ANNUAL REVIEWS

Annual Review of Nutrition

Short Bowel Syndrome: A Paradigm for Intestinal Adaptation to Nutrition?

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Annu. Rev. Nutr. 2020. 40:299–321

First published as a Review in Advance on July 6, 2020

The *Annual Review of Nutrition* is online at nutr.annualreviews.org

https://doi.org/10.1146/annurev-nutr-011720-122203

Keywords

intestinal failure, parenteral nutrition, microbiota, intestinal adaptation, hyperphagia, glucagon-like peptide-2

Abstract

Short bowel syndrome (SBS) is a rare disease that results from extensive resection of the intestine. When the remaining absorption surface of the intestine cannot absorb enough macronutrients, micronutrients, and water, SBS results in intestinal failure (IF). Patients with SBS who suffer from IF require parenteral nutrition for survival, but long-term parenteral nutrition may lead to complications such as catheter sepsis and metabolic diseases. Spontaneous intestinal adaptation occurs weeks to months after resection, resulting in hyperplasia of the remnant gut, modification of gut hormone levels, dysbiosis, and hyperphagia. Oral nutrition and presence of the colon are two major positive drivers for this adaptation. This review aims to summarize the current knowledge of the mechanisms underlying spontaneous intestinal adaptation, particularly in response to modifications of luminal content, including nutrients. In the future, dietary manipulations could be used to treat SBS.

Contents

1. SHORT BOWEL SYNDROME: DEFINITION AND CAUSES

In adults, short bowel syndrome (SBS) results from an extensive resection of the small bowel, in which the bowel length is less than 150–200 cm. The colon may also be partially or completely removed. There are three types of SBS, classified on the basis of the anatomical anastomosis: jejunostomy (the ileum, the ileocecal valve, and the colon are removed and the remaining jejunum is directly anastomosed to the skin), jejunocolic anastomosis (the ileum and ileocecal valve are removed and the jejunum is joined to a part of the colon), and jejunoileal anastomosis (parts of the jejunum and the ileum are removed and the ileocecal valve and the colon remain intact) (**Figure 1**). In Europe, the estimated prevalence of SBS is 1.4 cases per 1 million people. It varies by country; for example, the prevalence of SBS in Poland is 0.4 cases per 1 million people and in Denmark it is 30 cases (57). Countries where there are no major intestinal rehabilitation centers have a lower prevalence of SBS likely because of underreporting and an inability to adequately treat these patients. Accordingly, accurate evaluations of the incidence of SBS are difficult to ascertain in the United States because of a lack of current disease registries, but approximately 3 per 1 million individuals are estimated to be affected (40). In other countries, the prevalence and incidence of SBS are unrecognized due to the absence of dedicated centers, which explains why the worldwide prevalence of SBS in adults is unknown.

The primary consequence of SBS is a marked reduction in the absorption surface of the intestine, leading to significant intestinal malabsorption, the degree of which depends on the extent

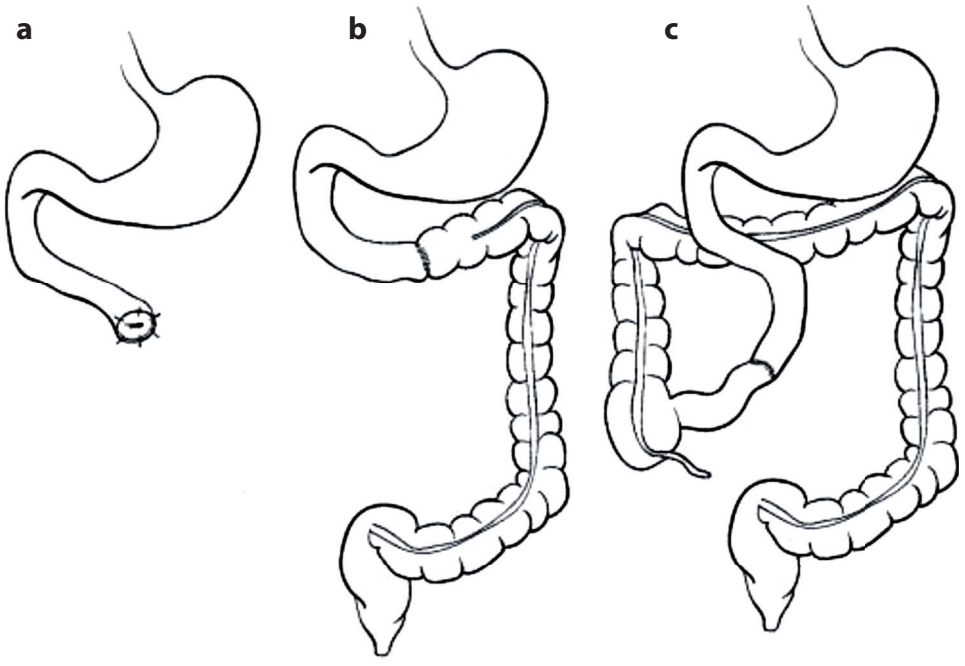

Figure 1

Three anatomical subtypes of short bowel syndrome. (*a*) Small bowel resection with high-output jejunostomy. (*b*) Small bowel resection with removal of ileum, ileocecal valve, and part of the colon, resulting in jejunocolic anastomosis. (*c*) Small bowel resection in which some ileum is preserved and the ileocecal valve and colon remain intact, resulting in jejunoileal anastomosis.

of the resection, the anatomy of the remnant bowel, the health of the remaining mucosa, and the presence of colon in continuity (109). In addition to malabsorption of macronutrients, there can be malabsorption of specific micronutrients (e.g., vitamins K, B6, and B12). The main complications resulting from such malabsorption are severe dehydration due to water–electrolyte imbalance, metabolic disorders, and a significant risk of undernutrition. In addition, SBS is responsible for an early gastric acid hypersecretion associated with hypergastrinemia, contributing to accelerated gastric emptying and aggravated loss of fecal energy and hydroelectrolytes (18).

SBS is the main cause of intestinal failure (IF), which is defined as a reduction of gut function below the minimum needed for absorption of macronutrients and/or water and electrolytes, resulting in intravenous supplementation to maintain health or growth (108). In addition to SBS, IF occurs in other gastrointestinal diseases, such as gut motility disorders, mechanical obstruction, intestinal fistula, extensive small bowel mucosal disease, and volvulus or systemic conditions such as mesenteric infarction and postradiation enteritis (65, 108). Three subtypes of SBS-associated IF are based on duration: (*a*) acute, short-term, and usually self-limiting conditions; (*b*) prolonged acute conditions, which often occur in metabolically unstable patients who require complex multidisciplinary care and intravenous supplementation over long periods; and (*c*) chronic, reversible or irreversible conditions, which occur in metabolically stable patients who require long-term intravenous supplementation (108). A remnant small bowel length of less than 100 cm is highly predictive of permanent IF that requires parenteral support (3, 18, 96). Physicians adjust parenteral nutrition and intravenous fluid support according to the degree of malabsorption and oral intake. Support by parenteral nutrition and intravenous fluids is complex and requires a multidisciplinary

Intestinal failure (IF): the inability of the gut to absorb sufficient water, macronutrients, and micronutrients to sustain life

Parenteral nutrition: intravenous administration of nutrition

team to decrease complications due not only to parenteral nutrition but also to the underlying disease responsible for SBS. Long-term parenteral nutrition can lead to specific complications, such as central vein access (e.g., infection, thrombosis, or loss of access) and metabolic complications (e.g., IF-associated liver disease, renal failure and oxalic lithiasis, or bone demineralization). These complications are responsible for increased morbidity and mortality in patients with SBS; patients receiving home parenteral nutrition experience a 5-year survival rate of 64% (65). Thus, physicians aim to reduce long-term dependence on parenteral support in order to decrease complications and increase a patient's quality of life and survival. Slowing down gastrointestinal transit and increasing total dietary intake are also strategies to maximize enteral calorie absorption. SBS is a complex disease that requires for each patient an accurate evaluation by a multidisciplinary team to lighten the burden this syndrome puts on patients.

2. ADAPTATION AFTER MASSIVE INTESTINAL RESECTION: THE CLINICIAN'S PERSPECTIVE

During the first years after resection, especially after restoration of intestinal continuity, dependence on parenteral nutrition decreases, indicating adaptation with improved nutrient absorption. In fact, intestinal adaptation occurs 1–2 years after resection in adults, but no objective clinical markers of time course or extent of adaptation have been identified (133). The probability that a patient will be weaned off parenteral nutrition is positively associated with a remnant small bowel longer than 75 cm, a large portion of remaining colon (4, 96), and a postoperative citrulline concentration greater than 20 μmol/L (24).

2.1. Clinical Evolutions and Outcome Improvement in Patients with SBS over Time: From Food Intake to Nutrient Absorption

Oral and enteral feeding and dietary interventions are essential to improve the outcome and to reduce dependence on parenteral nutrition in patients with SBS (52). Postsurgery continuous tube feeding (exclusively or in conjunction with oral feeding) significantly increases the net absorption of lipids, proteins, and energy compared with oral feeding (66). When oral feeding is possible, oral dietary intake is recommended. In addition, based on clinical experience, spontaneous hyperphagia is reported in 70% of adult patients with SBS (25). Hyperphagia is defined as oral intake 1.5 times greater than patient resting energy expenditure (25). The spontaneous rise of hyperphagia remains an essential mechanism to reduce the need for parenteral nutrition (97). Indeed, as hyperphagia leads to an increased amount of nutrients passing through the gastrointestinal tract, it may indirectly contribute to the structural and functional adaptations of the mucosa observed in the remaining gut (25, 97). The signals that drive hyperphagia are currently unknown, but understanding its mechanisms is of importance for clinicians who encourage hyperphagia for their patients with SBS.

2.2. Importance of Intestine Length, Type of Surgery, and Presence of the Colon

Clinical studies report that preserving the colon is critical for reducing the need for parenteral nutrition in patients with SBS (4, 96). Due to the importance of the length of the remaining intestine and the role of the colon in patients with SBS, the restoration of the gastrointestinal tract is favored by clinicians. Indeed, the probability of parenteral nutrition dependence is important

when the length of the remaining small bowel is less than 115 cm in the case of jejunostomy, less than 60 cm in the case of jejunocolic anastomosis, and less than 35 cm in the case of jejunoileal anastomosis with ileocecal valve and colon in continuity (4). Conservation of the terminal ileum and ileocecal valve also plays an important role because of the ileal brake (85).

The adult large intestine, or colon, measures approximately 1.5 m in length and consists of four parts: the ascending colon, the transverse colon, the descending colon, and the sigmoid colon. Physiologically, once the food chyme reaches the colon, almost all nutrients and 80–90% of water have been absorbed by the small intestine. At this point, electrolytes, such as sodium, magnesium, and chloride, and indigestible carbohydrates, known as dietary fiber, are left. By metabolizing dietary fiber, bacteria from the gut microbiota play a crucial role in the nourishment of the colon and in calorie sparing. Thus, rapid restoration of intestinal continuity in patients with SBS not only helps control loss of fluids and electrolytes but also provides the metabolic benefits of the colon.

A physiological adaptation occurs when the colon is in continuity, allowing energy and hydroelectrolytic recovery. In patients with SBS, the absorption of medium-chain C8–C10 triglycerides by the colon is improved (61). Some starches and soluble nonstarch polysaccharides are not digested by the small intestine. They are fermented by colonic bacteria into hydrogen, methane, and short-chain fatty acids (SCFAs) such as propionate, butyrate, and acetate. Up to 1,000 kcal in the form of SCFAs may be absorbed daily by the adult human colon in patients with SBS with colon compared with patients without colon (103). Thus, in patients with SBS, energy salvage driven by the colon is important (27). During the postresection adaptation phase, an increase in the capacity of colonic bacteria to ferment carbohydrates further increases energy absorption by the colon (15). This may be due to changes in colonic microbiota in patients with SBS as well as increased concentration or activity of various enzymes, such as galactosidase, over time during the adaptation phase (15). In addition, the colon may exert a braking effect on the rate of early gastric emptying of liquid after a major small intestinal resection (100, 101). Based on clinician experience, the presence of colon in continuity may help improve residual intestinal absorption and decrease parenteral nutrition in patients with SBS.

2.3. Evaluation of Absorption Improvement

The most obvious signs of intestinal adaptation toward improvement of absorption are a decrease in fecal or stoma losses, weight gain, and a decrease in parenteral nutrition dependence. In 2000, Jeppesen & Mortensen (62) suggested that, in stabilized adult patients with SBS, IF could be defined objectively in subjects who had either a wet weight absorption of <1.41 kg/day or $<84\%$ of the calculated basal metabolic rate in 48-h metabolic balance studies. Still, only a few centers in the world routinely use metabolic balance studies, which are recognized as the gold standard for determining absorptive capacity. The technique is complex and time consuming. Patients need to be admitted for at least 4 days to collect urine, feces, and an exact duplicate of their oral intake over 96 h. Intestinal energy absorption is calculated as the difference between oral energy intake and stool energy excretion (62). Evaluation of energy absorption is helpful in the day-to-day management of patients with SBS, but metabolic balance studies cannot be performed in clinical settings at most rehabilitation centers for IF.

The concentration of postabsorptive citrulline in plasma correlates with small bowel length and is a prognostic factor for parenteral nutrition dependence (4, 24). An increase in citrulline levels in plasma has been observed in patients after improvement of absorption (24). However, the optimal timing of citrulline measurement in relation to meal consumption has yet to be clarified.

Jeppesen and colleagues (38) recently evaluated in 8 patients with SBS-IF and 8 healthy controls the citrulline levels in plasma before and after a standardized mixed-meal test. They reported that the optimal time to measure citrulline was during fasting. However, citrullinemia was insufficiently discriminative to serve as a valid biomarker of bowel length, bowel absorptive function, or dependence on parenteral nutrition in patients with SBS-IF (38). Furthermore, whether citrulline levels accurately reflect the functional absorptive capacity of the small intestine remains unresolved. Additional biomarkers of adaptation need to be identified to improve the management of parenteral nutrition dependence.

Adaptive changes (e.g., increase in intestinal absorption or increased capacity to eat) occur mostly within 2 years following resection (133) and allow the number of infusions per week to progressively decrease, which explains why some patients can eventually be weaned off parenteral nutrition. However, an increase in intestinal absorption associated with a decrease in parenteral support dependence is possible mostly in patients with jejunocolic anastomosis. Therefore, the global prognosis remains better for patients with SBS with colon in continuity with small intestine than for patients with SBS with jejunostomy.

3. ADAPTATION AFTER MASSIVE INTESTINAL RESECTION: THE BIOLOGIST'S PERSPECTIVE

3.1. Physiological Intestinal Homeostasis: Maintaining Functions with Great Plasticity

The intestine is lined by a monolayer epithelium that constantly renews itself, allowing the intestine to rapidly adapt to nutrients and metabolic states. Homeostasis and functions of the intestinal epithelium depend on the precise spatiotemporal coordination of proliferation and differentiation signals from epithelial and mesenchymal cells that surround the intestinal stem cells.

3.1.1. General functions of the gastrointestinal tract (absorption, barrier, and secretion).

The gastrointestinal tract, the gateway for nutrients, is a key player in energy homeostasis (80). The principal role of the gastrointestinal tract is to complete digestion and absorb nutrients (**Figure 2**). The length and the specific architecture of the tract, including the multiple folds through the crypts of Lieberkühn, villi, and cellular microvilli, lead to the development of a large surface in contact with the outside environment, which includes the nutrients. This surface helps optimize absorption, with an efficient uptake of macronutrients, micronutrients, and water. Another role of the intestinal mucosa is to protect the organism from harmful luminal substances and nutrient- or microbiota-derived compounds, and the cells of the intestinal epithelium form a physical barrier between the external and internal compartments. Finally, the gastrointestinal tract, through its endocrine properties, informs the other peripheral organs and the brain of the arrival of nutrients and the metabolic state. More than 30 hormone-coding genes are expressed in the gastrointestinal tract, which makes the gut the largest hormone-producing organ in the body. The hormones are produced and secreted by endocrine cells, particularly in response to meals, and are important mediators of the luminal microenvironment-derived signals (125). These hormones participate directly or indirectly in the control of absorption, acting on the gastrointestinal tract itself, e.g., regulating gastric emptying and intestinal transit [peptide YY (PYY), glucagon-like peptide-1, -2 (GLP-1, GLP-2), and cholecystokinin (CCK)], modulating nutrient transporters, and having a trophic effect on intestinal mucosa (GLP-2). They also affect other tissues and participate in the control of food intake by the central nervous system (CCK,

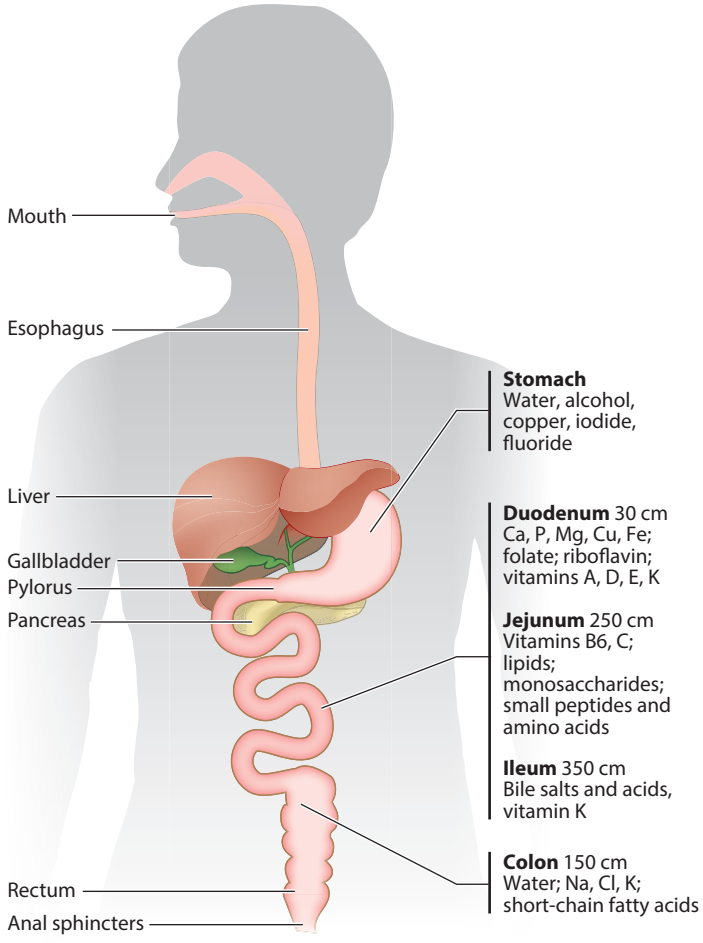

Figure 2

Nutrient absorption along the gastrointestinal tract. Micronutrients such as iron and fat-soluble vitamins are preferably absorbed in the upper part of the gastrointestinal tract (duodenum), whereas macronutrients (lipids, monosaccharides, and small peptides) are absorbed along the jejunum, and water and electrolytes are absorbed within the colon.

ghrelin, GLP-1, PYY) or in the control of glucose homeostasis by regulating pancreatic secretion of insulin or glucagon (GLP-1, glucose-dependent insulinotropic polypeptide) (125).

3.1.2. Intestinal stem cells and intestinal cell types. The intestinal tract is organized into crypt-villus units lined by a monolayer epithelium covering the stromal compartment and directly interacting with the luminal compartment. Crypts are invaginations into the intestinal wall. Villi are finger-like protrusions in the intestinal lumen and their length decreases from the duodenum to the ileum. The colon tract lacks villi and exhibits a flat epithelial surface with invaginated crypts.

One characteristic of the intestinal epithelium is its constant and rapid self-renewal. Most intestinal cells are renewed every 2–3 days in the rodent and 5–7 days in human (6), except for

Paneth cells, which are renewed every 3–6 weeks (56). Renewal is enabled by the multipotent intestinal stem cells (ISCs), located at the bottom of the crypts between Paneth cells. ISCs continually generate progenitor cells and differentiated cell types of the epithelium in strictly controlled proportions (6). Two main epithelial cell lineages, absorptive and secretory, arise from ISCs. The absorptive enterocytes account for approximately 80% of intestinal epithelial cells, whereas absorptive microfold cells are rare. Secretory cells comprise Paneth cells, goblet cells (which produce mucus), enteroendocrine cells (which produce and secrete hormones), and the rare tuft cells. All these cells, with the exception of Paneth cells, differentiate while migrating along the crypt toward the villus. At the apex of the villi, these differentiated cells undergo anoikis and are exfoliated into the intestinal lumen (39, 83, 141). The Paneth cells located at the base of the crypts participate in the barrier function but also play key roles in the stem cell niche (118). Indeed, ISCs are surrounded by Paneth cells, which contribute to the stemness state by secreting critical factors such as Wnt ligands. ISCs are actively cycling, dividing every day, to fuel the crypt-villus axis and they are characterized by their selective expression of Wnt target genes, such as the gene encoding leucine-rich repeat–containing G protein–coupled receptor 5 (LGR5) (7). Since the discovery of *Lgr5*, many other specific markers have been identified. The development of lineage tracing technology has greatly improved our knowledge and understanding of intestinal homeostasis (137) and our mastery of in vitro organoid cultures, facilitating the development of tools for regenerative medicine (128, 145).

The maintenance of ISCs and the resulting intestinal epithelial homeostasis, integrity, and function are therefore based on a dynamic process that requires balanced and integrated control, in time and space, of cell proliferation, differentiation, and apoptosis. Intestinal homeostasis involves the genetic program of intestinal epithelial cells (e.g., transcription factors and genome structure) and the components of the surrounding cellular microenvironment, i.e., the niche (e.g., cellular interactions and secreted factors) as well as the components of the luminal and metabolic environment (e.g., nutrients, microbiota, hormones, and immune cells). Constant renewal confers to the gastrointestinal epithelium high plasticity and adaptability to the qualitative and quantitative changes in its luminal microenvironment (30, 80), as well as maintenance of its barrier function as defective cells are rapidly extruded.

3.1.3. Physiologically regulating signals of proliferation and differentiation. Different signaling cascades are key regulators of intestinal homeostasis. Homeostasis of the intestinal epithelium is maintained because continuously dividing ISCs reside sequestered at the bottom of the crypt and rely on signals from their surrounding environment, i.e., their niche. The niche consists of an epithelial component (Paneth or Paneth-like cells) and a mesenchymal component, both of which provide key signaling activators or inhibitors of WNT (71, 105, 118, 119), epidermal growth factor (EGF) (9, 118, 119, 142), and bone morphogenetic protein (BMP) (53, 91) pathways (reviewed in 43).

The Wnt pathway is the most important pathway for stemness and overrules the other regulating pathways (71, 118) to control proliferation in the crypts. Wnt ligands or Wnt signaling potentiators are highly abundant at the bottom of the crypts, inducing high Wnt pathway activity, and they exhibit a decreased gradient toward the crypt-villus axis. When the cells derived from the ISCs move upward out of the crypts, decreased Wnt activity due to the new cell position directs cells toward lineage commitment and differentiation. An inverse gradient of BMP, which favors epithelial differentiation, is observed along the crypt-villus axis, and BMP inhibitors are secreted at the bottom of the crypt to protect ISCs. In addition, EGF and transforming growth factor α are highly produced at the bottom of the crypts by Paneth cells and surrounding mesenchymal cells and stimulate stemness and proliferation (43).

The Notch pathway is also involved in stem cell maintenance at the bottom of the crypt, where the Wnt signals are elevated (116). But, higher up in the crypt, the Notch pathway controls cellular commitment and establishes, by lateral inhibition, the absorptive fate of cells expressing Notch receptors and the secretory fate of cells expressing Notch ligands. The cells expressing Notch ligands induce Notch activation in the surrounding cells, ensuring a constant proportion of the different cell lineages (116). Other signals, such as interleukin-22 (82) and Hippo (47), play a role in stem cell regulation and lineage commitment.

3.2. Morphological and Functional Modifications After Intestinal Resection

Intestinal resection is a massive modification of the gastrointestinal tract. In addition to causing intestinal insufficiency, this modification leads to a profound change in the luminal environment of the intestinal and colonic epithelia. These alterations induce adaptations of homeostasis and functions of the remaining intestine.

3.2.1. Use of animal models to study intestinal adaptation after massive intestinal resection. Using intestinal samples from patients with massive intestinal resection to study adaptation is difficult if not impossible. For more than 50 years, researchers have developed animal models of SBS to understand and master at the cellular and molecular levels the mechanisms of spontaneous adaptation. Pigs, mice, rats (reviewed in 117), and more recently, zebrafish (120) have been developed as models to study the effects of parenteral, oral, and enteral nutrition and to evaluate new treatments. The most performed type of surgical intervention is jejunoileal resection with jejunoileal anastomosis or with jejunocolic anastomosis. Partial colonic resection associated to a resection of 80% of the small intestine does not seem to be commonly performed (44). While patients with SBS with jejunostomy are the most challenging subjects to manage because of the massive loss of the small and large intestine and associated functions, very few studies, using mostly pigs, have reported complete colonic resection with jejunostomy anastomosis (5, 136, 139). Clearly, animal models are useful for finding novel therapies that improve adaptation; the development of treatments with GLP-2 analogs is an example (16, 42, 69, 70, 75, 90, 121, 123).

The time course of the studies should also be taken into consideration. For example, many studies of resected rat models focus on adaptation between 1 and 2 weeks postsurgery (16, 29, 44, 46, 69, 70, 88, 89) and, less often, 3 to 4 weeks postsurgery (54, 110). In the case of rodents that have undergone intestinal resection, the first 4 days can be considered an acute phase of postoperative recovery with a gradual recovery of oral feeding. Given that the life expectancy of a rat is 2–3 years (112), studying the rats 6–7 days after the resection is comparable to studying humans in the early phase of adaptation, 6–7 months postresection.

3.2.2. Cellular adaptation after massive intestinal resection. In 1959, Booth et al. (13) first demonstrated that extensive intestinal resection in rat leads to hypertrophy of the remaining intestine (**Figure 3**). Hypertrophy results from an increased proliferation rate in crypts, leading to an increase in villus height and crypt depth in animal models (44, 79, 89), and could be associated with an expansion of ISCs (54).

In animal models of SBS, morphological adaptation all along the intestine (jejunum, ileum, and colon) has been described but seems to depend on the length of the resection (44, 89), the type of anastomosis (44, 46), and probably the time postresection. For example, in models with jejunoileal anastomosis, jejunal or ileal, but not colonic, hyperplasia has been reported 1 week after resection (44, 89; J. Le Beyec, unpublished observations), whereas in models with jejunocolic anastomosis, colonic hyperplasia has been observed 1 week after resection (44). A peculiar luminal content,

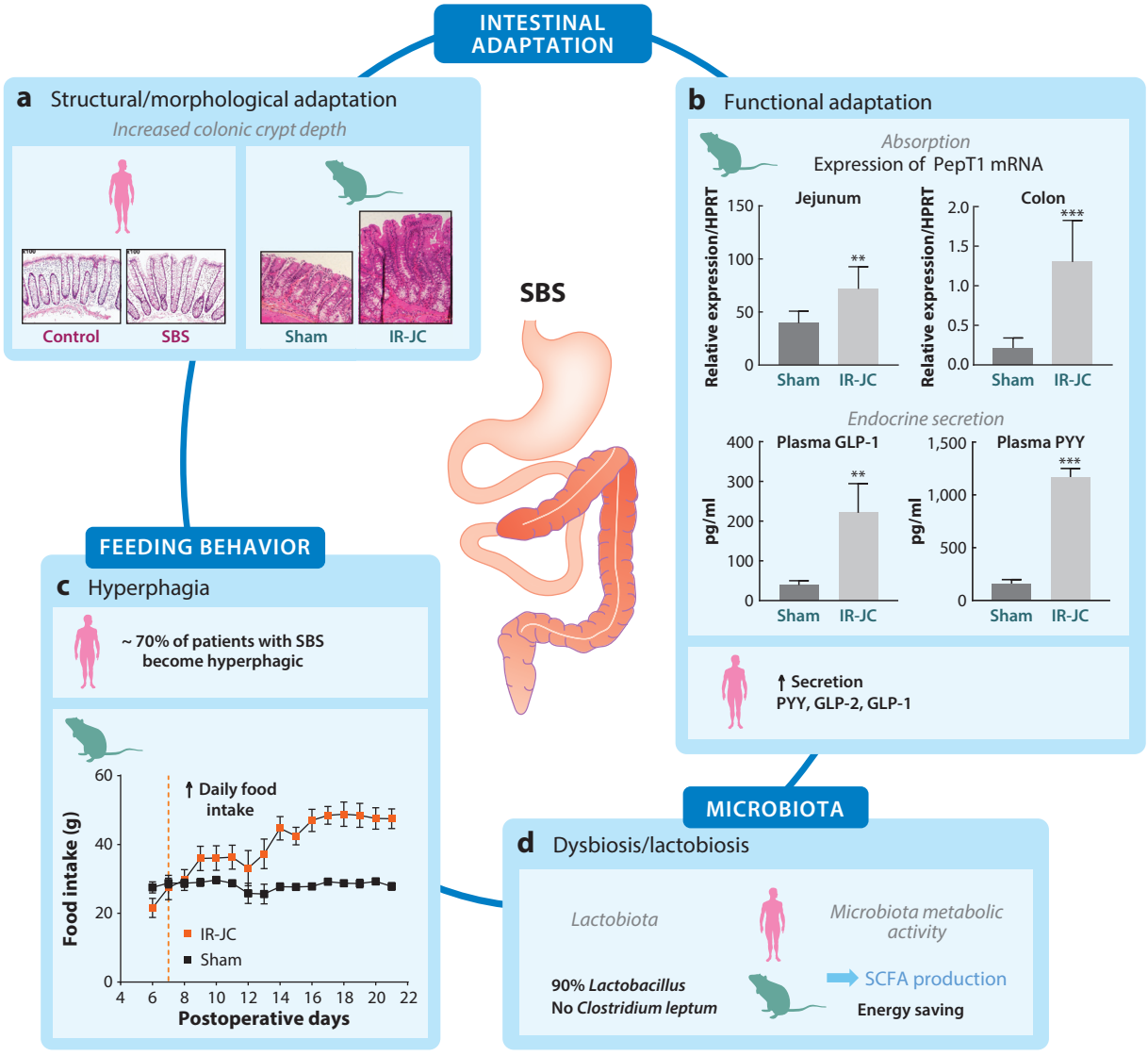

Figure 3

Spontaneous adaptations in SBS–IF. Spontaneous physiological adaptation occurs within 2–3 years after massive intestinal resection in humans (SBS) and 1–2 weeks in animal models (IR-JC). Adaptation is characterized by (*a*) intestinal morphological and (*b*) functional adaptations, with (*a*) increased intestinal surface, (*b*) expression of nutrient transporters and secretion of intestinal hormones (PYY, GLP-1), (*c*) development of compensatory hyperphagia, and (*d*) dysbiosis of the intestinal microbiota. Hyperphagia reduces dependence on parenteral nutrition by increasing net nutrient absorption. The increase in enterohormones (PYY, GLP-1, GLP-2) helps improve energy recovery, particularly by the intestinal trophic effect (GLP-2) or by slowing gastrointestinal motility (GLP-1, PYY). Dysbiosis has a putative positive effect of producing SCFAs, which fuel colonocytes. Left-side images in panel *a* are reproduced with permission from Reference 68. Panels *b* and *c* present unpublished personal data from J. Le Beyec. Abbreviations: GLP, glucagon-like peptide; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IF, intestinal failure; IR-JC, intestinal resection–jejuno colonic anastomosis; mRNA, messenger RNA; PepT1, peptide transporter 1; PYY, peptide YY; SBS, short bowel syndrome; SFCA, short-chain fatty acid.

including nutrients in contact with different intestinal segments, seems to be a determinant of early adaptation and depends on the surgical arrangement. A longer follow-up of rat models of SBS with jejunocolic anastomosis reveals the appearance of jejunal hyperplasia upstream of the resection (J. Le Beyec, unpublished observations), suggesting other mechanisms are at play in long-term morphological adaptations.

Few studies of humans have reported morphological adaptations in the intestinal mucosa. A study of children showed a significant increase in villus height and crypt depth in the mucosa of the small intestine over time (94). McDuffie et al. (94) also found that the extent of morphological adaptation was correlated with the length of the resected bowel. The appearance of colonic hyperplasia with an increase in crypt depth was reported for adult subjects with SBS but not control subjects (68). The increase in crypt depth and colonic epithelial cell number could participate in the decrease in parenteral nutrition dependence within 2 years after restoration of intestinal continuity in patients with SBS. Guo et al. (52) have shown that enteral nutrition and glutamine have a direct positive effect on the morphological adaptations of the intestinal mucosa in patients with SBS and that this adaptation is associated with an increase in net nutrient absorption.

Intestinal hyperplasia increases the intestinal surface that comes in contact with nutrients (i.e., the absorptive surface) and participates in absorption improvement in SBS subjects. Modifications to cell lineage commitment have also been reported, with either expansion of intestinal secretory lineages following a massive small bowel resection in mice (54) or increased differentiation toward absorptive progenitors (129). On the contrary, other studies reported an increase in enteroendocrine cell numbers resulting from hyperplasia without any difference in cell lineage commitment (44). Thus, at this stage of research on this topic, there is no consensus concerning intestinal epithelial differentiation. This aspect could be further explored with well-established animal models and with the use of in vitro mini-gut technology (84, 118).

In addition to these changes, functional adaptations have been reported but remain controversial and could result from an increase in the surface exchange rather than from a net increase in the activity or expression levels of specific nutrient transporters (reviewed in 80) (**Figure 3**). Finally, the main modification to the function of the intestinal epithelium concerns its endocrine function.

3.2.3. Modification of hormonal secretions. In physiological conditions, GLP-2, GLP-1, and PYY are secreted by enteroendocrine cells, which are localized mainly in the ileum and colon but are also present in the proximal intestine. The production and secretion of these hormones are increased in patients with SBS (44, 60) and in murine models of intestinal resection (29, 44, 89) when the colon is in continuity. In SBS subjects, increases in hormone levels are observed during both fasting and postprandial states (**Figure 3**). This increase may result from intestinal hyperplasia and modified function of enteroendocrine cells (44) but also from altered luminal contents, which can stimulate more distal and abundant enteroendocrine cells (44, 78). These hormones are biological markers of intestinal homeostasis, but through the numerous roles they exert on the gastrointestinal tract, they are also key drivers of spontaneous intestinal adaptation. They help improve nutrient absorption by inducing hyperplasia, slowing down the accelerated transit time in the intestine, inhibiting gastric emptying, and increasing blood flow (49, 50, 89, 100, 124).

Higher concentrations of fasting and postprandial ghrelin, the unique orexigenic gut hormone, in plasma of subjects with SBS have also been reported, suggesting that a change in gastrointestinal hormonal secretions could also play a role in the occurrence of hyperphagia (44).

3.2.4. The microbiota: cause or consequence of adaptation? The composition of the gut microbiota of patients with SBS highly differs from the common profile observed in healthy humans

with an intact gastrointestinal tract (87). The fecal microbiota of healthy humans is composed mainly of a phylogenetic core containing *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*. The human gastrointestinal tract is colonized by a dense, complex community of microorganisms, consisting mainly of anaerobic bacteria in adults, and the dominant groups are *Clostridium leptum*, *Clostridium coccoides*, and *Bacteroides prevotella*.

The overall bacterial diversity is reduced in SBS subjects (patients and animal models) and the composition of the fecal and colonic mucosa microbiota is deeply disturbed: *Lactobacillus* dominates and anaerobic bacteria (*C. leptum*, *C. coccoides*, and *B. prevotella*) are underrepresented (32, 37, 67, 77). The short length of the remnant small intestine and colon in patients with SBS or animal models maintains high levels of oxygen that are unfavorable to the growth of anaerobic bacteria. In addition, the rapid transit time, the low fecal pH, the disruption of enterohepatic circulation of bile acids, and the amount of undigested nutrients in the remaining colon lumen are modified and may create a favorable niche for lactic acid–producing bacteria to proliferate. *Lactobacillus* overload should be considered massive, because in healthy humans this group accounts for less than 1% of the complex microbiota population. Thus, this specific SBS microbiota is named lactobiota (67, 93).

The metabolic capacity of lactobiota and the cross talk between the lactobiota and the colonic mucosa give the colon an essential role in patients with SBS. After extensive intestinal resection, abundant and poorly digested nutrients or substrates reach the colon lumen, where their fermentation by gut bacteria helps maintain colon mucosa homeostasis, ecosystem diversity, and energy recovery (15, 95, 102, 103). The colonic microbiota seems to play an important role in postsurgery adaptation in patients with SBS by promoting caloric absorption. However, the biological signals arising from the SBS microbiota need to be better understood, as they are both beneficial (with a high ability to recover energy) and deleterious (with the potential to overproduce D-lactate) to patients (93) (**Figure 3**).

Understanding intestinal renewal and ISC biology, through the use of animal models and organoid culture, is essential for identifying new therapeutic targets that can be transferred to clinical applications.

4. NUTRITIONAL AND LUMINAL SIGNALS INVOLVED IN SPONTANEOUS ADAPTATION

Excess or exclusion of nutrients in the intestinal lumen has long been known to directly impact the cellular mass of the intestinal epithelium. In rodent models, total parenteral nutrition leads to hypoplasia (55) and long-term fasting leads to an important reduction in intestinal epithelial mass (36, 41, 114). In addition, depending on the type of anastomosis leading to SBS, the nature of nutrients that pass through the different intestinal segments differs, contributing to specific localized adaptation. Nutrients trigger intestinal adaptation directly by stimulating mucosal hyperplasia and expression of their own transporters (80) or indirectly by modifying microbiota composition and stimulating trophic gastrointestinal hormone secretions.

4.1. Caloric Content or Quality of Nutrients?

Yilmaz et al. (144) have shown that caloric restriction reduces the proliferation of intestinal progenitors and the numbers of differentiated enterocytes while increasing the niche function and the number of ISCs. In this case, the epithelial surface is reduced but the stem cell compartment is ready for immediate reinforcement upon refeeding.

Conversely, Mao et al. (86) have shown that overnutrition directly stimulates intestinal epithelium proliferation. They found that proliferation of intestinal epithelial cells induced by excessive

food intake correlated with activation of the glycogen synthase kinase-3 (GSK-3)/β-catenin signaling pathway, suggesting that nutrient-induced activation of this pathway in the intestinal epithelium contributes to increased nutrient absorption (86). An in vitro study demonstrated that glucose and free fatty acids directly stimulate intestinal epithelial cell proliferation through β-catenin activation (86). More recently, the Yilmaz group (11) showed that a high-fat diet leads to a decreased number of Paneth cells but an increased number of ISCs, which become independent of Paneth cell signaling. In those conditions, ISCs were responsive to lower Wnt signals, enlarging the stemness zone in the crypt (1).

In rodent models, total parenteral nutrition leads to hypoplasia but introduction of glutamate into drinking water preserves the epithelium, emphasizing the role of nutrients in epithelial homeostasis (55). Similarly, treatment of patients with SBS under parenteral nutrition with enteral nutrition associated with glutamine enables a significant adaptive process characterized by an enlarged absorptive surface with an increased proliferative rate of ISCs (52).

In a normal gastrointestinal tract, most of the ingested food is broken down into small molecules and absorbed by cells of the jejunum and transferred into the bloodstream. In a remodeled gastrointestinal tract, by either bariatric surgery or a large resection of the small intestine, the accelerated flow of nutrients associated with the shorter jejunum length allows the ingested food to reach more distal segments of the intestine (20, 26). These undigested nutrients trigger new signals for distally located cells and may induce proliferation and hyperplasia as well as improve intestinal endocrine function. Improvement of endocrine cell function is well illustrated in a recent study by Larraufie et al. (78), who showed that increased secretion of GLP-1 after bariatric surgery in mice arises from an accelerated delivery of undigested nutrients to the distal gut, where there is a high density of GLP-1-producing cells. In SBS subjects with jejunoileal or jejunocolic anastomosis exhibiting accelerated gastrointestinal transit, one can hypothesize that the secretions of GLP-1, GLP-2, and PYY from distal colonic cells are boosted by these new signals arriving more distally than physiologically. The nutrient-induced endocrine signals, particularly GLP-2, could in a second step partly take over to stimulate proliferation in the proximal remaining segments of the gut (see Section 4.3).

4.2. Microbiota Signals

It is well recognized that luminal nutrients shape the composition of the microbiota and that the microbiota participates in intestinal homeostasis (19, 106, 107). Fecal lactobiota transfer from a patient with SBS to germ-free rats triggered an increase in crypt depth that reached that of conventional rats (45). In addition, SBS lactobiota induces an increase in plasma of GLP-1 and ghrelin (45), two hormones, together with PYY and GLP-2, induced in patients with SBS (44). Thus, the SBS lactobiota seems to be a reservoir of multiple, complex signals that could contribute to postresection adaptive mechanisms (92).

Lactate-producing bacteria, such as *Lactobacillus* species, support renewal of intestinal epithelial cells (81). Through its interaction with its receptor, Gpr81, expressed on niche cells (i.e., Paneth cells and ISCs surrounding stromal cells), lactate seems to play a pivotal role in stimulating the Wnt/β-catenin signaling pathway and accelerating the proliferation rate and intestinal regeneration of ISCs (81).

4.3. Hormonal Signals

Ultimately, intestinal hormones are important signals that link nutrients, microbiota, and possibly other luminal contents with mucosal adaptation. The most important hormone is probably GLP-2 because of its pleiotropic effect on the gut (17, 33, 34). GLP-2 activates various signaling pathways

involved in cell proliferation; for example, it increases β-catenin nuclear translocation and c-Myc expression (35, 115).

Surprisingly, the precise cellular and molecular mechanisms of action of GLP-2 remain unclear (34). They are reported to be indirect because expression of intestinal GLP-2 receptors, which decrease from the proximal to the distal part of the intestine, seems to be restricted to subepithelial myofibroblasts, a subset of enteric neurons and enteroendocrine cells that is not detectable in ISCs (48, 59, 146). Multiple molecular mediators of GLP-2, including insulin-like growth factor 1 (IGF1), EGF, and avian erythroblastic leukemia viral oncogene homolog (ErB) family members, relay its action in the gastrointestinal tract and induce proliferation (reviewed in 17). EGF signaling is a key pathway controlling the division rate of ISCs, although it is not necessary for maintaining stem cell identity (9, 119). Nevertheless, the exact mechanisms by which IGF1 and EGF relay trophic effects of GLP-2 to the gut have yet to be characterized. The use of intestinal organoids derived from animal models of SBS or patients with SBS could help further our understanding of how these different factors interact to induce intestinal hyperplasia (84, 118, 119).

Since the trophic action of GLP-2 on the gut was first discovered by Drucker et al. (33) in 1996, GLP-2 treatments have been rapidly developed to improve adaptation. Long-acting GLP-2 analogs, such as teduglutide, have been developed and used as a specific therapy in patients with SBS. Treatment with GLP-2 analogs enhances or accelerates spontaneous adaptation and reduces the need for calories to be administered intravenously. In a controlled clinical trial, the administration of teduglutide reduced by more than 20% the need for intravenous nutrition in 63% of patients after a 6-month treatment (63). Teduglutide significantly reduces stool wet weight and fecal energy excretion (64). Teduglutide significantly increases villus height, crypt depth, and mitotic index in the jejunum of patients with SBS with jejunostomy, but not in colonic biopsies of patients with SBS with an intact colon (64). This peculiar observation may reflect the scarcity of GLP-2 receptors in the colon (146). With teduglutide, some patients can be weaned off parenteral nutrition, but a greater number of patients require persistent support with a reduction in the number of their infusions per week (63). Patients who received teduglutide showed a significant increase in citrulline levels in plasma compared with patients receiving a placebo in two phase III studies, indicating an increase in enterocyte mass in these patients (122). However, whether citrulline levels accurately reflect the functional absorptive capacity of the small intestine remains unresolved.

Oral feeding is a positive driver of intestinal adaptation. Our understanding of the signals relaying the presence of nutrients has led to the development of long-acting GLP-2 analogs. Further studies of the mechanisms by which lactobiota participates in SBS adaptation could help researchers develop combined therapies.

5. NUTRITION INTERVENTIONS

After the immediate and acute postoperative phases requiring parenteral nutrition, a regular oral diet should be introduced as soon as possible in patients with SBS because, as described above, adaptation requires enteral stimulation. Dietary interventions through oral supplements or enteral feeding, in addition to spontaneous and conventional food intake, are considered as clinicians look for specific nutritional constituents that could trigger, stimulate, or maintain intestinal adaptation. In the last few years, researchers have developed nutrient strategies in animal models to complement pharmacologic treatment with GLP-2 analogs (16). The importance of the different macronutrients (carbohydrates, fat, and proteins) is briefly discussed, as this topic has been recently reviewed elsewhere (58, 76, 99).

5.1. Carbohydrates and Short-Chain Fatty Acids

Although randomized controlled trials are still missing, clinical experience tends to suggest that complex carbohydrates are better tolerated than monosaccharides due to lower risk of osmotic diarrhea. In addition, in rats maintained with total parenteral nutrition, disaccharide intestinal infusions stimulated mucosal growth more than monosaccharide intestinal infusions did (140).

Most complex carbohydrates, the indigestible fibers, are not directly absorbed by the intestine but are fermented by the microbiota into SCFAs (essentially acetate, butyrate, and propionate). SCFAs are the preferred energy source for colonocytes driving colon mucosa trophicity in normal subjects as in patients with SBS (8). Accordingly, diet supplemented with SCFA or pectin improves adaptation of the small intestine and colon in animal models of SBS (134, 135). In addition, secretion of serotonin or GLP-2 in response to SCFAs may contribute to these trophic effects (113, 134).

5.2. Lipids

Several studies of rat models of SBS, mostly with jejunoileal anastomosis, reported that a low-fat diet impairs intestinal adaptation (131), whereas a high-fat diet stimulates adaptation (21, 130). In addition, high-fat diet supplementation, together with enhanced expression of CD36, a fat transporter/receptor, and microsomal triglyceride transfer protein, an enzyme involved in chylomicron formation, further increases structural and proliferative changes in the intestine (22). The effect appears to be mediated by long-chain triglycerides, saturated or not. Diets enriched in medium-chain triglycerides do not stimulate intestinal adaptation to the same degree (138), although medium-chain triglycerides offer the advantage of being easily absorbed (58, 61). Nevertheless, translation to clinical practice is complicated, and because diarrhea is associated with steatorrhea (58), a low-fat diet is generally recommended for patients with SBS with a preserved colon.

5.3. Proteins and Amino Acids

Expression of PepT1, the major transporter of dipeptides and tripeptides, is increased in colonocytes of patients with SBS (67) and is induced after massive intestinal resection in rats (44) (**Figure 3**), suggesting spontaneous adaptation that favors absorption of protein-derived products. Accordingly, a recent study demonstrated that a high-protein diet results in greater weight gain in mice with massive intestinal resection (132). In children with SBS, provision of hydrolyzed versus nonhydrolyzed proteins results in similar intestinal permeability, weight gain, and nitrogen balance (72). The exact formula of proteins is still a matter of debate, but peptides may help reduce intestinal inflammation (104).

Glutamine is a major substrate for intestinal cells as well as for rapidly dividing cells. Because glutamate in the drinking water of mice under total parenteral nutrition seems to preserve the epithelium (143), numerous studies have addressed the efficacy of glutamine for the treatment of IF. Even though some studies showed favorable effects (52), the efficacy is still debated (2).

In conclusion, we still do not know which macronutrients (carbohydrates, lipids, or proteins) have the most significant impact on intestinal adaptation. It appears that in murine models, as in humans, complex food creates the strongest stimuli compared with supplementation with individual nutrients (12, 58). The trophic capacity of macronutrients is related to how they are digested. Indeed, the digestive workload needed to absorb them, including the work of hydrolysis, plays an important role in driving intestinal adaptation (99). Finally, if diet composition or elevated nutrient intake is beneficial for nutrient absorption, it could also aggravate overall loss of fluids and electrolytes by stimulating various hypersecretions; thus, nutrition interventions should also be adapted to each patient.

Up to now, dietary recommendations for patients with SBS have been based only on short-term observational studies and clinical experience. Additional studies are required, as are evidence-based data, especially of combinations of nutritional approaches, for instance, with probiotics or prebiotics. On the basis of the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, experts recommend specific dietary advice according to the anatomical aspects of SBS (108).

6. FUTURE DIRECTIONS AND CONCLUSION

Because luminal nutrients are key components of intestinal adaptation and improvement in patients with SBS, hyperphagia observed in some patients with SBS should be encouraged or stimulated. The signals responsible for this eating behavior are currently unknown. Changes in the ratio of fat mass to fat-free mass are believed to generate integrated peripheral signals that drive eating behavior (127). Bétry et al. (10) recently suggested that fat-free mass could be a strong predictor of oral energy intake in patients with SBS, whereas hyperphagia is not associated with a decrease in fat mass nor with a decrease in leptin, a well-known anorexigenic hormone (44, 98). Very few studies focus on gastrointestinal hormones and hyperphagia in SBS (23, 44). We have shown that patients with SBS and resected rats exhibit increased levels of circulating fasting ghrelin compared with control subjects (44). Furthermore, the expected postprandial decrease in ghrelin is delayed in patients with SBS, suggesting that a hunger signal persists after a meal is initiated in these patients (44). In patients with Prader-Willi syndrome, major hyperphagia with loss of appetite control is observed (31, 73) and is correlated with ghrelin concentrations (31, 51, 73), reinforcing the role of ghrelin in the occurrence of hyperphagia. But to date, no correlation between ghrelin levels and food intake in patients with SBS has been demonstrated. It is therefore unclear whether increased ghrelin levels are involved in hyperphagia in these patients. The eating behavior of patients with SBS may depend on a balance between orexigenic and anorexigenic hormones. Accordingly, patients with Prader-Willi syndrome exhibit a higher ghrelin-to-PYY ratio, suggesting that this ratio could be a marker, or stimulus, of orexigenic drive (51). This hypothesis needs to be tested in patients with SBS.

The relationships among microbiota, gastrointestinal hormones, and eating behavior have been established in different physiopathological situations (14, 28, 74, 111, 126). The lactobiota observed in patients with SBS may represent a reservoir of microorganisms of interest contributing to intestinal adaptation but also to the control of food intake (14, 126). Exploring animal models of SBS, particularly during long-term follow-up, will improve our understanding of SBS adaptation and allow us to develop interventional studies targeting microbiota and intestinal hormones to ameliorate intestinal absorption and eating behavior.

Finally, there is a need to identify a panel or combination of biomarkers that could be used, instead of metabolic balance studies, to easily characterize the intestinal absorption ability of patients with SBS and to predict the effectiveness of their adaptation. In the future, a therapeutic approach could be to stimulate intestinal adaptation through nutritional manipulation, including stimulation of hyperphagia, to rapidly wean patients with SBS off parenteral nutrition.

SUMMARY POINTS

1. Adaptation to intestinal resection involves adaptation of the remnant bowel (hyperplasia and secretion of gut hormones) and changes in eating behavior (hyperphagia).

2. Spontaneous intestinal adaptation is stimulated by enteral nutrition through modification of luminal contents (nutrients and microbiota-derived metabolites).
3. Gut hormones such as glucagon-like peptide-2 (GLP-2) could be relay signals of luminal contents acting on intestinal renewal.
4. The most important aspect of dietary management in patients with short bowel syndrome (SBS) is to encourage hyperphagia.

DISCLOSURE STATEMENT

F.J. and L.B. have received honoraria from SHIRE/TAKEDA, which markets teduglutide for the treatment of intestinal failure. The other authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank all present and past members of our team for their invaluable contributions. We also thank the Institut National de la Santé et de la Recherche Médicale, Sorbonne Université, Université de Paris, and Assistance Publique-Hôpitaux de Paris for their financial support.

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