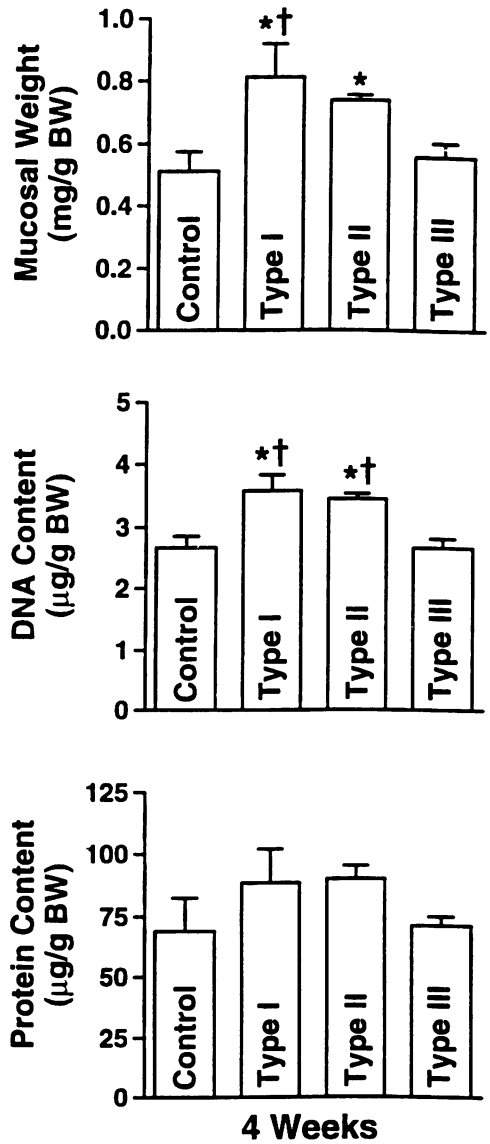

Figure 5. Mucosal weight, DNA, and protein content of duodenum corrected over body weight (n = 5, mean ± SEM, * $p < 0.05$ *vs.* control, † $p < 0.05$ *vs.* Type III).

DISCUSSION

The regulation of proliferation of highly dynamic intestinal epithelium is an active area of investigation, but the mechanisms of regulation are largely unknown. Possible mechanisms of this regulation may involve, at least in part, 1) intraluminal nutrition or 2) growth factors (hormone or peptides) acting in autocrine, paracrine, or endocrine fashion.

Studies have shown the importance of intraluminal nutrition on epithelial proliferation of small intestine.[15–19] Intraluminal nutrition is required to maintain mucosal mass in both normal physiologic and surgically altered states.[18–19] Our finding that transposition of distal ileum to the most proximal portion of jejunum (Type I IJT) induces the greatest amount of proliferation at the transposed segment again emphasizes the importance of intraluminal nutrition.

The proliferative indices (mucosal weight, DNA, and protein content) of duodenum, proximal ileum, and pancreas significantly increased after Type I and II IJT compared with the sham-operated group. These findings suggest that factors other than intraluminal nutrition are involved in the regulation of intestinal proliferation, because duodenum is in the same position as control, the proximal ileum is more distal from duodenum compared with control, and the pancreas did not come into

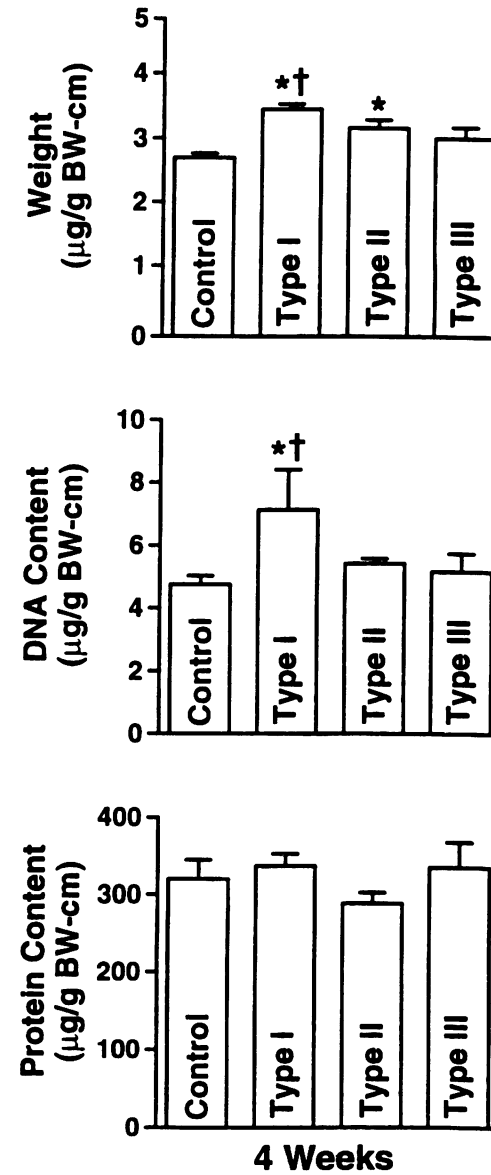

Figure 6. Weight, DNA, and protein content of pancreas (n = 5, mean ± SEM, * $p < 0.05$ *vs.* control, † $p < 0.05$ *vs.* Type III).

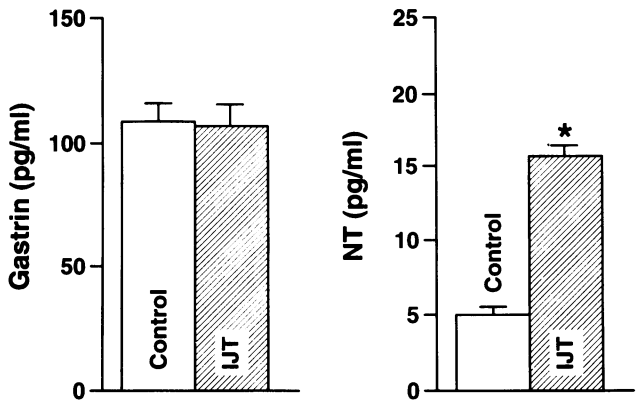

Figure 7. Plasma levels of gastrin and neurotensin from sham-operated control and Type I IJT groups (n = 10 for gastrin, n = 3 for neurotensin; mean ± SEM, * $p < 0.05$ *vs.* control).

contact with luminal nutrition. The factors likely to be involved in these proliferations are most probably humoral. Although the most distally transposed group (Type III IJT) did not induce any significant increase in proliferation compared with the control group, the increase in proliferative effect was greater when distal ileum was transposed more proximal to duodenum. Thus, this humoral proliferative mechanism also is dependent on the proximity to the duodenum. One possible explanation is that intraluminal nutrition may stimulate the release of trophic factors to affect the pancreas and other parts of the small intestine. Whether this humoral stimulation is via nutrition or other means, such as the nervous system, it appears to be stimulus-dependent and may have a threshold, because most distal transposition (Type III) did not induce proliferation in any other gastrointestinal organs except the transposed ileum.

Significant differences in the trophic effect were observed 3 and 4 weeks after IJT . At 4 weeks, the proliferation of transposed ileum was manifested by both hyperplasia and hypertrophy compared with hyperplasia alone after 3 weeks. The increase in proliferative indices of duodenum and proximal ileum were much less at week 4 compared with week 3. These changes are most obvious in the Type I IJT group, in which the proliferative effect was most significant at week 3. This indicates that the presumed humoral stimulation may be transient; previous studies appear to support this notion. Grönqvist and colleagues[38] showed that the villus height of the jejunum significantly increased 2 weeks after IJT and decreased 10 weeks after IJT. Gleeson and colleagues[32] observed no change in jejunum 8 months after IJT, and Altmann and Leblond[20] observed that the villus height of jejunum decreased to size of surrounding ileum 2 months after IJT.

Our findings suggest that the intestinal adaptation after IJT involves humoral regulation such as those of neurotensin, and its intensity may be dependent on the amount of stimulus, probably intraluminal nutrients, or it may respond in all-or-none fashion after a certain threshold of stimulation is reached. This humoral response may be transient and induce pancreatic proliferation. Humoral regulation may play an important role in supplementing nutrition stimulation or in fine-regulation of the proliferation to maintain mucosal mass homeostasis.

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