Glucagon-Like Peptide-2 and Short-Chain Fatty Acids: A New Twist to an Old Story\textsuperscript{1,2}

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ABSTRACT The nutritional regulation of intestinal adaptation extends beyond the route of nutrient administration as specific nutrients are known to mediate the adaptive response. Dietary carbohydrates are known to enhance intestinal adaptation in patients with short-bowel syndrome. This review discusses SCFA-induced adaptation in intestinal structure and function in adult rat and neonatal piglet models. Potential mechanisms relate to the salvage of energy as SCFA in the colon, direct mediation of intestinal adaptation by SCFA and stimulated release of glucagon-like peptide-2 (GLP-2) from enteroendocrine L cells by SCFA. Among the produced SCFA, butyrate appears to be responsible for increasing plasma GLP-2 concentration, in addition to the enterotrophic effects. Emerging evidence reveals that physiological concentrations of butyrate acutely upregulate the expression of key enterocyte-associated nutrient transporters. Focused experiments are needed to carefully identify the critical components of intestinal adaptation and yield conclusions regarding the relative contributions of SCFA and GLP-2 during the various phases of this process. J. Nutr. 133: 3717–3720, 2003.

KEY WORDS: intestinal adaptation \textbullet short-bowel syndrome \textbullet nutrient transport \textbullet butyrate \textbullet piglet

The small intestine is a remarkable organ with a distinct structure aimed at meeting the digestive and absorptive demands of the host. The length of the adult small intestine is \textasciitilde 20 ft. However, this absorptive surface area is further amplified by numerous mucosal folds of Kerckring, containing finger-like villi, lined by a polar epithelium displaying a brush border membrane adjacent to the intestinal lumen. This structural configuration results in a surface epithelium estimated to be 600-fold greater than if a simple smooth cylinder. As a result, the normal healthy intestine is estimated to greatly exceed the digestive and absorptive requirement of the host, wherein the majority of nutrients are absorbed within the jejunum.

Intestinal adaptation

Short-bowel syndrome (SBS) typically follows resection of 50\% or more of the small intestine and is associated with diarrhea, dehydration, electrolyte disturbances, malabsorption and progressive malnutrition. However, the administration of nutrients intravenously inhibits the process of intestinal adaptation, a key phenomena wherein the residual intestine undergoes structural (i.e., dilation, lengthening and thickening) and functional (i.e., digestive and absorptive) enhancements. The nutritional regulation of intestinal adaptation extends beyond the route of nutrient administration because specific nutrients are known to mediate the adaptive response. Whereas the other contributors to this symposium have demonstrated that glucagon-like

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Dietary carbohydrate and SCFA
by means of the indirect actions of GLP-2 (13).

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peptide-2 (GLP-2) is intestinotrophic (13–16), the focus of this paper is to examine the evidence supporting the hypothesis that SCFA, indeed butyrate alone, enhance structural and functional adaptations following massive small bowel resection by means of the indirect actions of GLP-2 (Fig. 1).

Dietary carbohydrate and SCFA
In patients with SBS, the presence of both the ileum and colon signiﬁcantly enhances the patient’s prognosis because of the preservation of intestinal transit rate, preserved absorption of vitamin B-12 and bile salts and the marked adaptive capacity of the ileum (3,17). In patients with SBS with an intact colon, energy absorption, but not fecal output, was reported to be enhanced following consumption of a high carbohydrate diet compared with a high fat diet in a 4-d crossover study (18). The concept of “carbohydrate salvage” supports this observation wherein malabsorbed carbohydrate and certain dietary fibers are fermented by anaerobic bacteria in the colon to SCFA (19). Among their various properties, SCFA are quickly absorbed by intestinal mucosa, are relatively high in caloric content, are readily metabolized by intestinal epithelium and liver, stimulate sodium and water absorption in the colon and are trophic to the intestinal mucosa (20). However, the favorable prognosis associated with maintenance of the distal gastrointestinal tract and a diet high in carbohydrate likely extends beyond simple energy recovery and SCFA absorption. Physiologically, SCFA are a logical mediator of GLP-2 release because the enteroendocrine L cells, which secrete GLP-2, are located in the terminal ileum and colon; a strategic position for monitoring the presence of malabsorbed food and SCFA release.

SCFA and intestinal adaptation
The addition of SCFA to TPN has been shown to prevent TPN-associated mucosal atrophy (21) and enhance structural markers of adaptation to small bowel resection in adult rats (22,23). In addition to determining that these structural adaptations occur as early as 3 d following intestinal resection (23), we examined functional adaptations augmented by the SCFA, acetate, propionate and butyrate. Ileal uptake of D-glucose is increased by systemic SCFA administration both 3 and 7 d following intestinal resection by increasing the maximal transport rate without altering the apparent Michaelis affinity constant or passive permeability coefficient (24).

Because SCFA were found to increase the functional capacity of the residual small bowel in adult rats, we examined the mRNA abundance of nutrient transporters within the enterocytes to provide potential cellular mechanisms underlying this increase in functional capacity (24). The results indicate that SCFA increased mRNA abundance of the facilitative glucose transporter, GLUT2, and tended to increase the mRNA abundance of the brush-border sodium/glucose cotransporter, SGLT-1 (Fig. 2). Subsequent acute studies in adult rats with healthy unresected intestine receiving TPN indicated that systemic SCFA markedly increase both mRNA and protein abundance of GLUT2 within 6 h of administration (25). These results are unique because they indicate that a specific nutrient (i.e., SCFA) may modulate the gene expression and transport capacity of other nutrients (i.e., glucose, galactose and fructose). Furthermore, the observed increase in nutrient uptake indicates that systemic nutrients (i.e., those provided to the basolateral pole of the enterocyte, as in TPN) can increase the transport of luminal substrates (via brush-border transporters) provided by oral or enteral nutrition. The concept that SCFA can be provided intravenously to prepare the intestinal brush-border for effective digestion and absorption of enteral nutrients is particularly attractive for patients with SBS.

The proposed mechanism that SCFA-induced intestinal adaptation is associated with upregulation of proglucagon mRNA abundance and plasma GLP-2 concentrations was assessed in these adult rat studies. Following intestinal resection, ileal proglucagon mRNA abundance and plasma GLP-2 concentrations were found to increase as early as 3 d following surgery and was sustained until d 7 (23). This association occurs independently of intestinal resection as both proglucagon mRNA and

FIGURE 1 Proposed mechanism for butyrate-induced intestinal adaptation. Butyrate enhances structural and functional adaptations following massive small bowel resection and is associated with increased plasma concentrations of GLP-2. Additional data are needed to discern the relative contributions of butyrate and GLP-2 during the various phases of intestinal adaptation.

FIGURE 2 SCFA and functional adaptation. SCFA-supplementation of total parenteral nutrition in following massive small bowel ressection increases glucose uptake and is associated with upregulated enterocyte expression of the monosaccharide transporters, SGLT-1 and GLUT2.
GLP-2 plasma concentration was increased as early as 6 h following SCFA-supplemented TPN administration (25,26). These results indicate that SCFA augment expression of functional proteins in both intact and adapting intestine and that these enhancements are associated with increased plasma concentration of GLP-2. Further studies are needed to extend this observation beyond the level of association by determining if the increased plasma GLP-2 is mandatory for SCFA-induced adaptations, thereby providing vital mechanistic information.

SCFA and the neonatal piglet

Although the adult rat model allowed initial examination of the role of SCFA in intestinal adaptation, a major limitation of this model is its applicability to the growing population of human infants with SBS. Similarities in nutritional requirements, gastrointestinal physiology and metabolism make the neonatal piglet an appropriate model for the parenterally supported neonate. Parenteral nutrition is a safe option even in small infants. Therefore, recent efforts have turned to parenterally supported neonatal piglet an appropriate model for the parenterally supported neonatal piglet. Studies have shown that parenterally supported piglets have a high survival rate and that SCFA administration is safe and beneficial in this setting.

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Butyrate, GLP-2 and GLUT2 transcriptional initiation

Regardless of the experimental model or species studied, a very marked and acute in vivo response to SCFA administration is increased mRNA and protein abundance of the facilitatory hexose transporter, GLUT2. To test the hypothesis that butyrate and/or GLP-2 increase GLUT2 mRNA abundance by activation of the GLUT2 promoter, the pGL3 reporter plasmid containing 1800 bases of the human GLUT2 promoter was cotransfected with renilla (a transfection efficiency control) into differentiated Caco-2BBe cells. In parallel experiments, both GLP-2 (unpublished data) and butyrate (33) activated the GLUT2 promoter in a dose-dependent manner. Consistent with the in vivo piglet data, studies conducted with a cocktail of SCFA including acetate, propionate and butyrate indicate that butyrate is indeed the stimulatory SCFA because acetate and propionate treatments did not differ from control (33). Additional studies are underway regarding the intriguing observation that both butyrate and GLP-2 independently activate the GLUT2 promoter. In addition to their independent effects, trials are focusing on potential synergistic effects that may exist between butyrate and GLP-2 and determining if each of these stimuli initiate GLUT2 transcription through activation of distinct regions of the promoter.

CONCLUSION

Historical clinical reports with human subjects and recent data obtained from adult rat and neonatal piglet SBS models support the hypothesis that the mechanism whereby SCFA-supplemented TPN enhances structural and functional aspects of intestinal adaptation is via upregulation of the intestinal trophic peptide, GLP-2. However, current data reveal only positive associations and definitive trials await specific GLP-2 antagonists, immunoneutralizing GLP-2 antibodies or GLP-2 receptor knockout mouse. It is yet possible that butyrate directly induces adaptive alterations, or alternatively that there is a synergism between GLP-2 and butyrate with each of these potential signals regulating different aspects of this complex process. Finally, it also remains possible that butyrate initiates adaptation directly; however, it is more likely involved in a cascade of adaptive mediators, of which GLP-2 is a strong candidate. Acute regulation of nutrient transporter expression by butyrate, in a GLP-2 independent manner, leads us to speculate that GLP-2 may have an important role in the chronic changes aimed at increasing steady-state levels of small intestinal function. Indeed, experimental evidence indicates that there are likely separate signals for acute versus chronic adaptations, as there are for structural versus functional adaptations (34). Therefore, focused experiments are needed to carefully identify the critical components of intestinal adaptation and to yield conclusions regarding the relative contributions of butyrate and GLP-2 during the various phases of this process.

LITERATURE CITED