Differential jejunal and colonic adaptation due to resection and IGF-I in parenterally fed rats

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SHORT-BOWEL SYNDROME (SBS) in humans is characterized by severe loss of intestinal absorptive capacity with resulting malabsorption, diarrhea, fluid and electrolyte losses, and wasting of lean body mass (38). Patients with SBS frequently require long-term total parenteral nutrition (TPN) to maintain their health and nutritional status. Although life saving, long-term TPN is expensive, and patients suffer from several serious complications, such as fatty liver, hepatic failure, catheter sepsis, and gut dysfunction (38). Significant adaptation of the remaining bowel may allow maintenance of the patient’s nutritional status with oral feedings and permit cessation of TPN.

In an effort to mimic the human condition of SBS requiring TPN, we adapted a 60% jejunoileal resection and cecocotomy surgical model developed by Kripke et al. (23) to rats maintained exclusively with TPN. The distal 60% of the small bowel and the cecum are surgically removed, and the remaining jejunum is anastomosed to the colon. This procedure produces prolonged diarrhea, malabsorption, and weight loss in orally fed rats (23, 27), symptoms similar to SBS in humans. The model differs from most resection models, because the ileal remnant, the ileo-cecal valve, and the cecum are removed. The majority of humans with SBS requiring TPN also have large amounts of ileum and colon removed (36). Eleven of twenty-four rats fed orally for 8 wk after this resection surgery died, indicating that these animals may require TPN for survival (35). The removal of the ileum may limit the ability of the small bowel to adapt, because the ileum is thought to be the major production site of growth factors that are associated with intestinal adaptation (5, 41). In the current study, we use the 60% jejunoileal resection and cecocotomy model for the first time in combination with TPN to examine how massive intestinal resection affects intestinal adaptation in the absence of luminal nutrients.

The ability of patients with SBS to transition from parenteral to enteral nutrition depends on the adaptation of the remaining bowel. Many patients with SBS show little intestinal adaptation and require long-term TPN, possibly because of a deficiency of endogenous intestinal growth factors (41). A variety of growth factors have been shown to enhance intestinal adaptation after resection in orally fed rats and are currently under investigation as possible therapeutic modalities for the treatment of intestinal disorders (12, 39). Few growth factors have been shown to significantly attenuate the gut atrophy induced by TPN in the rat: we have confused IGF-I with TPN solution (32) and Chance et al. (9) confused glucagon-like peptide 2 (GLP-2) with similar results. Both peptides increased jejunal mass, protein, DNA, villus height, and crypt depth. In addition, we have demonstrated that infusion of IGF-I in rats maintained with TPN normalizes the aberrations in epithelial ion transport induced by TPN (32). In the current experiment, we also examined whether infusion of IGF-I with TPN solution stimulates intestinal adaptation after a 60% jejunoileal resection and cecotony.
Resection-induced intestinal adaptation is characterized by mucosal hyperplasia and increased absorptive surface area in the remaining bowel. Factors that control intestinal adaptation are incompletely understood but are thought to include luminal nutrients, pancreaticobiliary secretions, and endogenous hormones (4, 40). In contrast, TPN is associated with intestinal atrophy in rats (20, 22, 32) and mucosal hypoplasia in humans (6, 17). Thus rats maintained with TPN after a 60% jejunoileal resection and cecectomy have two opposing factors influencing the remaining gastrointestinal structure and function: TPN-induced gut atrophy and resection-induced gut adaptation. The present experiment evaluated the following: 1) whether the intestine adapts after a 60% jejunoileal resection and cecectomy; and 2) whether IGF-I treatment modifies intestinal adaptation to gut resection; and 3) whether IGF-I modifies whole body anabolism in response to the stress of gut resection.

METHODS

Animals and Experimental Design

The animal facilities and protocols were approved by the University of Wisconsin Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (Harlan, Madison, WI), weighing 225–250 g, were housed in individual stainless steel cages with free access to water in a room maintained at 22°C on a 12:12-h light-dark cycle. Animals were adapted to the facility for 4 days while being fed a semipurified diet ad libitum. Three days before surgery, animals were fed a fiber-free, semielemental, liquid diet ad libitum as a bowel preparation (Vital; donated by Ross Labs, Columbus, OH).

Animals were randomized into four TPN groups, using a 2 × 2 factorial treatment design to separate the independent effects of resection and IGF-I on intestinal adaptation, as follows: 1) gut resection, 2) gut resection and IGF-I, 3) sham operated (transection), and 4) transection and IGF-I. Seventy-six percent and eighty-one percent of animals that underwent resection and transection surgery, respectively, survived and had patent catheters after 7 days of TPN. The final number of animals in each treatment group used for the majority of the data analysis was as follows: gut resection, n = 9; gut resection and IGF-I, n = 7; transection, n = 11; and transection and IGF-I, n = 11.

Animals were anesthetized by an intraperitoneal injection of 2.5 mg acepromazine, 75 mg ketamine, and 0.02 mg atropine/kg body wt. Resected animals had bowel 40 cm distal to the ligament of Trietz to 1 cm distal to the cecum removed. The jejunum was measured using a 40-cm length of methanol solution (Histochoice; Amresco, Solon, OH) for 6 days after surgery (days 1–6). Animals received 3.2 mg recombinant human IGF-I/kg body wt · day−1 concurrent with continuous infusion of TPN. The infusion rate of the TPN solution was gradually increased from 20 g on day 0 to 40 g on day 1 and 60 g on days 2–6, providing the sole source of nutrition until the end of the experiment. Body weights were recorded daily, and the infusion bags containing the TPN solution were weighed daily to calculate the amount of TPN solution infused. Urine was collected into containers containing a final concentration of 0.01% boric acid and then stored at 4°C before determination of nitrogen concentration. After 7 days of TPN, rats were anesthetized by injection of 75 mg ketamine and 8 mg/kg xylazine and then killed by exsanguination.

Composition of TPN Solution

TPN solution was prepared aseptically using commercial preparations of amino acids (Travasol 8.5% with electrolytes; Baxter Healthcare, Deerfield, IL), dextrose, 20% lipid emulsion (Intralipid; Kabi Pharmacia, Clayton, NC), vitamins, trace elements, and electrolytes, as previously reported (26). TPN solution contained (in g/l) 45 amino acids, 180 dextrose, and 28 lipid (142 ml Intralipid), providing 32% nonprotein energy from fat and 68% of nonprotein energy from dextrose. The density of the solution was 1.088 g/ml.

Serum and Urine Analysis

Total serum IGF-I concentrations were determined by RIA after IGF-binding proteins were removed by HPLC under acid conditions, as previously described (29). Serum glucose concentrations were determined by the glucose oxidase technique (7). Serum insulin was determined by RIA (Linco Research, St. Charles, MO). The procedure for determining nitrogen balance was previously outlined in detail (43).

Mucosal Composition and Histology

On day 7 the remaining small and large intestines were removed and flushed with ice-cold saline. The first 5 cm of jejunum distal to the ligament of Trietz and the first 3 cm of colon at least 1 cm distal to the anastomosis were used to determine wet and dry weight. The next 1 cm of jejunum and colon were fixed in a 10% buffered paraformaldehyde-methanol solution (Histochrome; Amresco, Solon, OH) for morphometric analysis. The following 5 cm of jejunum were used for the analysis of protein (bicinchoninic acid protein assay; Pierce Chemical, Rockford, IL) and DNA (32) content of the mucosa. Sucrase activity was measured in mucosal homogenates using established techniques (10). The segments of jejunum were slit along the mesenteric border, and the mucosa was scraped from the muscularis with a glass slide. The colon segment was weighed intact.

Fixed tissue was paraffin embedded, cut into 5-µm sections, stained with hematoxylin and eosin, and examined. Digital images of each slide were captured from a light microscope using a digital camera (Sensys; Photometrics, Tucson, AZ) and imaging software (Metamorph; Universal Imaging, West Chester, PA). E jaunul villus height and crypt depth were measured on at least 10 crypt-villus axes per animal using SigmaScan software (Jandel Scientific, San Rafael, CA). Colon crypt depth was measured similarly. All measurements were performed by one investigator to prevent interobserver differences in measuring techniques.
Jejunal Mucosa Kinetics

Animals selected to evaluate epithelial migration rates received an intravenous bolus of bromo-2'-deoxyuridine (BrdU; Sigma Chemical, St. Louis, MO) at a dose of 0.2 mg/g body wt at 1 or 25 h before death. One-centimeter segments of jejunum were fixed in Carnoy's or Histochrome solution. Fixed tissue was embedded in paraffin, cut into 5-µm sections, and processed for immunoperoxidase staining of BrdU-labeled cells as previously reported (31). Briefly, sections were exposed to the primary antibody (anti-BrdU; Sigma Chemical) at a dilution of 1:500 overnight at 4°C and exposed to a 1:50 dilution of the secondary antibody (biotinylated horse anti-mouse IgG; Vectastain Laboratories, Burlingame, CA) for 30 min. Staining was accomplished by incubating sections in peroxidase reagent (ABC reagent; Vectastain Laboratories), followed by incubation in peroxidase substrate (0.02% hydrogen peroxide and 0.1% diaminobenzidine tetrahydrochloride, made in 0.1 M Tris buffer, pH 7.6). Control sections were prepared by incubating with a nonspecific mouse IgG diluted in PBS instead of the primary antibody. All sections were counterstained with Mayer's hematoxylin.

Only well-oriented crypt-villus columns were assessed. For each, the total number of cells and the number and position of BrdU-labeled cells were recorded. A labeling index distribution profile was established for the 1- and 25-h sample points. The distribution profile was used to determine the median cell position at which peak BrdU labeling occurred (42). Migration rate was calculated as the difference between peak labeled cell positions of paired animals injected at 1 and 25 h and expressed as change in peak labeled cell position over 24 h. In addition, proliferation was assessed by counting the number of crypt cells in a column, the total number of labeled cells per column, and the ratio of labeled cells to total cells in the crypts of animals injected 1 h before death.

Ussing Chamber Experiments

The remaining jejunal segments and the proximal one-half of colon were mounted as flat sheets in Ussing flux chambers. The serosal surface area exposed was 0.5 cm². Solutions bathing mucosal and serosal sides of the tissues contained (in mM) 120 NaCl, 6 KCl, 1.2 MgCl₂·6 H₂O, 1.2 NaH₂PO₄·H₂O, 14.4 NaHCO₃, and 2.5 CaCl₂·2H₂O. D-Glucose (11.5 mM) and mannitol (11.5 mM) were present in the serosal and mucosal solutions, respectively. Tissues were bathed by a recirculating reservoir with 10 ml of solution gassed with 95% O₂-5% CO₂, buffered at pH 7.4, and maintained at 37°C.

Transmural potential difference (PD) and short-circuit current (Isc), a measure of active ion transport, were measured using conventional techniques (8). Tissue conductance (Gt), a measure of ionic permeability, was calculated as the ratio of short-circuit to open-circuit values of PD or the current necessary to increase the PD to 2.5 mV in jejunum and 8.0 mV in colon. Basal electrical parameters were taken 10 to 15 min after tissues were mounted. Jejunal and colonic tissue responses to a secretory agonist (10 µM carbachol) and jejunal response to an absorptive agent (25 mM D-glucose) were measured as a change in Isc and recorded on a chart recorder. The change in Isc was determined by subtracting the basal current before the addition of the agent from the peak current after the addition of the agent and normalizing the difference to the serosal area exposed in the flux chambers.

Statistical Analysis

All treatment groups were compared using two-way ANOVA (SAS Institute, Cary, NC). Individual differences between groups were determined by one-way ANOVA. Group means were considered significantly different at P ≤ 0.05, as determined by the protected least-significant difference technique. Data are shown as means ± SE. Statistics were performed on log transformed data for serum IGF-I, jejunal mucosa DNA content, jejunal basal and stimulated ion transport parameters, and colon crypt depth, because residual plots of these data sets indicated that there was an unequal variance between groups.

RESULTS

Growth Response

Body weight and nitrogen balance. Changes in daily body weight are shown in Fig. 1. There were no significant differences in body weights among the groups selected to evaluate epithelial migration rates. Differences in daily body weight were not significantly different between groups during the presurgery phase (day -4 to day -1). Jejunal DNA content at day 0 was significantly lower postoperatively than before surgery due to the removal of jejunum. Values are means ± SE; n = 7–11; *P < 0.0001 vs. I, and R. **P < 0.0001 vs. I, and T (3-way ANOVA). Inset: nitrogen retention in the same animals over 7 days. Values are means ± SE; n = 5–8. Means with different letter superscripts are significantly different (P = 0.05).

Fig. 1. Changes in body weight of 4 groups of rats maintained with total parenteral nutrition (TPN) for 7 days after sham surgery (transsection; T), sham surgery + recombinant human insulin-like growth factor I (IGF-I) (I), 60% jejunoileal resection + resection (R), or resection + IGF-I (R-I).

N Retention

<table>
<thead>
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<th>Days</th>
<th>T</th>
<th>I</th>
<th>R</th>
<th>R-I</th>
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<tr>
<td>0</td>
<td>280</td>
<td>290</td>
<td>270</td>
<td>280</td>
</tr>
<tr>
<td>1</td>
<td>290</td>
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<td>2</td>
<td>290</td>
<td>290</td>
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<td>290</td>
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</table>

Comparison of nitrogen retention in the same animals over 7 days. Values are means ± SE; n = 5–8. Means with different letter superscripts are significantly different (P = 0.05).
before surgery (day –4 to day –1). After surgery, the resection animals had a significantly lower body weight due to the removal of gut tissue (6–9 g) during surgery (day 0). After 7 days of TPN, the resected animals lost weight (–3 ± 3 g/7 days) and the transected animals gained slightly above their postsurgical weight (+4 ± 4 g/7 days). IGF-I treatment improved weight gain in resected (+13 ± 5g/7 days) and transected (+20 ± 4g/7 days) animals, respectively. Repeated measures analysis of body weight confirmed that IGF-I significantly increased and resection significantly decreased body weight, as demonstrated by significant effects for time, interaction of time and IGF-I, and interaction of time and resection (P < 0.0007), without significant interaction of IGF-I and resection over time.

Total nitrogen retention data over 7 days of TPN are summarized in Fig. 1, inset. Nitrogen intake was not significantly different among groups, but nitrogen excretion was significantly greater in animals not given IGF-I. Thus treatment with IGF-I resulted in significantly greater nitrogen retention in both resected and transected rats. Nitrogen retention was positively correlated with change in body weight (r = 0.88, n = 24, P < 0.0001), suggesting that body weight change reflected changes in lean body mass. There were no significant differences between resected and transected animals given TPN alone.

Serum hormone and substrate concentrations. Serum concentrations of total IGF-I, glucose, and insulin are given in Table 1. Total IGF-I concentrations were approximately twofold greater in animals treated with IGF-I than in animals given TPN alone. There was no difference in serum IGF-I concentration between resected and transected animals after 7 days of TPN. There was no difference in glucose concentration between groups, but the insulin concentration was at least twofold greater in resected rats not given IGF-I compared with other groups.

Jejunal mucosal composition and architecture. Jejunal mucosa dry weight, protein content, and DNA content are shown in Fig. 2. Two-way ANOVA demonstrated that the changes in the dry weight of jejunal mucosa are due to the effects of IGF-I treatment and not due to the effects of resection surgery (Fig. 2A, inset, P < 0.003). One-way ANOVA demonstrated that jejunal mucosa from transected animals treated with IGF-I had a significantly greater dry weight than transected animals maintained with TPN alone. The protein and DNA content of the mucosa was also significantly greater in animals treated with IGF-I compared with both resected and transected animals. Parallel increases in protein and DNA indicate that the greater jejunal mass of animals treated with IGF-I can be attributed to cellular hyperplasia. There were no significant differences between resected and transected rats not treated with IGF-I.

Table 1. Serum total IGF-I, insulin, and glucose concentrations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>IGF-I, µg/l</th>
<th>Insulin, pmol/l</th>
<th>Glucose, mmol/l</th>
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<td>Trans</td>
<td>11</td>
<td>474 ± 26*</td>
<td>74.3 ± 9.3*</td>
<td>10.0 ± 0.5</td>
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<tr>
<td>Trans + rhIGF-I</td>
<td>11</td>
<td>774 ± 48†</td>
<td>80.4 ± 35.0†</td>
<td>9.3 ± 0.9</td>
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<tr>
<td>Resec</td>
<td>9</td>
<td>468 ± 23*</td>
<td>194.9 ± 16.8†</td>
<td>7.1 ± 0.5</td>
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<tr>
<td>Resec + rhIGF-I</td>
<td>7</td>
<td>838 ± 75†</td>
<td>43.5 ± 14.9*</td>
<td>9.1 ± 0.4</td>
</tr>
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</table>

Values are means ± SE; n, No. of rats; IGF-I, insulin-like growth factor I; rhIGF-I, recombinant human IGF-I; Trans, transection (sham surgery); Resec, 60% jejunoileal resection and cecectomy. Values in the same column with different superscripts are significantly different (P < 0.05).
A pattern similar to that observed in the mucosal protein and DNA content was seen in the morphology (Fig. 3). IGF-I treatment significantly increased villus height in resected (417 ± 17 µm) and transected (360 ± 32 µm) rats compared with non-IGF-I-treated resected (322 ± 12 µm) and transected (317 ± 16 µm) rats maintained with TPN alone (main effects IGF-I, 2-way ANOVA, P < 0.004). Crypt depth was greater in resected (173 ± 6 µm) and transected (183 ± 20 µm) animals treated with IGF-I compared with non-IGF-I treated resected (144 ± 6 µm) and transected (135 ± 8 µm) animals maintained with TPN alone (main effects IGF-I, 2-way ANOVA, P < 0.005). There were no significant differences between resected and transected rats not treated with IGF-I.

Jejunal kinetics. There was no difference in peak labeled cell position between groups of animals injected 1 h before death. However, the peak labeled cell position in animals injected 25 h before death was significantly greater in resected and transected animals treated with IGF-I compared with resected and transected maintained with TPN alone (Fig. 4). Thus the migration rate was greater in IGF-I-treated animals compared with animals not treated with IGF-I (Fig. 4, inset). In addition, the number of cells in a crypt column and the number of BrdU-labeled cells were signifi-

![Fig. 3. Light micrographs of jejunum stained with hematoxylin and eosin in 4 groups of rats maintained with TPN for 7 days after sham surgery (A), 60% jejunoileal resection + cecectomy (B), sham surgery + IGF-I (C), or resection + IGF-I (D). Scale bar, 200 µm.](http://ajpgi.physiology.org/)
significantly greater in animals treated with IGF-I than in animals not treated with IGF-I (Table 2, main effects IGF-I, 2-way ANOVA, \( P < 0.01 \)). The proliferation index, or the percentage of cells in the crypt incorporating BrdU, was the same across groups (Table 2), indicating that although IGF-I increased the total crypt cell population, the percentage of cells proliferating was similar to animals not treated with IGF-I. In summary, IGF-I treatment increased crypt cell populations and established a greater number of cell births and a greater rate of cell migration.

Colonic weight and architecture. Postanastomosis colon showed a resection-induced increase in mass and crypt depth independent of IGF-I treatment and luminal nutrients (Fig. 5). Resected animals with or without IGF-I had significantly greater colonic dry weights than transected animals. Two-way ANOVA indicated there were significant main effects of resection, but not IGF-I, to increase colon dry mass (Fig. 5A, inset). Similarly, colon crypt depth was significantly greater in resected animals with or without IGF-I compared with the transection control group not treated with IGF-I. Two-way ANOVA demonstrated that the increase in colon crypt depth was due primarily to resection but that IGF-I also had a modest effect (Fig. 5B, inset).

Functional responses. There was no difference in sucrase specific activity between resected and transected rats (Fig. 6). Sucrease specific activity was reduced by the administration of IGF-I in resected and transected groups (main effects IGF-I, 2-way ANOVA, \( P < 0.02 \)), although the effect was most apparent in the transected rats. Sucrease segmental activity was not significantly different across groups.

Basal electrical parameters for jejunal tissue are given in Table 3. Supplementation of TPN solutions with IGF-I decreased \( I_{sc} \) and increased PD in both the transected and resected groups (main effects IGF-I, 2-way ANOVA, \( P < 0.02 \)), although the effect was most apparent in the transected rats. Sucrease segmental activity was not significantly different across groups.

Despite the twofold increase in mass of colonic tissues of resected rats compared with transection controls (Fig. 5), basal electrical parameters of colonic
tissues were similar among the groups (Table 4). There were also no differences among the groups in $I_{sc}$ responses to carbachol, which stimulates Cl− secretion in the colon (data not shown) (30). There was a trend for IGF-I to increase basal $I_{sc}$ and PD in resected rats ($P = 0.088$), suggesting an increase in active ion transport, but the difference was not statistically significant.

**DISCUSSION**

Multiple factors, including luminal nutrients, intestinal secretions, and hormonal agents have been implicated in controlling intestinal adaptation after bowel resection. Several reports (14, 15, 28) have demonstrated that jejunal tissue does not adapt structurally or functionally in parenterally fed rats after a 60% jejunooileal resection and cecectomy. In contrast to the jejunum, resection surgery induced significant structural adaptation in the colon and coinfusion of TPN solutions with IGF-I had minimal effect on colonic structure. Although resection significantly increased colonic mass, there were no effects of resection on colonic ion transport function compared with transection controls.

In this study, we saw no evidence of jejunal structural adaptation in parenterally fed rats after resection. Jejunal protein and DNA content, histology, and kinetics did not differ between resected and transected animals after a 60% jejunooileal resection and cecectomy. A plausible explanation for the jejunal adaptation noted by Goodlad et al. (16) but not observed in the current study is the use of different surgical models. The previous study (16) used a 75% small bowel resection, which leaves residual jejunum, ileum, and the entire colon. In our study, we removed some of the

<table>
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<th>Treatment</th>
<th>No. of Tissue Sections</th>
<th>$I_{sc}$, $\mu$A/cm²</th>
<th>PD, mV</th>
<th>$G_{t}$, mS/cm²</th>
<th>Glucose, $\Delta$µg</th>
<th>Carbachol, $\Delta$µg</th>
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<tbody>
<tr>
<td>Trans</td>
<td>6</td>
<td>37</td>
<td>$59.1 \pm 11.7^*$</td>
<td>$1.1 \pm 0.1^*$</td>
<td>$30.2 \pm 2.1^*$</td>
<td>$46.2 \pm 18.6$</td>
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<tr>
<td>Trans + rhIGF-I</td>
<td>5</td>
<td>31</td>
<td>$29.8 \pm 5.0^*$</td>
<td>$2.14 \pm 0.6^*$</td>
<td>$15.2 \pm 1.6^*$</td>
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<tr>
<td>Resec</td>
<td>6</td>
<td>31</td>
<td>$68.3 \pm 10.1^*$</td>
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<td>$30.0 \pm 2.8^*$</td>
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<tr>
<td>Resec + rhIGF-I</td>
<td>6</td>
<td>35</td>
<td>$29.9 \pm 4.4^*$</td>
<td>$1.9 \pm 0.2^*$</td>
<td>$14.6 \pm 1.3^*$</td>
<td>$26.6 \pm 3.3$</td>
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</table>

Values are means ± SE. $I_{sc}$, short-circuit current; PD, potential difference; $G_{t}$, tissue conductance. Values in the same column with different superscripts are significantly different ($P < 0.02$).
jejumum and all of the ileum and the cecum. This suggests that the presence or absence of ileum may play a role in intestinal adaptation.

GLP-2 is synthesized predominately in the ileum (5) and has recently been shown to induce small bowel hyperplasia in parenterally fed rats (9). GLP-2 is a peptide derived from the proglucagon gene. Proglucagon is spliced in the L cells of the small intestine to form GLP-1, GLP-2, glicentin, and/or oxyntomodulin, which are collectively referred to as the enteroglucagons (33). Many investigators (21, 34) have noted increased enteroglucagon levels in serum of animals after a 70–80% small bowel resection. Proglucagon mRNA is increased in the remaining intestine of animals after a 70–80% small bowel resection (33). Resection surgery may induce the ileum to synthesize and secrete GLP-2, which, in turn, induces small bowel proliferation and resection-induced adaptation. If this hypothesis is correct, the absence of ileal tissue would limit the ability of the remaining small bowel tissue to adapt as noted in the current study.

The current 60% jejunoileal resection and cecectomy model has been used previously in intragastrically fed rats with similar results. Kripke et al. (23) found no difference in jejunal mass, protein, or RNA content between resected and transected animals. Even in the presence of luminal nutrients, thought to be an important stimulator of adaptation, no jejunal adaptation occurred when the ileum was removed. These observations support the idea that residual ileum is important in promoting small bowel adaptation.

We also observed no functional adaptation in the jejunum after resection. Both sucrase specific and segmental activity were similar between transected and resected rats. Basal ion transport parameters were also similar, indicating no difference in ion permeability or active ion transport. In addition, there was no difference in glucose- or carbachol-stimulated responses between resected and transected rats. Thus resection surgery did not alter jejunal epithelial function as measured by sucrase activity or ion transport parameters.

There is a significant colon or postanastomosis resection-induced adaptation that is not observed in the 75% small bowel resection model by Goodlad et al. (16). In the current study, colonic mass and crypt depth were significantly increased with resection. Other studies using this model in orally or intragastrically fed rats also found significant colonic adaptation (23, 27). Removal of just the cecum or just the distal small bowel results in a mild or absent proliferative response in the colon (35). Thus the combination of ileal and cecal resection has a dramatic effect on colonic adaptation. This effect may be related to the colonic tissue being exposed to secretions from the small bowel not previously seen by the colon. Even in the absence of luminal nutrients, significant pancreaticobiliary secretions are present in the lumen of the bowel. In fact, TPN for 14 days in rabbits appears to reduce intestinal secretions by only ~50% (11). Other investigators (2) have demonstrated that intestinal secretions induce intestinal hyperplasia.

Colonic electrical parameters were similar between resected and transected animals. Thus, despite a significant effect on colonic mass, ionic permeability and active ion transport were not altered by resection. However, Fabritius et al. (13) reported an increase in electroneutral NaCl absorption in proximal colon after a similar resection protocol in intragastrically fed rats. Because we did not conduct ion flux studies, we cannot rule out a resection-induced increase in NaCl absorption by an electrically neutral pathway.

Confusion of IGF-I with TPN solutions significantly improved weight gain in resected rats and transected animals compared with resected and transected animals not given IGF-I, respectively. In addition, IGF-I treatment decreased nitrogen excretion, thereby improving nitrogen retention. The whole body anabolic effects of IGF-I observed in this model are similar to effects we have observed in other parenterally fed rat models consistent with an increase in lean body mass (25, 43). Our observation is particularly relevant to children with SBS who demonstrate growth failure and appear to be growth hormone resistant (3). Administration of IGF-I may improve both growth and intestinal function in these children.

In the jejunum, IGF-I treatment significantly increased jejunal mucosal mass, protein and DNA content, villus height, crypt depth, total crypt cell number, and enterocyte migration rate. We have previously reported similar changes in jejunal of nonresected rats given TPN (31). Steeb et al. (37) have reported increases in total crypt cell number but a similar proliferation index in orally fed rats treated with IGF-I compared with rats not treated with IGF-I. Based on a greater absolute number of crypt cells that incorporated BrdU, we conclude that IGF-I treatment stimulated jejunal growth by increasing proliferation of enterocytes in both transected and resected rats.

Jejunal sucrase specific activity was significantly reduced by IGF-I treatment in transected rats. Decreased sucrase specific activity is most likely related to the effects of IGF-I on intestinal growth. Well-differentiated enterocytes have increased expression of sucrase and several other disaccharidases compared with less mature cells (19). IGF-I treatment increased enterocyte migration rate, producing a greater number of less mature cells expressing lower levels of sucrase. Segmental activity was preserved because the lower specific activity was offset by the increased mass in IGF-I-treated rats. The effect of IGF-I on sucrase activity in this model is similar to that in our previous report (31).

In both transected and resected rats, jejunal active ion transport and ionic permeability were decreased by IGF-I treatment, as previously reported in nonresected rats given TPN (32). In that study (32), these effects of IGF-I normalized the respective values to those measured in orally fed controls in association with jejunal growth. Together, these studies suggest that the effects of IGF-I on ion transport function may be related to the
ability of the peptide to improve jejunal mass and architecture.

Unlike the jejunum, IGF-I had only mild effects on colonic mass and crypt depth. There were slight increases in colon crypt depth in IGF-I-treated groups, but the effect was much smaller than the effect of resection itself. This is particularly interesting given several reports that colon tissue has a greater number of IGF-I receptors than jejunum (18). It appears that the colon does not respond to exogenous IGF-I like the jejunum. Mantell et al. (27) observed a significant increase in colonic IGF-I mRNA after the same surgical resection in orally fed rats with no significant change in IGF-I receptor mRNA. Other models of colonic stress such as chemically induced enterocolitis have also observed increased colonic IGF-I mRNA (44). It is possible that resection-induced adaptation in the colon is mediated by increased local IGF-I synthesis and increased sensitivity of the tissue to the mitogenic effects of IGF-I. If resection stimulates these local changes in the IGF-I system, additional exogenous IGF-I may be expected to have only mild effects because the tissue is already highly stimulated by endogenous secretions.

IGF-I treatment had no significant effect on active ion transport or ionic permeability in the colon of transected or resected rats. However, there was a trend (P = 0.088) for IGF-I to increase basal PD and Isc in resected but not transected animals, suggesting an increase in active ion transport across the colonic epithelium. Although IGF-I did not significantly increase colonic mass in our model, oral administration of IGF-I to neonatal piglets has been shown to significantly enhance basal Isc and PD in the jejunum with no effect on tissue mass or architecture (1). Whether parenteral IGF-I has a similar effect on electrolyte transport in colonic epithelium of resected rats will require further study.

In conclusion, we demonstrate for the first time, using an appropriate model for human SBS requiring TPN, that no jejunal adaptation but significant colonic structural adaptation occurs in parenterally fed rats after a 60% jejunoileal resection and cecectomy. Similar results were observed in rats fed intragastrically after the same surgical procedure (23). Thus in the presence or absence of luminal nutrients, differential regulation of intestinal adaptation is observed. That is, the colon but not the jejunum increases in mass after a 60% jejunoileal resection and cecectomy. We hypothesize that the absence of jejunal adaptation is related to the absence of ileal tissue, which synthesizes such hormonal factors as GLP-2. In addition, IGF-I induces jejunal adaptation but has minimal effects on colonic growth. In humans with SBS requiring TPN, an enterotrophic growth factor such as IGF-I may significantly improve small bowel adaptation and facilitate the transition from parenteral to enteral nutrition.

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