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The assessment, and glucagon-like peptide-2 modulation, of intestinal absorption and function

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The treatment of patients with short bowel syndrome is hampered by a lack of treatment and measurement methods. This article reviews our evolving understanding of the role of glucagon-like peptide 2 (GLP-2) in controlling the adaptive process. The ability of the remnant intestine to produce GLP-2 appears to be predictive of the adaptive process; exogenous GLP-2 may be a therapy to augment adaptation. Strategies for monitoring patients, including conventional means, such as anthropomorphic measurements, plasma levels of specific nutrients, and vitamins and radiological contrast studies are reviewed. Investigational methods, such as nutrient balance studies, plasma citrulline levels, and the absorption of inert sugars (3-0 methyl glucose, mannitol, and lactulose) are discussed with the evidence to support their use.

The care of infants and children with short bowel syndrome (SBS) is primarily focused on meticulous nutritional support, whereas the remaining intestine undergoes adaptation, or upregulation of nutrient absorptive capacity (see review by McMellen and Warner in this issue). Clinical experience and animal studies have demonstrated that the small intestine adapts through hypertrophy of the mucosa and increased absorptive abilities.[1-4] Grossly, the bowel dilates, lengthens, and thickens, and microscopically there is villus hyperplasia, increased crypt depth, and increased muscle thickness.[5] An increased production of brush border enzymes occurs along with increases in mucosal weight, protein, RNA, and DNA content.[5,6] Intestinal adaptation begins within 24-48 hours of resection, but may take several years to complete, especially in the growing child.[7] Although systematic studies in human beings are practically difficult, the data available support similar histological and functional adaptation in infants.[8] Adequate intestinal adaptation is required before a patient with extensive gastrointestinal resection is able to be weaned from the support of parenteral nutrition (PN) and to absorb sufficient nutrients by the enteral route.

Clinical factors associated with successful intestinal adaptation include younger age, limited extent of resection, jejunal vs ileal resection, presence of ileocecal valve, continuity of the colon with the small intestine, and adequate general nutritional status.[8,9] The markedly improved outcome of infants who have any remnant, however short, of ileum has long been appreciated; this suggests an ileal factor that helps stimulate intestinal adaptation. The enteroendocrine hormone glucagon-like peptide 2 (GLP-2) seems to be this factor. GLP-2 is a 33 amino acid peptide produced with GLP-1 from the proglucagon gene; this gene produces glucagon in the pancreas, but undergoes specific posttransla-

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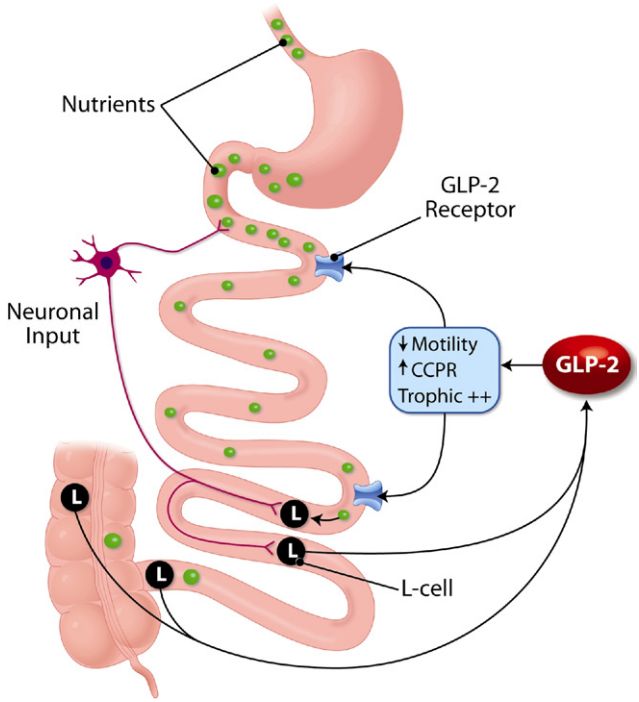

Figure 1 Glucagon-like peptide-2 release by enteral nutrients and signaling effects. (Color version of figure is available online.)

tional processing in the enteroendocrine L cells of the small intestine to produce the GLP proteins. GLP-2 (with GLP-1) is released by the L-cells primarily in response to direct contact with luminal nutrients, especially long-chain fatty acids in the terminal ileum (Figure 1).[7,10-12] The levels of GLP-2 are significantly elevated after a major proximal intestinal resection in animal and human subjects.[1,13,14] GLP-2 has a short half-life of 7 minutes as an endocrine hormone .[15] It acts to stimulate intestinal mucosal crypt cell proliferation by increasing insulin-like growth factor-1 production by the pericryptal fibroblasts, which increases nutrient absorptive capacity. It also acts to slow proximal motility.[16-18] In enterally fed animals subjected to massive resection, GLP-2 levels were highly correlated with spontaneous adaptation, with an ongoing elevated baseline production even after nutrient malabsorption has corrected, suggesting that GLP-2 is important in initiating and maintaining spontaneous adaptation.[1] In animals maintained with enteral nutrition, exogenous GLP-2 increased nutrient absorption by 20%-100%, depending on the length of residual bowel.[19-21] These studies are focused on the "adaptation" of nutrient absorption after intestinal resection; however, it is important to recognize that this form of adaptation it is a subtype of the normal physiological regulation of nutrient absorption which occurs in all mammals. The intestine must respond to such stresses as the wide variations in nutrient availability which occurs in the wild, increased nutrient requirements, as seen during pregnancy, or decreases in absorptive capacity as occurs after mucosal damage from disease or toxicity.[5,6,22] In this context, GLP-2 can be viewed as "master-mregulator" of intestinal response to nutrient load (Figure 1).

In adult human studies, GLP-2 or its analogues have been shown to have moderate effects on nutrient and fluid absorption;[23,24] a phase 3 trial with teduglutide (long acting agonist of GLP-2) has been completed in a population of stable adult patients with SBS, who have been PN-dependent for many years; results are positive (NPS Web site, November 2007). At present, studies in pediatric patients are in the planning stages. It is important to note that this system is active in premature infants; in fed premature neonates, levels of GLP-2 are very high (up to 450 pM/L), but low in infants who do not tolerate feeds, showing a regulatory role in this age group.[25] Basal levels are high in these infants without meal stimulation, suggesting a potential role in inducing gut growth in the final weeks of gestation.[25-27] In infants with SBS, serum GLP-2 concentrations were noted to correlate with residual small intestinal length and markers of intestinal absorption.[14] Importantly, in these studies, infants without remnant ileum did not produce significant levels of GLP-2, even if the colon was intact. Furthermore, all infants unable to produce GLP-2 levels $>$ 15 pM/L with feeds of $>$ 40 kCal/kg died of complications of SBS.[14] In infants with gastroschisis, there is a clear association of GLP-2 production with tolerance of enteral nutrition. Infants with gastroschisis have reduced fasting and stimulated levels of GLP-2 production in the initial weeks of life; when they do begin to tolerate feeds there seem to be a phase of hyper responsiveness.[28] Given that infants with gastroschisis are at an increased risk of developing long-term intestinal failure, it is reasonable to use GLP-2 as a therapy to improve gut function in this population.[2,29]

Thus, the mechanism of action of GLP-2 is to stimulate an organ-specific increase in intestinal mucosal crypt cell proliferation, which in turn increases villus height, intestinal length, and the surface area available for nutrient absorption. An improved understanding of the biology of GLP-2 in controlling adaptation and intestinal growth in human patients should be useful in planning a dietary support for pediatric patients with SBS, and for planning future studies using GLP-2 ligands as a direct therapy for improving nutrient absorption postresection.

Assessment of nutrient absorptive capacity

The day-to-day clinical management of patients with SBS is largely based on empiric observations of well-being, abdominal distension, and stool output.[30-32] These methods are reasonably adequate for the ongoing monitoring within a specific patient, but they do not allow for comparisons between patients or predictive quantification of absorptive capacity. The general parameters that have been used to monitor SBS are outlined in Table 1, and will be reviewed here. Many of these methods are readily available in clinical