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Intestinal Adaptation for Oligopeptide Absorption via PepT1 After Massive (70%) Mid Small Bowel Resection

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Abstract

Introduction—Proteins are absorbed primarily as short peptides via PepT1.

Hypothesis—Intestinal adaptation for peptide absorption after massive mid-small intestinal resection occurs by increased expression of PepT1 in the remnant small intestine and colon.

Methods—Peptide uptake was measured in duodenum, jejunum, ileum, and colon using Glycyl-Sarcosine 1 wk (n=9) and 4 wk (n=11) after 70% mid-small bowel resection, and in corresponding segments from unoperated rats (n=12) and after transection and reanastomosis of jejunum and ileum (n=8). Expression of PepT1 (mRNA, protein) and villus height were measured.

Results—Intestinal transection/reanastomosis did not alter gene expression. Compared to non-operated controls, 70% mid-small bowel resection increased jejunal peptide uptake ($p<0.05$) associated with increased villus height (1.13 vs 1.77 and 1.50 mm resp, $p<0.01$). In ileum although villus height increased at 1 and 4 wk (1.03 vs 1.21 and 1.35 mm resp; $p<0.01$), peptide uptake was not altered. PepT1 mRNA and protein were decreased at 1 wk, and PepT1 protein continued low at 4 wk. Gene expression, peptide uptake, and histomorphology were unchanged in the colon.

Conclusions—Jejunal adaptation for peptide absorption occurs by hyperplasia. Distal Ileum and colon do not have a substantive role in adaptation for peptide absorption.

Keywords

Peptide absorption; short bowel syndrome; PepT1; intestinal adaptation; protein absorption; malabsorption

INTRODUCTION

Short bowel syndrome arises from malabsorption of nutrients in response to a marked decrease in the intestinal absorptive area after intestinal resection/loss for a multitude of reasons. The current treatment options for this condition include intestinal rehabilitation, chronic parenteral nutrition, intestinal transplantation, and intestine lengthening procedures, all of which carry a variable prognosis and outcome [1,2]. A better understanding of the etiology of the pathophysiologic changes occurring in short bowel syndrome may engender

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novel methods for improving the absorptive potential of the remnant small intestine in these patients.

Because the small intestine demonstrates a remarkable ability to adapt its absorptive capacity for nutrient absorption after a marked decrease in effective absorptive surface, many approaches have been directed at augmenting this adaptive mechanism(s) ([3,4]). Prior experiments from our laboratory have investigated the adaptive mechanisms mediated by brush border transporters for glucose and peptide absorption in the ileum after 70% proximal intestinal resection [5]; however, the adaptive changes in the jejunum and duodenum have not been well characterized for the transport proteins that regulate the uptake of peptides by epithelial cells. The role of terminal ileum and colon in improving survival in patients with short bowel syndrome is well established [6]. Recent studies have suggested an increase in expression of peptide transporter 1 (PepT1) mRNA in the colon of patients with short bowel syndrome [7,8]; however, the absorptive function of the colon for peptides has not been studied.

The current study was designed to determine the effects of a marked, mid-small bowel resection (70%) on the expression and function of the peptide transporter PepT1 in the duodenum, proximal jejunum, distal ileum, and proximal colon. Our hypothesis was that the remnant small bowel adapts to this marked loss of absorptive area by increasing expression and function of PepT1 per enterocyte in addition to the expected mucosal/epithelial cell hyperplasia.

METHODS

This study was approved by our Institutional Animal Care and Use Committee, and all experiments were carried out in accordance with the NIH guidelines for the humane use and care of laboratory animals.

Design

Male Lewis rats (Harlan Laboratories, Indianapolis, IN) weighing approximately 200 g were maintained in a 12-h light-dark cycle (6AM lights on, 6 PM lights off) and were allowed free access to water and standard rat chow (5001 Rodent Diet, PMI Nutrition International, LLC, Brentwood, MO). They were first allowed a week to acclimatize to the housing conditions, after which a 70%, mid-segmental, jejunoileal resection was performed; the rats were studied subsequently at 1 wk (n=8) and at 4 wk (n=11) after intestinal resection. An additional group of rats (n=9) that underwent transection and immediate primary reanastomosis of their small intestine at points corresponding to the sites of transection in the resection groups were studied 1 wk postoperatively and served as 'operated control' for the non specific effects of anesthesia, celiotomy, and disruption of the enteric nervous system. Another group of 12 rats served as non operated controls. A final group of 8 rats were maintained in similar conditions to determine weight changes over 4 weeks in non-operated control rats.

Intestinal resection—Mid-ventral celiotomy was performed after anesthetizing the rats with pentobarbital (50 mg/kg). The ligament of Treitz was identified and the length of the jejunoileum measured. A 70%, mid-segmental, jejunoileal resection was performed with primary end-to-end anastomosis of the remnant jejunum and ileum using a single-layer anastomosis with 6-0 silk sutures. The ventral abdominal wall muscles were reapproximated with a running 6-0 silk suture, and the skin was closed with subcuticular 5-0 vicryl sutures. Buprenorphine (0.05–0.1 mg/kg) was administered subcutaneously for analgesia every 12 h for one day. The rats were maintained on water for 24 h before being given free access to rat chow.

Operated control—These rats underwent celiotomy under anesthesia as in the resection group. After measuring the length of the jejunoileum, the intestine was transected and reanastomosed as above at the two places corresponding to the transections in the resection groups; however, the intervening intestine was not resected. The abdomen was closed and analgesia provided as above.

Tissue harvest—Tissue from all rats was harvested consistently at 9 AM due to known diurnal variations in gene expression of PepT1 [9,10]. The rats were anesthetized as described previously and a secondary mid-ventral celiotomy performed. The duodenum was cannulated just distal to the pylorus and the small and large intestines were flushed with cold (4°C) Ringers solution. The duodenum, remnant jejunum, ileum, and proximal colon were harvested from the rats that had undergone intestinal resection 1 wk and 4 wk prior to harvest. In the non operated controls and the operated controls, the proximal jejunum and distal ileum, which corresponded to the remnant segments in the resection group, along with the duodenum and colon were harvested at 0 and 1 wk, respectively. The mucosa of the jejunum, ileum, and colon was scraped using a glass slide and stored in a RNA stabilizing solution (RNALater, Qiagen, Valencia, CA) for mRNA analysis, and in RIPA buffer containing protease inhibitors (Halt protease, Pierce, Rockford, IL) and phenylmethane sulfonyl fluoride solution (PMSF) (Sigma Aldrich, St. Louis, MO) for protein analysis. There was not enough duodenal tissue to harvest mucosa. The mucosal tissues were frozen in liquid nitrogen and stored at -80°C for later batch analysis. A piece of intestine was pinned carefully onto a silicon elastomer support and fixed in 10% formalin for histomorphologic analysis after staining with hematoxylin and eosin.

In vitro peptide uptake/everted sleeve technique—The harvested segments of gut were placed in cold (4 °C) Ringers solution oxygenated with 95% O₂/5% CO₂. Rate of transport of the non hydrolyzable dipeptide glycyl-sarcosine (Gly-Sar) (Sigma Aldrich, St. Louis, MO) was measured using the everted sleeve technique using 1-cm segments of bowel everted over steel rod as described previously [5,9,11,12]. The sleeves were incubated initially for 3 min in a warm (38°C) buffer solution (129 mM NaCl, 5.1 mM KCl, 1.4mM CaCl₂, 1.3 mM NaH₂PO₄, 1.3mM Na₂HPO₄ adjusted to a pH of 6). The sleeves were then incubated for 1 min in 8 ml of test solution containing Gly-Sar at various concentrations (0.02–40 mM). Test solutions were prepared by isosmolar replacement of NaCl with Gly-Sar in the buffer solution. To each test tube, 1 mCi of ¹⁴C-labeled Gly-Sar (Moravek Biochemicals, Brea, CA) was added. After incubating for 1 min, the intestinal sleeves were dissolved in 1 ml of tissue solvent (Solvable, Perkin Elmer, MA), mixed in 15 ml of scintillation cocktail (Optiflour, Perkin Elmer, MA), and ¹⁴C radioactivity was measured in a Beckman LS6000SC counter (Beckman Coulter, Brea, CA). Carrier-mediated (active) transport was calculated as nmol/cm/min as described previously [9,12].

Protein analysis—The mucosal samples were thawed on ice and homogenized in RIPA buffer containing protease inhibitor and PMSF using a Kontes pestle (Fischer Scientific, Pittsburg, PA). The protein content was estimated by bicinchoninic acid method (Pierce, Rockford, IL). Protein (200 µg) from each sample was resolved on 10% SDS PAGE gel (Bio-Rad, Hercules, CA) and transferred electrically onto PVDF membranes (Millipore, Bedford, MA). PepT1 was detected using IgG antibodies raised in rabbits (Santa Cruz Biotechnology, Santa Cruz, CA). GAPDH was detected using IgG antibody raised in mice (US Biological, Swampscott, MA)). Corresponding secondary antibodies conjugated with horseradish peroxidase (Sigma Aldrich, St. Louis, MO) were used to identify the protein bands using Opti-4CN calorimetric substrate kits (Bio-Rad). The PepT1 band was enhanced with Amplified Opti-4CN substrate kit Band intensity and measured using ImageJ 1.42 (NIH, Bethesda, MD). The amount of PepT1 was normalized to levels of the stably

expressed housekeeper gene GAPDH. Values are represented relative to protein expression levels in non operated control rats.

mRNA analysis—Mucosal scrapings frozen in RNALater at -80°C were thawed on ice and homogenized. RNA was extracted using a RNeasy Midi Kit (Qiagen) according to the manufacturer's instruction. RNA concentration was estimated by spectrophotometry. From this RNA, cDNA was reverse transcribed with Superscript II kit (Invitrogen, Carlsbad, CA) and random hexamer primers. The cDNA was stored at -80°C . Pept1 mRNA was quantified by real time RT-PCR using a 7500 Thermocycler and Taqman® chemistries with primers and fluorescently-labeled probes in assay mixes according to the manufacturer's instructions (Applied Biosystems, San Francisco, CA). All samples were run as duplicates with 2 μl of sample cDNA (or known standard) added to 23 μl of master mix for a total sample volume of 25 μl . Real-time PCR was carried out at 95°C for 10 min followed by 40 cycles of 15 s at 95° and 1 min at 60°C during which fluorescence was measured. mRNA levels were normalized to levels of GAPDH, a housekeeper gene. Values are represented relative to mRNA expression levels in non operated control rats.

Histomorphometry—The formalin-fixed tissues from the duodenum, jejunum, ileum, and colon from 6 rats in each group were embedded in paraffin and sectioned along the villus axis. A minimum of 8 sections were cut from each tissue sample, and hematoxylin and eosin staining was performed. Maximum villus height and crypt depth was measured from the top of the crypt to the tip of the villus at 10X magnification. A minimum of 6 sections were reviewed per each segment with at least three measurements of villus height per section so that at least 18 measurements were made for each segment per rat.

Data Analysis

Data are represented as median (interquartile range). Data were analyzed by Kruskal-Wallis test and Wilcoxon test using JMP 8.0 (SAS Institute Inc., NC). P value of <0.05 was considered significant. Bonferroni correction was performed where applicable.

RESULTS

Body Weight

All animals appeared healthy and ate normally. At 1 wk postoperatively, the rats that underwent 70% resection lost more weight than the control group and the operated control group (-6% vs 8% and 1% , $p<0.05$, Figure 1). By 4 wk, the resection group had gained 29 (22, 31)% of their initial weight, however, this weight gain was less than the weight gained by non operated control rats over 4 wk of 33% (30, 37) ($p<0.05$) pointing to the establishment of a transient malabsorptive state. In the resection group, both proximal and distal small intestine was found to have undergone progressive dilation along with an increase in wall thickness at time of tissue harvest. The small intestine of the operated control rats appeared normal without apparent dilation.

Peptide Transport

No difference was observed in the rate of peptide uptake between the non operated and operated control groups when expressed as uptake per cm ($p>0.05$, Figure 2A and B), suggesting that the anesthesia and operative procedure did not affect peptide uptake measured at 1 wk postoperatively. In contrast, at 1 and 4 wk after 70% mid-small bowel resection, peptide uptake in the remnant segments was altered.

In the duodenum, compared to non operated controls, the mean Gly-Sar uptake (nmol/cm/min) was increased at 1 wk post-resection to 6.6 (3.8, 16.2) vs 22.0 (7.8, 22.2), but at 4 wk

post-resection, Gly-Sar uptake decreased to levels not different from the non operated control group 8.2 (−0.7, 12.8); these changes were not statistically significant. In the jejunum, Kruskal-Wallis rank sum showed a change in peptide uptakes after intestinal resection ($p<0.05$), and uptake at 1 wk and 4 wk were greater than in the control group (32.5 vs 49.5 and 69.0 resp, Figure 2A and B). In the remnant (distal) ileum, there were no changes in rate of peptide uptake after resection compared to the distal ileum in the non operated control group. We could not measure any substantive Gly-Sar uptake in the colon in non operated control, operated control and post resection groups (Figure 2A and B).

Protein Expression

Protein levels of PepT1 were normalized to levels of GAPDH, a stably expressed housekeeper gene, to estimate relative expression levels per enterocyte in the 4 groups. Non-operated controls had similar PepT1 protein levels in the proximal jejunum and distal ileum compared to the operated controls. After 70 % mid small intestinal resection, no differences were seen in expression levels of PepT1 protein in the remnant jejunum at 1 wk and 4 wk post-resection when compared to non-operated and operated control rats ($p>0.05$, Figure 3A). In contrast, in the ileum, the amount of PepT1 was decreased at both 1 wk and 4 wk time points at 0.50 (0.46, 0.86) and 0.65 (0.53, 0.72) vs 1.00 (0.89, 1.07), resp ($p<0.01$). In the colon, although PepT1 was measurable in all groups, no changes were noted in PepT1 protein content in operated controls and after small intestine resection (Figure 3B).

mRNA Analysis

PepT1 mRNA levels were also normalized to levels of GAPDH, a stably expressed housekeeper gene, to estimate relative expression level per enterocyte in the 4 groups. Operated controls had similar PepT1 mRNA levels in all segments of the intestine compared to the non operated controls. In contrast, in the remnant distal ileum, PepT1 mRNA was decreased at 1 wk after intestinal resection compared to non operated controls ($p<0.01$, Figure 4). However, no differences were observed at 4 wk after resection. PepT1 mRNA levels were not altered in the jejunum and colon in all groups.

Histomorphometry

In the duodenum, there were no significant changes in the height of villi in operated control and post resection groups when compared to non-operated control group. The villus height of the jejunum after intestinal resection was increased at both 1 and 4 wk ($p<0.01$, Figure 5). Villus height was also greater in the operated control group also ($p<0.02$). In the ileum, no difference was noted between the non operated and operated control groups. After intestinal resection, however, when compared to the non-operated controls, the villus height was increased at 1 and at 4 wk ($p<0.01$). There were no changes observed in the colon across the groups.

DISCUSSION

Our study was designed specifically to evaluate the ability of the duodenum, proximal jejunum, distal ileum, and proximal colon to adapt its capacity for peptide absorption after a massive mid small bowel resection. This study showed that in rats, the jejunum increased its absorptive capacity for peptides not by up-regulating the gene expression of peptide transporter PepT1 but rather by mucosal hyperplasia and intestinal dilatation. In contrast, the distal ileum did not increase its capacity for peptide uptake despite the hyperplasia that occurred, suggesting a different adaptive process than in the jejunum. These findings may have important clinical implications after massive intestinal loss/resection.

Recent interest in the intestinal peptide transporter PepT1 arises from its ability to transport a variety of peptide-like drugs, including β lactams [13], angiotensin converting enzyme inhibitors[14], and several antiviral drugs[15–17]; indeed the literature on PepT1 is dominated by its pharmacologic investigation. The importance of peptide transport in health and disease, as well as the limited understanding of the physiology of PepT1 expression and function captured our interest as we have studied hexose transport. Because PepT1 is capable of transporting all dietary di- and tri- peptides[18,19], it serves as the primary pathway for absorption of the ingested protein after luminal digestion into di- and tri-peptides [20]. Hence, understanding the regulatory mechanism(s) of the transporter could provide newer treatment options for improving nutrient absorption in short bowel syndrome.

Our interest focused on mechanisms by which the gut can adapt to loss of absorptive surface area. Intestinal adaptation to increase absorption after resection can occur by epithelial hyperplasia with an increase in number of enterocytes through an increase in villous height resulting in an increase in absorptive surface area, or by cellular upregulation of gene expression of selective transporters resulting in an increase in (absolute or functional) number of transport proteins per enterocyte. In this study, we investigated the adaptive changes occurring in the rat duodenum, proximal jejunum, distal ileum, and colon after a 70% mid small intestinal resection that led to a “short bowel” syndrome. The jejunum appears to be the principle site of peptide absorption in the non operated control rats. After 70% resection, we showed that there was an increase in rate of peptide uptake per cm of proximal jejunum of about 40%. The proximal jejunum underwent a rapid increase in villus height combined with dilation of the intestine, both of which serve to increase mucosal absorptive area. The villus height was increased as early as 1 wk post operatively and did not show any further change 4 wk post resection, suggesting that the epithelial proliferation reached its adaptive change by 1 wk. In contrast, PepT1 mRNA and PepT1 protein per enterocyte at 1 and 4 wk post resection as estimated by the PepT1 expression levels normalized to the stably expressed housekeeper gene GAPDH was comparable to the non-operated rats. These findings of an apparent lack of an increase (upregulation) in gene expression (mRNA and transport protein per cell) suggest that the jejunal adaptation to an acute operative loss of 70% of the mid small intestine occurs primarily by hyperplasia. These findings refute our study hypothesis but are consistent with our prior work with hexose transporters (SGLT1 and GLUT2) where the increase in glucose uptake per cm of intestine after massive small bowel resection appeared to occur solely by increased mucosal surface area (villus hyperplasia, intestinal dilation) and not via increase in gene expression per enterocyte for these two hexose transporters [5].

The distal most ileum (terminal 10 cm) also demonstrates progressive villous hyperplasia after resection. Unlike in the jejunum, however, the processes promoting hyperplasia continue beyond 1 wk, and the villi were taller at 4 wk post resection compared to the 1 wk time point. Interestingly, this increase in effective ileal absorptive surface area did not increase functional peptide uptake after resection as measured by everted sleeve technique. Furthermore, the amount of PepT1 protein per enterocyte was decreased at both 1 and at 4 wk post resection, and Pept1 mRNA content was also decreased at 1 wk post resection. These findings suggest, potentially, a more immature, undifferentiated epithelium. These data differ from previous studies from our lab (unpublished data) where we measured adaptation in the mid ileum for peptide and hexose transport [11] in rats that had undergone a 70% proximal jejunoileal resection with the entire jejunum being resected. Adaptive regulation of PepT1 gene expression has been shown to occur in response to substrate concentration in the lumen ([21–23]). The presence of proximal jejunum with an increased capacity for peptide absorption might decrease the amount of dietary peptides reaching the terminal ileum and thereby alter ileal adaptation; other possibilities, of course, might include an inability of the distal ileum, in contrast to the mid ileum, to undergo a rapid adaptation to

increase absorption. We have no data on long term adaptive potential of distal ileum that might occur later than 4 wk after this 70% mid small bowel resection.

The changes occurring in the colon of people with short bowel syndrome have received considerable interest in terms of the role of proximal colon in adapting its functional absorption of luminal nutrients. Of note, we were unable to show any substantive uptake of dipeptides into everted sleeves of proximal rat colon or any changes in PepT1 mRNA, and protein levels, or histomorphometry. These findings appear to be in contrast to studies in humans with short bowel syndrome that demonstrated an increase in PepT1 mRNA and colonic absorptive surface [7,8]. The presence of a large functional cecum in rats may prevent a meaningful comparison of colonic adaptation in rats and humans.

Our study has several limitations. First we could not estimate PepT1 expression in the duodenum due to the limited length of the duodenal segment; the rat duodenum is only about 6–7 cm, and most the duodenum was used to measure peptide uptake by everted sleeves. In addition, rats have a very large functional cecum which may affect adaptive need. Also, our technique for protein analysis can not distinguish membrane-bound PepT1 transporter (functional protein) from the intracytoplasmic pool of PepT1 protein (non-functional protein). Cellular regulatory processes might alter intracellular translocation of pepT1 into and out from the apical membrane to increase peptide absorption without altering total cellular PepT1 content as occurring with other transport proteins such as GLUT2 [24].

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Figure 1.

Weight change expressed as percentage change in initial weight in non operated control rats at 1 wk (NC 1 wk), operated controls at 1 week (OC) and 1 week post resection rats (1 wk rsxn), and weight change in non operated control rats at 4 weeks (NC 4wk) compared to resection rats at 4 weeks (4wk rsxn). Weight change in resection group is less than OC at 1 wk, and less than non operated controls over 4 wk.

Figure 2.

Carrier mediated Gly-Sar uptake at A) 1 mM and B) 5 mM Gly-Sar concentrations in the 4 anatomic segments of the intestine in non operated control (NC), operated control (OC), 1 week post resection group (1wk rsxn), and 4 weeks post resection group (4wk rsxn). Gly-Sar uptake is increased significantly 4 weeks after resection in the jejunum

Figure 3.

Variations in relative cellular levels of PepT1 protein in A) proximal jejunum and distal ileum, and B) proximal colon in non operated control (NC), operated control (OC), 1 week post resection group (1wk rsxn), and 4 weeks post resection group (4wk rsxn). PepT1 protein levels are decreased in ileum after resection. No change noted in colon.

Figure 4.

Variations in relative cellular levels of PepT1 mRNA in proximal jejunum, distal ileum, and proximal colon in non operated control (NC), operated control (OC), 1 week post resection group (1wk rsxn), and 4 weeks post resection group (4wk rsxn). PepT1 mRNA levels are decreased in ileum 1 wk after resection. No change noted in colon

Figure 5.

Change in villous height / colonic crypt depth in the 4 anatomic segments of the intestines in non operated control (NC), operated control (OC), 1 week post resection group (1wk rsxn), and 4 weeks post resection group (4wk rsxn). Villus height is increased in jejunum and ileum after resection.