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Novel Agents in the Treatment of Intestinal Failure: Humoral Factors

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Modalities to care for patients who suffer from intestinal failure comprise 2 basic approaches: supportive care and interventions that promote the normal adaptive process of the gastrointestinal tract. During this adaptation, the gastrointestinal tract and other organs release a number of humoral factors, which are critical to promote increased intestinal growth and function. The 3 lectures, summarized below, discuss 3 of the more well-known factors: human growth hormone, epidermal growth factor, and glucagon-like peptide-2. Details regarding these factors will be discussed in the remainder of this section. In addition, a variety of other factors possess similar trophic activity and may have great functional relevance in the adaptive process. This summary will briefly discuss factors involved in the process of short bowel syndrome (SBS) adaptation and where future directions will go in taking these factors toward clinical usage.

Introduction

An increasing number of factors have been identified that can promote epithelial growth, increase epithelial absorptive function, and affect intestinal growth (Table 1). This section highlights 3 of the most well-described of these factors: glucagon-like peptide 2 (GLP-2), epidermal growth factor (EGF), and human growth hormone (GH). As an introduction to these state-of-the-art lectures, below is a brief introduction to humoral growth factors and several points which must be taken into consideration before the usage of these factors in a clinical setting.

Short Bowel Syndrome Adaptation

The process of SBS adaptation has been well-appreciated by investigators for over 100 years.^{1,2} The essential components to the process include an increase in nutrient, electrolyte, and fluid absorption. This is carried out by both physical, as well as functional, changes to predominately the small and the large bowel. Although all layers of the intestine are involved, the predominant changes occur in the mucosa. The end-result is an expansion in mucosal surface area via increases in the number of epithelial cells, villus length, crypt depth, and number of microvilli per epithelial cell. Functionally, there is an increase in substrate transport across the mucosal surface during the adaptive process. While a predominant modality driving this effect is epithelial cell proliferation, other factors are required. There is a remodeling of the crypt-villus architecture. A key observation regarding this was the finding of an increase in epithelial cell apoptosis, during the early phase of adaptation.³ Precisely how the intestine “senses” the loss of intestinal length has not been determined, however, very rapidly a number of humoral factors are released either locally or distantly that act to carry out this adaptive process. Additionally, the marked villus lengthening observed in rodent models of SBS⁴ are

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not classically observed during the adaptive process in human SBS.⁵ Thus, translating observations of adaptation from animal models to humans may not demonstrate the same observed actions—emphasizing the need for a greater understanding of normal human adaptation with SBS, and a critical selection of outcome measures for future clinical trials. The 3 subsequent articles detail the actions of glucagon-like peptide 2, epidermal growth factor, and growth hormone. Below is a summary of these articles, as well as a discussion of issues that must be considered in the development of future clinical studies of humoral factors in the treatment of SBS.

Humoral Factors After Formation of SBS

The large number of factors that promote intestinal epithelial cell growth, and the marked redundancy of the system, clearly emphasizes the importance of this action (Table 1). The appreciation that the system is truly redundant is best shown by demonstrating normal intestinal development with the production of IGF-1, IGF-1 receptor, or IGF-2 knockout mice.⁶ An important question regarding the role of these humoral factors during adaptation is what happens to levels of these factors post-resection? Interestingly, the expression of some of these factors has been shown to decrease, including the finding that GH levels are depressed in many SBS patients.⁷ Whereas many other humoral factors are markedly increased after the development of SBS, including IGF-1, KGF, GLP-1 and 2, and EGF,^{8–12} it appears that levels of some of these factors may help predict the clinical status of SBS patients. SBS patients with failure to thrive have been correlated to lower IGF-1 levels.¹³ Further the levels of GLP-2 have been correlated with the ability to wean infants off of TPN.¹⁴ As nicely illustrated in the article by Jeppesen, using exogenous delivery of humoral factors, the gastrointestinal tract appears to have the potential to further adaptation beyond that mediated by the normal adaptive process (refer to Figure 1 in Jeppesen article).

The Effect of Multiple Factors

Although each of the subsequent articles deals predominately with single humoral growth factors, this strategy clearly does not replicate the normal adaptive process, whereby a number of these factors are simultaneously expressed. The combination of growth factors, or growth factors and enteral factors, may have a greater effect than isolated factors. This is well-illustrated by the studies of Iannoli et al, in which a combination of GH and EGF were given in a rabbit SBS model.^{15,16} In these studies, the combination of these two growth factors led to a greater increase in microvillus height and enhanced nutrient transport than could be achieved by either single factor. Additionally, although the administration of either GH or EGF had no benefit in promoting villus hypertrophy, the combination improved enterocyte function.¹⁶ This additive effect of factors may help to explain the lack of observed action in some reports.¹⁷

Additionally, enteral factors (see section on Novel Luminal Factors) may also work in conjunction with humoral growth factors to augment the adaptive process. In a study by Ziegler et al, the combination of glutamine (GLN) and IGF-1 was examined in rats.¹⁸ In this study, adaptation was increased (as measured by DNA content) with either agent. However, the combination of both factors had an additional benefit of synergistically increasing the plasma levels of IGF-1 above those found in non-resected rats. Similarly, Zhou et al showed that a combination of fiber and GH can also act synergistically to improve SBS adaptation.¹⁹

Humoral Factor Articles

At the Intestinal Failure Workshop associated with this supplement, Dr. Brad Warner nicely details the decade-long effort by his laboratory to better understand the role EGF has on small bowel adaptation. The finding that salivary EGF is the dominant source of EGF for SBS

adaptation suggests that the mode of EGF delivery may have importance—particularly since they observed no concomitant increase in serum levels of EGF. Such findings suggest that EGF may have a greater role via an enteral route. This remains somewhat controversial, as Goodlad et al have suggested that EGF may have its greatest effects via the intravenous route.²⁰ In addition to demonstrating that EGF is increased in a mouse SBS model, these authors have nicely shown that receptors to EGF (EGFR and another EGFR family member ErbB2 [c-neu]) increased significantly in this model. The distribution of these receptors was quite interesting, being found predominantly in the crypt of the mucosa, but as well within the muscularis of the gut wall. The article nicely details the importance of EGFR signaling in the adaptive process and emphasizes the fact that a number of other trophic factors, including TNF- α , may mediate their action via EGFR signaling. Emphasizing this latter point is the fact that SBS adaptation is markedly impaired in an EGFR null mouse—the waved-2 mutation. Additionally, the mechanism by which the action of EGF is mediated may go beyond induction of proliferation, but also includes a modulation of the expression of bcl-2 proteins, to reduce the rate of apoptosis.

Dr. Jeppesen has led the way in the examination of the clinical efficacy of GLP-2 in patients with SBS. Two clinical studies in adult SBS patients show extremely encouraging results. In a non-masked study of 8 SBS patients, a number of positive effects of GLP-2 were noted.²¹ These patients lacked a distal small bowel and colon and thus had very little endogenous GLP-2 and were without the normal post-prandial elevation in GLP-2 levels. Nutrient absorption was carefully measured in this study and was found to increase by 3.5%. A significant increase in protein absorption, and a nonsignificant increase in carbohydrate absorption, was noted; however, no significant change was found in fat absorption. Morphometric analysis of the small intestine demonstrated an increase in villus height and crypt depth in the majority of their patients. In a follow-up study of 10 SBS patients using the dipeptidyl peptidase IV resistant recombinant human GLP-2 analog, teduglutide, for a 21-day period, similar increases in wet nutrient absorption were noted; however, intestinal energy absorption was not found to be significant. Results of an on-going multi-institutional study of this agent should provide critical information on the clinical applicability of this agent.

Dr. Scolapio nicely reviewed the clinical literature which has studied the use of human GH in patients with SBS. As he points out, of the 5 clinical studies performed, 3 controlled trials failed to show efficacy and 2 trials (one controlled the other uncontrolled) showed efficacy. The perceived weight gain in some of these patients was due to extracellular water accumulation as opposed to actual anabolism, which emphasizes the importance of detailed measurements of nutrient absorption in the performance of these trials. The benefits of GH in the two latter studies maintain the possibility that GH may have clinical applications. The fact that human GH is the only FDA approved drug emphasizes the importance of his review, and all clinicians considering use of this agent should carefully read this section.

Considerations for Clinical Application of Humoral Factors

The subsequent articles deliver a state of the art lecture on the current application of these factors to the clinical setting. Clearly, bringing the use of these factors to the clinical setting has finally come to fruition with the FDA approval of human GH in the treatment of patients with SBS and advancement of human trials for GLP-2. Still, there are numerous areas which need to be addressed. Little attention has been directed to the pediatric SBS patient in many of these studies—a group which bears some of the highest rates of morbidity and mortality.^{22–24} Additionally, several other growth modulating factors may also be applicable for clinical study—including KGF, EGF, and HGF—with only EGF having undergone a Phase I trial.²⁵ One obstacle to the use of many of these factors is the small targeted population, which may

have little appeal for many pharmaceutical companies. Another obstacle is the fact that some of these factors (eg, EGF) no longer have an active patent.

Another consideration is defining what outcome measures should be used to determine clinical efficacy. As noted previously, humans do not show the marked degree of villus hypertrophy observed in rodents, dogs, and other laboratory animals. Additionally, some humoral factors may be efficacious on one aspect of adaptation, but not others. Finally, some of these “growth” factors have many other properties including anti-apoptotic effects and anti-oxidative injury actions, which have not been routinely examined in many clinical trials.^{26–28} Thus, a negative effect may be due to selecting an incorrect or non-applicable outcome measure. It is also important to consider that humoral factors may have much less efficacy in already established SBS patients. Finally, it is possible that a lack of observed efficacy may be due to a deficiency of another enteral or humoral factor that acts synergistically with the factor being studied (eg, use of GH with glutamine and a modified enteral diet).

Potential Risks with the Usage of These Factors

Another potential obstacle to bringing humoral factors to clinical usage is the fear that use of agents which promote epithelial growth may lead to inappropriate levels of proliferation, or potentially carcinomatous changes, either within the gastrointestinal tract or elsewhere. Clearly, agents such as EGF have been shown to promote growth of several tumor lines; and the ErbB receptors for EGF have been closely linked to the invasiveness of breast carcinoma.²⁹ A recent publication has also implicated high endogenous serum levels of insulin and IGF-I to the presence and advancement of adenomatous colonic polyps.³⁰ Thus, caution must be exercised with the use of some of these agents, particularly on a long-term nature. Additionally, many of these factors, including IGF-1, KGF, IL-11, and EGF, can also promote epithelial proliferation outside of the gastrointestinal tract. As an example, early trials of KGF for treatment of mucositis in patients receiving chemotherapy have been associated with development pancreatitis and airway narrowing due to the epithelial proliferative response.³¹

Another critical question is how long an individual must remain on these growth factors. In Jeppesen’s studies, the patients were treated for no more than 5 weeks. Although clinical benefit was observed, it is not known whether these benefits (increased nutrient absorption and villus hypertrophy) remain after termination of GLP-2. In the studies by Byrne et al, long-lasting effects were noted (40% remained off TPN at 1 year); however, these studies did involve more than just a humoral factor—including optimization of enteral feeding and glutamine supplementation as well.³² In studies of GH alone, the improvement in nutrient absorption was lost after the drug was discontinued.³³ Thus, it is possible that the decision to use humoral factors in SBS patients may commit such patients to life-long therapy with these agents.

Finally, one must consider the great costs that many of these factors will contribute to the overall care of SBS patients. Clearly, one would want to see not just a measurable improvement with the use of these factors, but a true ability to impact on cost-reduction before advocating for the wide-spread usage of these drugs. Nevertheless, as pointed out by Dr. Warner at the Intestinal Failure Workshop, even a 5% reduction in the usage of TPN by SBS patients could result in a 50 million dollar annual reduction in health-related costs.

In conclusion, a growing number of humoral growth factors have been shown to have the potential to augment intestinal adaptation in patients suffering from SBS. Recent clinical trials offer the potential of a new modality to care for such patients. Selection of appropriate patients for these new therapies, and ensuring efficacy of these factors will be important objectives over the next several years.

References

1. Flint JM. The effect of extensive resections of the small intestine. *Bull Johns Hopkins Hosp* 1912;23:127.
2. Monari. *Beitr Z Klin Chir* 1896;16:479.
3. Helmrath MA, Erwin CR, Shin CE, Warner BW. Enterocyte apoptosis is increased following small bowel resection. *J Gastrointest Surg* 1998;2:44–49. [PubMed: 9841967]
4. Reynell P, Spray G. Small intestinal function in the rat after massive resections. *Gastroenterology* 1956;31:361. [PubMed: 13365843]
5. Porus R. Epithelial hyperplasia following massive small bowel resection in man. *Gastroenterology* 1965;48:753–757. [PubMed: 14300172]
6. Wolf E, Dramer R, Blum W, Foll J, Brem G. Consequences of postnatally elevated insulin-like growth factor-II in transgenic mice: endocrine changes and effects on body and organ growth. *Endocrinology* 1994;135:1877–1886. [PubMed: 7525257]
7. Nucci AM, Reyes J, Yaworski JA, Mazariegos G, Beserock N, Barksdale EM Jr. Serum growth factors and growth indices pre-and post-pediatric intestinal transplantation. *J Pediatr Surg* 2003;38:1043–1047. [PubMed: 12861535]
8. Iannoli P, Miller JH, Ryan CK, Gu LH, Ziegler TR, Sax HC. Human growth hormone induces system B transport in short bowel syndrome. *J Surg Res* 1997;69:150–158. [PubMed: 9202662]
9. Yang H, Wildhaber BE, Teitelbaum DH, Harry M. Vars Research Award. Keratinocyte growth factor improves epithelial function after massive small bowel resection. *JPEN J Parenter Enteral Nutr* 2003;27:198–206. [PubMed: 12757114]discussion 206–207.
10. Yang H, Antony PA, Wildhaber BE, Teitelbaum DH. Intestinal intraepithelial lymphocyte $\gamma\delta$ -T cell-derived keratinocyte growth factor modulates epithelial growth in the mouse. *J Immunol* 2004;172:4151–4158. [PubMed: 15034027]
11. Stern LE, Falcone RA Jr, Kemp CJ, Braun MC, Erwin CR, Warner BW. Salivary epidermal growth factor and intestinal adaptation in male and female mice. *Am J Physiol Gastrointest Liver Physiol* 2000;278:G871–G877. [PubMed: 10859216]
12. Jeppesen PB, Hartmann B, Thulesen J, Hansen BS, Holst JJ, Poulsen SS, Mortensen PB. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon. *Gut* 2000;47:370–376. [PubMed: 10940274]
13. Barksdale EM Jr, Koehler AN, Yaworski JA, Gardner M, Reyes J. Insulin-like growth factor 1 and insulin-like growth factor 3: indices of intestinal failure in children. *J Pediatr Surg* 1999;34:655–661. [PubMed: 10359158]discussion 661–662.
14. Sigalet D, Martin G, Meddings J, Hartman B, Holst J. GLP-2 levels in infants with intestinal dysfunction. *Pediatr Res* 2004;56:1–6. [PubMed: 15152053]
15. Iannoli P, Miller JH, Sax HC. Epidermal growth factor and human growth hormone induce two sodium-dependent arginine transport systems after massive enterectomy. *JPEN J Parenter Enteral Nutr* 1998;22:326–330. [PubMed: 9739038]
16. Iannoli P, Miller J, Ryan C, Gu L, Ziegler TR, Sax HC. Epidermal growth factor and human growth hormone accelerate adaptation after massive enterectomy in an additive, nutrient-dependent, and site-specific fashion. *Surgery* 1997;122:721–729. [PubMed: 9347848]
17. Vanderhoof JA, Kollman KA, Griffin CA. Growth hormone and glutamine do not stimulate intestinal adaptation following massive small bowel resection in the rat. *J Pediatr Gastro Nutr* 1997;25:327–331.
18. Ziegler T, Mantell M, Chow J, Rombeau J, Smith R. Gut adaptation and the insulin-like growth factor system: regulation by glutamine and IGF-I administration. *Am J Physiol* 1996;271:G866–875. [PubMed: 8944702]
19. Zhou X, Li YX, Li N, Li JS. Effect of bowel rehabilitative therapy on structural adaptation of remnant small intestine: animal experiment. *World J Gastroenterol* 2001;7:66–73. [PubMed: 11819735]
20. Goodlad RA, Wilson TJ, Lenton W, Gregory H, McCullagh KG, Wright NA. Intravenous but not intragastric urogastrone-EGF is trophic to the intestine of parenterally fed rats. *Gut* 1987;28:573–582. [PubMed: 3110021]

21. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, Tofteng F, Poulsen SS, Madsen JL, Holst JJ, Mortensen PB. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon [see comment]. *Gastroenterology* 2001;120:806–815. [PubMed: 11231933]
22. Coran AG, Spivak D, Teitelbaum DH. An analysis of the morbidity and mortality of short-bowel syndrome in the pediatric age group. *Eur J Pediatr Surg* 1999;9:228–230. [PubMed: 10532263]
23. Teitelbaum D, Drongowski R, Spivak D. Rapid development of hyperbilirubinemia in infants with the short bowel syndrome as a correlate to mortality: Possible indication for early small bowel transplantation. *Trans Proc* 1996;28:2677–2678.
24. Spencer A, Safran J, Neeaga A, Brown P, Btaiche I, Teitelbaum D. Mortality and outcomes of pediatric short bowel syndrome: redefining predictors of success. *Ann Surg* 2005;242:1–10. [PubMed: 15973094]
25. Sigalet DL, Martin GR, Butzner JD, Buret A, Meddings JB. A pilot study of the use of epidermal growth factor in pediatric short bowel syndrome. *J Pediatr Surg* 2005;40:763–768. [PubMed: 15937810]
26. Jonas C, Gu L, Nkabyo Y, Mannery Y, Avissar N, Sax HC, Jones D, TR Z. Glutamine and KGF each regulate extracellular thiol/disulfide redox and enhance proliferation in Caco-2 cells. *Am J Physiol* 2003;285:R1421–R1429.
27. Wildhaber BE, Yang H, Teitelbaum DH. Keratinocyte growth factor decreases total parenteral nutrition-induced apoptosis in mouse intestinal epithelium via Bcl-2. *J Pediatr Surg* 2003;38:92–96. [PubMed: 12592627]
28. Helmrath MA, Shin CE, Erwin CR, Warner BW. The EGF/EGF-receptor axis modulates enterocyte apoptosis during intestinal adaptation. *J Surg Res* 1998;77:17–22. [PubMed: 9698526]
29. Spencer K, Graus-Porta D, Leng J, Hynes N, Klemke R. ErbB2 is necessary for induction of carcinoma cell invasion by ErbB family receptor tyrosine kinases. *J Cell Biol* 2000;148:385–397. [PubMed: 10648571]
30. Schoen R, Weissfeld J, Kuller L, Thaete F, Evans R, Hayes R, Rossen C. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. *Gastroenterology* 2005;129:464–475. [PubMed: 16083703]
31. Farrell C, Rex K, Chen J, Bready J, DiPalma C, Kaufman S, Rattan A, Scully S, Lacey D. The effects of keratinocyte growth factor in preclinical models of mucositis. *Cell Proliferation* 2002;1:78–85. [PubMed: 12139710]
32. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. *Ann Surg* 1995;222:243–254. [PubMed: 7677455]discussion 254–255.
33. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study [see comment]. *Gastroenterology* 2003;124:293–302. [PubMed: 12557135]
34. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, Tofteng F, Poulsen SS, Madsen JL, Holst JJ, Mortensen PB. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. *Gastroenterology* 2001;120:806–815. [PubMed: 11231933]
35. Tsai C, Hill M, Drucker D. Biological determinants of intestinotrophic properties of GLP-2 in vivo. *Am J Physiol* 1997;272:G662–G668. [PubMed: 9124589]
36. Drucker D, Ehrlich P, Asa SL, Brubaker P. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci U S A* 1996;93:7911–7916. [PubMed: 8755576]
37. Boismenu R, Chen Y, Havran WL. The role of intraepithelial $\gamma\delta$ T cells: a gut-feeling. *Microbes Infect* 1999;1:235–240. [PubMed: 10801235]
38. Johnson W, DiPalma C, Ziegler T, Scully S, Farrell C. Keratinocyte growth factor enhances early gut adaptation in a rat model of short bowel syndrome. *Vet Surg* 2000;29:17–27. [PubMed: 10653491]
39. Xia G, Martin A, Michalsky M, Besner G. Heparin-binding EGF-like growth factor preserves crypt cell proliferation and decreases bacterial translocation after intestinal ischemia/reperfusion injury. *J Ped Surg* 2002;37:1081–1087.

40. Sukhotnik I, Yakirevich E, Coran AG, Siplovich L, Krausz M, Hirsh M, Sabo E, Shiloni E. Effect of transforming growth factor- α on intestinal adaptation in a rat model of short bowel syndrome. *J Surg Res* 2002;108:235–242. [PubMed: 12505047]
41. Falcone RAJ, Stern LE, Kemp CJ, Erwin CR, Warner BW. Intestinal adaptation occurs independent of transforming growth factor α . *J Ped Surg* 2000;35:365–370.
42. Drucker D. Epithelial cell growth and differentiation I. Intestinal growth factors *Am J Physiol* 1997;273:G3–G6.
43. Liu Q, Du XX, Schindel DT, Yang ZX, Rescorla FJ, Williams DA, Grosfeld JL. Trophic effects of interleukin-11 in rats with experimental short bowel syndrome. *J Pediatr Surg* 1996;31:1047–1050. [PubMed: 8863231]discussion 1050–1051.
44. Fiore NF, Ledniczky G, Liu Q, Orazi A, Du X, Williams DA, Grosfeld JL. Comparison of interleukin-11 and epidermal growth factor on residual small intestine after massive small bowel resection. *J Pediatr Surg* 1998;33:24–29. [PubMed: 9473093]
45. de Miguel E, Gomez de Segura IA, Bonet H, Rodriguez Montes JA, Mata A. Trophic effects of neurotensin in massive bowel resection in the rat. *Dig Dis Sci* 1994;39:59–64. [PubMed: 8281868]
46. Schlemminger R, Lottermoser S, Sostmann H, Kohler H, Nustede R, Schafmayer A. [Metabolic parameters and neurotensin liberation after resection of the small intestine, syngeneic and allogeneic segment transplantation the rat]. *Langenbecks Archiv fur Chirurgie* 1993;378:265–272. [PubMed: 8412434]
47. Andrews NJ, Irving MH. Human gut hormone profiles in patients with short bowel syndrome. *Dig Dis Sci* 1992;37:729–732. [PubMed: 1563315]
48. Mannon P. Peptide YY as a growth factor for intestinal epithelium. *Peptides* 2002;23:383–388. [PubMed: 11825653]
49. Wu X, Spies M, Chappell V, Herndon D, Thompson J, Wolf SE. Effect of bombesin on gut mucosal impairment after severe burn. *Shock* 2002;18:518–522. [PubMed: 12462559]
50. Alexander AN, Carey HV. Oral IGF-I enhances nutrient and electrolyte absorption in neonatal piglet intestine. *Am J Physiol* 1999;277:G619–G625. [PubMed: 10484387]
51. O'Brien DP, Nelson LA, Williams JL, Kemp CJ, Erwin CR, Warner BW. Selective inhibition of the epidermal growth factor receptor impairs intestinal adaptation after small bowel resection. *J Surg Res* 2002;105:25–30. [PubMed: 12069497]
52. Erwin CR, Helmrath MA, Shin CE, Falcone RAJ, Stern LE, Warner BW. Intestinal overexpression of EGF in transgenic mice enhances adaptation after small bowel resection. *Am J Physiol* 1999;277:G533–G540. [PubMed: 10484377]
53. Byrne TA, Cox S, Karimbakas M, Veglia LM, Bennett HM, Lautz DB, Robinson MK, Wilmore DW. Bowel rehabilitation: an alternative to long-term parenteral nutrition and intestinal transplantation for some patients with short bowel syndrome. *Transplant Proc* 2002;34:887–890. [PubMed: 12034223]
54. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. *J Parent Enteral Nutr* 1995;19:296–302.
55. Schwartz MZ, Kato Y, Yu D, Lukish JR. Growth-factor enhancement of compromised gut function following massive small-bowel resection. *Pediatr Surg Int* 2000;16:174–175. [PubMed: 10786975]
56. Nishimura S, Takahashi M, Ota S, Hirano M, Hiraishi H. Hepatocyte growth factor accelerates restitution of intestinal epithelial cells. *J Gastroenterol* 1998;33:172–178. [PubMed: 9605945]
57. Pearson P, O'Connor D, Schwartz M. Novel effect of leptin on small intestine adaptation. *J Surg Res* 2001;97:192–195. [PubMed: 11341798]
58. Todisco A, Ramamoorthy S, Witham T, Pausawasdi N, Srinivasan S, Dickinson C, Askari F, Krametter D. Molecular mechanisms for the antiapoptotic action of gastrin. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G298–307. [PubMed: 11208554]
59. Dockray G, Varro A, Dimaline R, Wang T. The gastrins: their production and biological activities. *Annu Rev Physiol* 2001;63:119–139. [PubMed: 11181951]

Table 1**Partial Listing of Some of the More Established Humoral Factors That Promote SBS Adaptation**

Mucosal-derived humoral factors
Glucagon-like peptide 2 ³⁴⁻³⁶
Keratinocyte growth factor ^{10,37,38}
Heparin-binding epidermal growth factor-like growth factor ³⁹
Cytokines: TGF- α , ^{40,41} IL-3 ⁴² IL-11, ^{43,44} and IL-15 ⁴²
Gut peptides: Neurotensin ^{45,46} ; Peptide YY ^{47,48} ; Bombesin ⁴⁹
Insulin-like growth factor I and II (as well as distally expressed) ^{6,50}
Distantly-derived humoral factors
Epidermal growth factor (as well as locally in mucosal gland cells) ^{51,52}
Human growth hormone ^{53,54}
Heaptocyte growth factor ^{55,56}
Leptin ⁵⁷
Gastrin ^{58,59}

TGF, transforming growth factor beta; IL, interleukin.

NOTE. Actions may be via epithelial proliferation, reduction in epithelial apoptosis, and/or increase in epithelial function. Source of the factor has been separated between those derived from the small bowel versus a distal source. In many cases this distinction is difficult to make, as the factor may be derived from several sources.