Published in final edited form as:

Semin Pediatr Surg. 2010 February ; 19(1): 35–43. doi:10.1053/j.sempedsurg.2009.11.010.

Growth Factors: Possible Roles for Clinical Management of the Short Bowel Syndrome

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Abstract

The structural and functional changes during intestinal adaptation are necessary to compensate for the sudden loss of digestive and absorptive capacity after massive intestinal resection. When the adaptive response is inadequate, short bowel syndrome (SBS) ensues and patients are left with the requirement for parenteral nutrition and its associated morbidities. Several hormones have been studied as potential enhancers of the adaptation process. The effects of growth hormone (GH), insulin-like growth factor-1, epidermal growth factor and glucagon-like peptide-2 (GLP-2) on adaptation have been studied extensively in animal models. In addition, GH and GLP-2 have shown promise for the treatment of short bowel syndrome in clinical trials in humans. Several lesser studied hormones, including leptin, corticosteroids, thyroxine, testosterone and estradiol, are also discussed.

Keywords

growth factor; adaptation; enterocyte; mucosa; proliferation

Introduction

The loss of a significant amount of small bowel length leads to the short bowel syndrome (SBS), a devastating problem encountered across a wide spectrum of medical and surgical conditions. The three most common causes of SBS in children are necrotizing enterocolitis, intestinal atresias, and midgut volvulus (1,2). Following massive intestinal resection, the remnant intestine demonstrates a critical adaptation response by increasing protein, DNA content, villus height and crypt depth, thus, compensating for the loss of absorptive and digestive capacity (3–5). Several factors have been found to be important for enhancing small bowel adaptation, including: pancreaticobiliary secretions, luminal nutrients and intestinal hormones (5).

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When the adaptation response is insufficient, the ravages of SBS ensue. Intestinal length is the major predictor of survival in these patients. In adult patients with <50 cm of intestinal length, 83% will require lifelong parenteral nutrition with a 5-year mortality of approximately 25% (6). Despite the advances in our understanding of short bowel syndrome and adaptation, the overall mortality in infants with short gut syndrome remains 15–25% (6,7). With a greater understanding of the factors that influence and enhance small bowel adaptation, new therapies can be explored to alleviate the suffering from SBS.

The effects of various hormones and specific growth factors have been studied in the setting of SBS and bowel adaptation. Among these, the most widely evaluated have been growth hormone, insulin-like growth factor-1, epidermal growth factor and glucagon-like peptide-2. Other hormones including glucocorticosteroids, leptin, testosterone, and thyroxine have also been explored.

Growth hormone

Growth hormone (GH) is a 191 amino acid, single chain protein produced in the anterior pituitary gland. This growth factor is known to be a major regulator of postnatal growth in mammals as well as playing an important role in the regulation of lipid and carbohydrate metabolism (8,9). Because GH has been shown to induce growth and proliferation in many different tissues and cell lines, its role in the setting of SBS has been studied extensively. The receptor for growth hormone has been found throughout the intestine: in cells of the muscularis propria, submucosa, muscularis mucosa, lamina propria and intestinal epithelium (10). Because of its widespread distribution in the intestine, GH has been proposed to directly stimulate intestinal growth. In addition to directly stimulating growth of the intestinal layers, GH is a major stimulus for the production of insulin-like growth factor-1, another growth-inducing hormone, whose role in intestinal adaptation will be discussed below (11).

In the laboratory, results using GH as a means to enhance adaptation have been encouraging. Studies have shown mucosal hyperplasia and increased absorptive capacity above and beyond the normal adaptive response after small bowel resection (SBR) (12,13). Other studies have demonstrated increased villus height and crypt depth, positive nitrogen balance and bowel growth when rats were given GH combined with glutamine and/or a diet high in protein (14, 15). Waitzberg et al showed a trend toward taller villi in rats given GH after SBR when compared to rats given a saline placebo. However, these findings did not reach statistical significance (14). The authors concluded that the biggest driver of mucosal proliferation in this study was the protein content of the diet fed to the rats, with the rats given a high protein diet exhibiting the greatest mucosal growth regardless of the other interventions (14). This study does not discredit GH as a driver of adaptation but underscores the interplay between the many factors involved in adaptation in SBS. Another very promising observation is that GH may augment the length of the remnant intestine after SBR (16). This finding is particularly important when you consider that remnant intestinal length is the greatest predictor for long term parenteral nutrition requirement (6).

Human clinical trials with recombinant GH have had promising results. One study in patients dependent on parenteral nutrition with SBS demonstrated increased absorption of nitrogen, carbohydrates, and fat when given low-dose GH (17). These patients were not required to maintain any specific diet, but instead, were allowed to eat a typical western diet. This allowed the researchers to avoid the confounding effects of dietary influence. This is not to say that patients can not benefit from multimodality therapy involving specific dietary modifications. A study by Bryne et al demonstrated increased nutrient absorption and decreased stool output in SBS patients when high-dose GH and glutamine supplementation were paired with a high-carbohydrate, low fat diet (18). Similarly, Scolapio et al demonstrated increased electrolyte

absorption with delayed gastric emptying when patients were given GH, glutamine, and a high carbohydrate-low fat diet (19). Wu et al also reported that patients were able to be weaned off of parenteral nutrition using dietary manipulation, growth hormone and glutamine (20). They noted that growth hormone had an additive effect to the dietary manipulation and glutamine treatments with regard to the absorption of D-xylose, ¹⁵N-Gly and ¹³C-palmitic acid. Although the increased nutrient absorptive effects were not maintained once growth hormone was discontinued, patients were able to remain off of parenteral nutrition (20). Whether the gains were from the dietary or hormonal modifications is again unclear but further illustrates the promise of multi-modality therapy designed to wean patients from parenteral nutrition.

A summary of 12 clinical trials in which GH has been used is shown in Table 1. It would appear that patients with 70–100 cm of remnant bowel and without an intact colon have the greatest benefit from GH as this group had the greatest rate of complete discontinuation of parenteral nutrition. Patients with extreme SBS (<70 cm) had less success in terms of promoting complete autonomy from parenteral nutrition.

Insulin-Like Growth Factor

Insulin-like growth factor-1 (IGF-1) is a hormone produced chiefly in the liver and to a lesser degree in the gastrointestinal tract and has received a large amount of attention as an enterotrophic hormone. Like GH, IGF-1 has been promoted for its ability to enhance enterocyte proliferation after SBR (29). These observations, along with the localization of IGF-1 production, its receptor, and regulatory binding proteins to the intestine, make IGF-1 an attractive target for modulating adaptation responses (30,31).

It has been theorized that IGF-1 is the mediator of the effects attributed to growth hormone (16,20). A study comparing transgenic mice that overexpress IGF-1 and transgenic mice that overexpress GH showed that both groups had increased bowel length after SBR when compared to control mice. Furthermore, the IGF-1 transgenics exhibited a two-fold greater increase in bowel length when compared to the GH transgenics (16). In addition, the IGF-1 transgenics exhibited increased crypt cell proliferation, a unique observation not seen in the GH transgenics (16).

Both functional and structural parameters of adaptation have been shown to be amplified by IGF-1. Vanderhoof et al. found an increase in the activity of the ileal digestive enzymes sucrase, maltase and leucine aminopeptidase when IGF-1 was given after SBR (32). In rats with SBS, IGF-1 treatment allowed the rats to be weaned from parenteral nutrition (33). Rats with SBS given IGF-1 were also found to have greater body weights and increased lean body mass when compared to rats with SBS that were not given IGF-1 (33).

In addition to the effects of IGF-1 on enterocytes, our lab has revealed a possible effect of IGF-1 on the smooth muscle of the intestine. We performed SBR procedures in a transgenic mouse line that overexpresses IGF-1 specifically in smooth muscle cells (34). Our experiments demonstrated that these mice responded to SBR by increasing the length of their remnant intestine far more (approximately 2-fold) than non-transgenic control mice that also underwent SBR. Of note, these transgenic mice did not exhibit the normal adaptive response of increasing villus height and crypt depth in the early phases of adaptation. The intestinal lengthening response preceded villus growth, which was noted at later postoperative time points (34). These experiments suggest that the IGF-1 stimulus for muscular lengthening might be an important trigger for subsequent enhanced villus and crypt growth. These findings underscore the complexity of adaptation and the need to fully understand specific responses of each intestinal wall component to massive intestinal loss.

Despite the promising bench work that has been done with IGF-1, no human clinical trials with IGF-1 have been reported. The modest success seen in human trials with GH administration, coupled with the bench research showing IGF-1 as the likely mediator of GH's effects point to the need for additional translational research with IGF-1 use in SBS.

Epidermal Growth Factor

Human epidermal growth factor (EGF) is a 53 amino acid protein found in platelets, macrophages, urine, saliva, breast milk and plasma (35,36). Epidermal growth factor is a member of a family of growth factors sharing a common EGF receptor (EGFR), which also includes transforming growth factor- α (TGF- α), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, epiregulin, epigen, betacellulin, and neuregulins 1–4 (37). This growth factor has been shown to induce growth in skin, lung, tracheal, corneal, and gastrointestinal epithelium (38). Epidermal growth factor has also been shown to be important in the healing of gastric ulcers and surgical wounds and for maintaining the normal architecture of the intestine (39,40).

A significant body of experimental evidence exists to support an important role for EGF in small bowel adaptation after intestinal resection (see Table 2 and reviewed in reference (49)). After a 50% small bowel resection, our lab was able to demonstrate increased levels of EGF in the saliva and reduced levels of EGF in the urine of mice (50). These findings are consistent with increased gut utilization of salivary-derived EGF during adaptation. We also found that mice that underwent SBR had a two-fold increase of EGFR expression in crypts compared to sham animals. The area of the crypt most affected was the zone of cell proliferation which supports the hypothesis that EGFR signaling is involved in the mitogenic stimulus of adaptation (51). Along these lines, Avissar, et al found that the EGFR is redistributed to the brush border membrane from the basolateral membrane in the intestinal mucosa of rabbits after SBR (52).

After finding that levels of EGF and EGFR increase after bowel resection, we tested whether administering exogenous EGF would augment the adaptation response. When given after SBR, we showed that EGF promotes adaptation at the cellular level by stimulating messenger RNA, DNA, and protein synthesis, at the microscopic level by increasing villus height and crypt depth, and at the macroscopic level by increasing animal weight, intestinal wet weight and bowel length (41,48,53). Further, we found that the most beneficial effect of EGF required a specific dose via oral gavage (54). We also found that administration of this growth factor was effective for enhancing adaptation only if given immediately following SBR and had minimal effect if administered after resection-induced adaptation had hit a plateau. Delay in the initiation of growth factor treatment may therefore account for the modest clinical outcomes using other growth factors in other reports. We further promoted EGF signaling by developing a transgenic mouse strain with increased EGF expression specifically in intestinal enterocytes. After SBR, EGF transgenic mice had markedly enhanced adaptation compared to nontransgenic mice (48).

To further elucidate the role of EGF in adaptation after SBR we tested whether impairing EGF signaling would inhibit adaptation. We removed the major source of endogenous EGF in mice, the submandibular glands, and found that sialoadenectomy significantly attenuated the increase in ileal villus height usually observed after SBR. Interestingly, the effects of sialoadenectomy could be at least partially reversed with either systemic or luminal administration of EGF (38). Next we studied the adaptation response in waved-2 mice which have attenuated EGFR tyrosine kinase activity (46). We found that villus height and crypt cell proliferation in crypts were less pronounced in the waved-2 mice after SBR (46). Therefore, enhancing EGF signaling augments intestinal adaptation, while inhibiting EGF signaling retards the adaptation response.

Various hypotheses have been explored to determine the mechanism by which EGF causes increased proliferation in the small intestine. One is that EGF retards the rate of apoptosis in the intestine, thus favoring increased mucosal growth in conjunction with enhanced proliferation. Following massive SBR in mice that received orogastric EGF, we have demonstrated reduced rates of apoptosis, decreased expression of the pro-apoptotic gene *bax*, and increased expression of the anti-apoptotic gene *bcl-w*, all of which favor cell survival (55). *In vitro* studies provided further insight into the role that EGFR signaling plays in the regulation of enterocyte apoptosis. We found that EGF stimulation enhanced cell survival by attenuating *bax* and p38 mitogen-activated protein kinase activation and reducing apoptosis (56).

Though EGF alone is known to enhance adaptation, several studies have examined synergistic effects of EGF and other agents to further enhance adaptation. Known enterotrophic factors like interleukin-11, neurotensin, and bombesin have all been shown to further enhance the effects of EGF on small bowel adaptation (44,45,57). Glutamine is often given to patients with short bowel syndrome because it is an important fuel for enterocytes. Jacobs, et al found that animals treated with both glutamine and EGF tended to have increased sucrase activity relative to controls, and had a significant increase in small-bowel mucosal protein and thickness relative to controls (58). Although somatostatin has been found to have a detrimental effect on intestinal adaptation when given alone, when given with EGF, it has been found to enhance the adaptation response of the remaining intestine after SBR in rats (59). Our lab showed that giving both an anti-apoptotic (pan-caspase inhibitor) and pro-proliferative (EGF) stimulus maximized intestinal adaptation after SBR (60).

Glucagon-like peptide-2

Glucagon-like peptide-2 (GLP-2), a growth hormone closely related to glucagon, is another well-studied intestinotrophic factor. This growth factor is a member of the PACAP (Pituitary adenylate cyclase activating peptide) glucagon superfamily and is synthesized in enteroendocrine L cells of the distal ileum and proximal colon (61,62). Within this 33 amino acid protein, the second amino acid in the sequence is alanine, which makes the hormone sensitive to degradation by the exopeptidase dipeptidyl peptidase-4 (DPP-IV) (63,64). Substitution of glycine for alanine at position two makes a synthetic analog of GLP-2 that is resistant to enzymatic degradation and significantly extends its half-life (65).

Glucagon-like peptide-2 exerts its effects through the GLP-2 receptor (GLP-2R), which has been identified on intestinal enteroendocrine cells, enteric neurons, and subepithelial myofibroblasts (66–68). Secretion of GLP-2 by intestinal L cells is driven by both direct stimulation of nutrients in the distal bowel and vagally-mediated pathways, which are activated by the presence of nutrients in the proximal bowel (69). Ingestion of nutrients, particularly long-chain fatty acids, plays a major role in GLP-2 secretion as levels of GLP-2 have been found to increase within minutes of a meal (70). In patients with SBS, the presence of a colon in continuity with the small intestine is important for nutrient-stimulated increases in GLP-2 (71,72). This finding may help explain why presence of the colon reduces the likelihood that an individual with SBS will require parenteral nutrition.

The enterotrophic effects of GLP-2 were first discovered when patients with glucagon-producing tumors were found to have small bowel hyperplasia (73). GLP-2 was confirmed as the mediator when glucagonoma tumor extracts were injected into mice, subsequently stimulating intestinal hyperplasia (74). The intestinal effects of GLP-2 have been studied both in animal models and in human clinical trials. When given to rodents, GLP-2, stimulates intestinal mucosal growth (75,76). Specifically, GLP-2 administration leads to elongated intestinal villi and crypts, in association with augmented crypt proliferation and attenuated apoptosis. While these effects are most pronounced in the small intestine, higher doses of

GLP-2 will lead to increased mucosal thickness in the colon (77). Although conflicting data exist, GLP-2 seems to improve glucose absorption in the gut (78). Other effects mediated by GLP-2 include reduced gastric motility, inhibited gastric acid secretion, and increased mesenteric blood flow (79–81). GLP-2 also acts on the enteric nervous system which may play a key role in its ability to stimulate mucosal growth. After administration of GLP-2, cellular changes occur in the enteric neurons before the intestinal crypts, suggesting that many of the effects of GLP-2 may be mediated by the enteric nervous system (62).

The above findings led researchers to investigate the effects of GLP-2 on animals with short bowel syndrome. Following massive intestinal resection in rats, serum levels of GLP-2 were found to increase (81,82). In addition, administering GLP-2 to rodents after small bowel resection augments parameters of intestinal adaptation including: crypt cell proliferation, expression of transport proteins and digestive enzymes, nutrient absorption, villus height, crypt depth, microvillus height, and mucosal DNA and protein content (83–85). Importantly, GLP-2 supplementation is capable of inducing intestinal adaptation in rats maintained on total parenteral nutrition, even in the absence of enteral nutrition (86). Recently, GLP-2 was found to cause crypt stem cell expansion when given immediately after SBR in mice (87). Interestingly, similarly to EGF, the timing of GLP-2 administration was crucial as giving it 6 weeks after SBR did not result in stem cell expansion (87). Although most of the data on GLP-2 as a therapy for SBS is encouraging, its administration to juvenile piglets after SBR led to impaired weight gain and reduced adaptive parameters (88). Clearly further study is needed before GLP-2 based therapies are applied to children with SBS.

There is an increasing body of evidence that GLP-2 protects the intestine against a variety of inflammatory states, including chemical-, chemotherapy-, and irradiation-induced enteritis (78–81). Vasoactive Intestinal Peptide (VIP) has been shown to mediate the protective effects of GLP-2, vis-à-vis the enteric nervous system (79). Finally, GLP-2 treatment has been shown to ameliorate ischemia-reperfusion injury in the gut (89).

Many clinical trials in humans have yielded encouraging results (Table 3). An earlier study treated 8 patients with SBS and no colon with GLP-2 for 5 weeks (92). Following treatment, the patients had improved nutrient absorption, increased body weight, increased gastric emptying, and enhanced histologic markers of adaptation from jejunostomy biopsy specimens (crypt depth and villus height)(92). Interestingly, patients treated with GLP-2 were also found to have improved vertebral bone mineral density scores suggesting calcium absorption may be enhanced (91).

While the half-life of exogenous GLP-2 is merely 7 minutes, the half-life of the synthetic analogue teduglutide is much longer allowing it to be injected subcutaneously as a once or twice daily dose (93). Teduglutide has repeatedly been found to be safe and well tolerated (65,96). In a phase II trial teduglutide administration increased intestinal wet weight absorption, decreased fecal wet weight excretion, and increased urine output (65). In patients with an end jejunostomy available for biopsy, teduglutide improved parameters of adaptation, including villus height, crypt depth, and mitotic index. Teduglutide therapy also improved quality of life and overall parameters of mental health (95). In a randomized, placebo-controlled phase III trial low-dose teduglutide reduced parenteral nutrition requirements compared to placebo. Although teduglutide initially required several subcutaneous injections each day, recent reports show efficacy when given once a day (96). Overall GLP-2 seems promising as a therapy for patients with SBS. However, further studies with larger cohorts are needed before it can be accepted as a standard of care. In addition, GLP-2's future for treating the pediatric population is particularly uncertain.

Other hormones

Glucocorticosteroids (GC) are a diverse group of hormones synthesized by the adrenal gland and regulated by feedback loops in the hypothalamic-pituitary-adrenal axis. In humans, the primary glucocorticosteroid is cortisol, but others are synthesized at varying levels. Glucocorticoids act on their specific receptors, which are located in the cytoplasm of many tissues. After ligand binding, the receptor translocates to the nucleus and acts predominantly as a stimulatory transcription factor (97). Glucocorticoids also alter signal transduction pathways, leading to the activation of adenylate cyclase and a resultant increase in cyclic AMP. This action is of particular interest because many growth factors, including GLP-2, act through G-protein-coupled receptors that exert their action through the activation of adenylate cyclase (98,99). Since GC's are known to have an additive effect on a variety of hormonal actions, including those of GH, TSH, and catecholamines, GC's represent an attractive target for further research into the efficacy of multimodal treatment protocols for short-bowel syndrome (100). Currently, there is little clinical data on the efficacy of GC's as treatment for short-bowel syndrome, but the possibility exists that GC's may potentiate the effects of other hormones in the induction of adaptation following massive SBR and be an important addition to multi-modality therapy.

Several other hormones warrant mention in the discussion of intestinal adaptation following SBR. It has been shown that a transient state of hypothyroidism is present following massive SBR (101). In rats, administration of exogenous thyroid hormone during this state enhances the adaptive process, quantified by increases in villus height, crypt depth, and proliferative processes (102).

Leptin, a hormone produced by adipocytes that is involved primarily in the regulation of metabolism and appetite, has been shown to participate in the regulation of the adaptive response in mice. Leptin-deficient mice show decreased enterocyte proliferation following SBR, and exogenous leptin administration appears to augment morphological changes seen in the normal adaptive response to SBR (103,104).

In castrated mice, the adaptive response to SBR is diminished, and exogenous testosterone eliminates this effect, indicating that testosterone may be necessary for normal intestinal adaptation to SBR (105). In the same study, however, estradiol did not show the same effects as testosterone on resection-induced adaptation.

Conclusion

When bowel adaptation is insufficient patients with short gut syndrome require parenteral nutrition to meet their caloric requirements. Parenteral nutrition is expensive and fraught with complications including line sepsis, venous thrombosis, and volume overload. Long term parenteral nutrition can ultimately lead to cholestatic liver failure necessitating liver transplantation. The average, estimated cost of parenteral nutrition is \$100,000 to \$150,000 per year per patient with newer data showing that pediatric patients receiving parenteral nutrition incur yearly cost ranging from \$70,000 to \$390,000 (106–108). With approximately 20,000 people in the United States receiving home parenteral nutrition, even a modest 10% reduction in the number of patients requiring parenteral nutrition would equal a yearly savings of \$140,000,000 to \$780,000,000 (109).

Hormonal modulation to enhance small bowel adaptation has had some very promising results. With the ultimate goal of reducing the number of patients on parenteral nutrition in mind, the efficacy of growth factor therapy to enhance the native adaptive response as a part of multi-modality therapy cannot be denied. All of the major hormones discussed were effective at enhancing intestinal adaptation in animal studies. Human trials with GH and GLP-2 have also

shown promise in SBS patients. A recent randomized, placebo controlled clinical trial with the long-acting analog of GLP-2, teduglutide, has been encouraging for its ability to reduce dependence on parenteral nutrition. This is perhaps the most promising example of laboratory results translating to direct benefits in patients with SBS. These findings shine a ray of hope on the many other hormones whose role in adaptation are only beginning to be understood. They point the way forward for further scientific inquiry into our ever-evolving understanding of the adaptation response.

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Table 1
Effects of GH therapy alone or with other agents on human small intestinal function in SBS patients

Study	n	Mean age	GH dose (mg/kg)	Treatment duration	Glutamine	Modified diet	Morphological change	Absorption change	note
Byrne et al. (21)	10	43 yrs	0.14	3–4 weeks	Yes	Yes	-	Yes	No control arm.
Byrne et al. (18)	47	46 yrs	0.14	3–4 weeks	Yes	Yes		Yes	No control arm, 40% of the treatment group weaned off PN.
Scolapio et al. (19,22)	8	48 yrs	0.14	6 weeks	Yes	Yes	No	No	Randomized, double-blind, placebo, cross-over study. Increased bodyweight
Ellegard et al. (23)	10	49 yrs	0.02	8 weeks	No	No	-	No	Randomized, double-blind, placebo, cross-over study. Increased body mass.
Szkudlarek et al. (24)	8	47 yrs	0.14	4 weeks	Yes	No	-	Yes	Randomized, double-blind, placebo, cross-over study. All patients had side effects.
Seguy et al. (17)	12	35 yrs	0.05	3 weeks	No	No	-	Yes	Randomized, double-blind, placebo, cross-over study. Increased bodyweight and mass.
Weiming et al. (25)	37	34 yrs	0.14	3 weeks	Yes	Yes	-	-	Open study. 57% weaned from TPN.
De Agustín et al. (26)	2	2 yrs	0.10	4 weeks	No	No	-	-	Case study. Increased tolerance to enteral feeding.
Velasco et al. (27)	1	6 mths	0.17	4 weeks	No	No	-	-	Case study. Weaned off PN. Decreased stool number.
Ladd et al. (28)	2	6 yrs	0.04	8.5 yrs, 3.3 yrs	Yes	No	-	-	Case study. Weaned off PN. Increased growth.

GH, growth hormone; PN, parenteral nutrition; SBS, short-bowel syndrome; TPN, total parenteral nutrition

Table 2

Effect of EGF therapy and modulation on the small intestine following resection in animal models of SBS

Study	Species	Administration route	Treatment duration (days)	Resection amount (%)	Morphological change	Proliferation	DNA/protein change	Functional increase
EGF therapy								
Chaet et al. (41)	Rat	Subcutaneous osmotic pump	150	75	Yes, increase	-	Yes, increase	-
O'Loughlin et al. (42)	Rabbit	Oral	40	66	-	No	-	Yes
Lukish et al. (43)	Rat	Subcutaneous osmotic pump	150	80	No	-	-	-
Fiore et al. (44)	Rat	Subcutaneous injection	200	85	Yes, increase	Yes	-	-
Iskit et al. (45)	Rat	Subcutaneous injection	270	75	No	-	-	-
EGF modulation								
Helmuth et al. (46)	Mouse	EGFR-deficient	-	50	Yes, decrease	-	Yes, decrease	-
Helmuth et al. (47)	Mouse	EGF-deficient	-	50	Yes, decrease	-	Yes, decrease	-
Erwin et al. (48)	Mouse	EGF-overexpression	-	50	Yes, increase	-	Yes, increase	-

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; SBS, short-bowel syndrome

Table 3

Effect of GLP-2 therapy on the small intestine following resection in clinical trials and animal models of SBS

Study	Species	GLP-2 dose	Treatment duration	Morphological change	Functional change	Other change
Washizawa et al. (83)	Rat	0.1 mg/kg, twice daily	7 days	Yes	Yes	Increase in protein and DNA content in the jejunum and ileum.
Martin et al. (84)	Rat	10 µg/kg per h	8 days	Yes	Yes	Decreased intestinal permeability.
Scott et al. (90)	Rat	0.1 µg/g/dose, twice daily	6, 14, 21 days	Yes	Yes	Restored d-xylose absorption to control levels.
Haderslev et al. (91)	Human	400 µg, twice daily	5 weeks	-	-	Increase in bone mineral density.
Jeppesen et al. (92)	Human	400 µg, twice daily	35 days	No	Yes	Weight gain. Increased relative absorption of protein.

GLP-2, glucagon-like peptide-2; SBS, short-bowel syndrome.