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REVIEW

Intestinal mucosal adaptation

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Abstract

Intestinal failure is a condition characterized by malnutrition and/or dehydration as a result of the inadequate digestion and absorption of nutrients. The most common cause of intestinal failure is short bowel syndrome, which occurs when the functional gut mass is reduced below the level necessary for adequate nutrient and water absorption. This condition may be congenital, or may be acquired as a result of a massive resection of the small bowel. Following resection, the intestine is capable of adaptation in response to enteral nutrients as well as other trophic stimuli. Identifying factors that may enhance the process of intestinal adaptation is an exciting area of research with important potential clinical applications.

Key words: Small intestine; Transport; Morphology; Resection; Short bowel syndrome; Absorption; Diet; Gene expression; Hyperplasia; Enterocytes

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STRUCTURAL AND FUNCTIONAL ADAPTATION

The intestine has an inherent ability to adapt morphologically and functionally in response to internal and external environmental stimuli. In fact, intestinal adaptation may be considered as a paradigm of gene-environment interactions. The array of phenotypic adaptations includes the modification of brush border membrane (BBM) fluidity and permeability, as well as up- or down-regulation of carrier-mediated transport. In animal models, intestinal adaptation occurs following the loss of a major portion of the small intestine ("short bowel syndrome", SBS), following chronic ingestion of ethanol, sublethal doses of abdominal irradiation, diabetes, aging, fasting and malnutrition[1-5]. Following intestinal resection, morphological and functional changes occur depending upon the extent of the intestine removed, the site studied, and the lipid content of the diet[6]. The increase in nutrient absorption compensates for the loss of absorptive surface area, and minimizes the malabsorption that could otherwise potentially occur. Therefore, intestinal adaptation has important implications in the survival potential and welfare of the host[7]. However, in some cases such as diabetes, intestinal adaptation may have deleterious effects, with enhanced nutrient uptake exacerbating prevailing hyperglycemia, hyperlipidemia and obesity[8].

The mechanisms of intestinal adaptation occur at a variety of levels: physiological, cellular and molecular. Signals of adaptation may relate to various hormone levels, transcription factors, ATP levels, or changes in the concentration of luminal solutes[5]. The signals and mechanisms of the adaptive process may be different for the jejunum and ileum, as well as in the intestinal crypt and villous tip, explaining the site-specific alterations and differences between crypt and villous enterocytes[3,4].

Rodents are commonly used in well-characterized models of assessing the process of intestinal adaptation[9]. Following small bowel resection in the rat, the remnant intestinal mucosa undergoes compensatory alterations in an attempt to restore normal absorptive capacity[10]. Morphologic and functional changes include increases in crypt depth and villous length, enterocyte proliferation, as well as increased electrolyte, glucose and amino acid uptake[9,10].

The adaptive process has been defined in terms of transport kinetics. Changes usually occur in the value of the maximal transport rate (Vmax) rather than in the Michaelis affinity (Km) constant of specific nutrient transporters (sugars and amino acids)[11,12]. Furthermore, there may be alterations in the passive permeability coefficients of nutrients transported passively such as short-, medium- and long chain fatty acids and cholesterol[3,4,13]. The increased Vmax results from either an up-regulation of the total number of transporters, an increased number of transporting mucosal cells, or an increase in the intrinsic activity fo the transporter[14,15]. Intestinal resection also selectively changes the passive permeability properties of the BBM, as demonstrated by the increased uptake of fatty acids following intestinal resection, an increase that was not due to the changes in the mucosal surface area or the effective resistance of

the intestinal unstirred water layer (UWL)[16]. Indeed, this altered permeability is due to changes in the lipophilic properties of the BBM due to variations in the lipid content of the BBM[17].

Intestinal adaptation in the rodent model of chronic diabetes involves changes at the transcriptional as well as the posttranscriptional level, leading to increased Na^+-coupled sugar absorption[18]. After inducing acute hyperglycemia in rats, there is rapid up-regulation of glucose transport across the basolateral membrane (BLM) of the enterocytes[19]. In this model, both the vascular as well as luminal glucose infusion causes an increase in the glucose transport capacity across the BLM[20]. However, no significant increase in BLM cytochalasin B binding or in GLUT2 protein abundance was observed, suggesting that there may be a post-translational event that increases the number of GLUT2 proteins available for transport, such as the movement of GLUT2 to the BLM from a preformed pool within the enterocyte. Alternatively, the "intrinsic activity" of the transporter may be altered in the absence of changes in the protein abundance. Changes in the intrinsic activity of glucose transporters have been observed with hyperglycemia[21], diabetes[22], low luminal glucose concentrations[14] and following the activation of MAPK and PI3K[15].

Following extensive intestinal resection, there is hyperplasia of the remaining bowel, which may be accompanied by the enhanced uptake of nutrients[23]. The alterations in the cell kinetics that result in modification of the nutrition status may be specific or non-specific. *Non-specific mechanisms* involve alterations that result in changes in the intestinal mucosal mass and/or the villous surface area, leading to modifications in the uptake of all nutrients, including those that are absorbed passively[24]. On the other hand, *specific mechanisms* involve up- or down-regulation of transporters responsible for the uptake of particular nutrients, such as sugars or amino acids[3,4].

The observation that morphological modifications may accompany intestinal adaptation in the rodent small bowel resection model was first made by Dowling and Booth[23]. The remaining intestine after resection is hyperplastic, with greater villous height and crypt depth, leading to enhance mucosal surface area. However, while enhanced nutrient absorption is observed, the morphological changes do not necessarily explain the alterations in nutrient uptake. For example, one week after an 80% small bowel resection, the remaining intestine increased its mass to 50%-70% of its pre-resection level, yet the uptake of glucose increased only to approximately 33% of the pre-resection level[10]. Thus, enhanced nutrient absorption may not be solely explained by intestinal hyperplasia and/or hypertrophy.

It is clear that dynamic morphologic parameters of the intestine may also adapt. For instance, the crypt cell production rates or the enterocyte migration rates change in some situations of intestinal adaptation[25]. It is important that morphological alterations are considered when estimating the kinetic parameters of absorption. Morphological modifications such as blunting of the mucosal growth or mucosal hyperplasia after intestinal resection are observed when Dexamethasone (Dex) is given subcutaneously[26]. Both kinetics and dynamic morphologic parameters are altered in the adaptive process, and the influence of resection on nutrient uptake is due in part to these kinetic alterations. This may be due to the altered cell kinetics changing the population of the enterocytes along the villus, thereby leading to variations in the number of cells with transporter, or the activity of the transporters[27,28].

Many animal models of intestinal adaptation have been described: glucose uptake has been found to be increased during pregnancy[24], lactation[30], with the ingestion of a high carbohydrate diet[31], hyperglycemia[32], with diabetes[33], high alcohol intake[34] and after intestinal resection[35]. On the other hand, glucose uptake is decreased with aging[36], external abdominal radiation[37] and with the use of total parenteral nutrition[38]. Most transporters are up-regulated by the levels of dietary substrate levels, whereas toxic substances and essential amino acids have the opposite effect[9,38-40]. These examples illustrate the diversity and variability of this intestinal adaptive process.

The adaptive response in humans is not well characterized. Increases in nutrient absorption have been documented[41-43] in humans following resection. The role of morphological changes in this process, however, has not been conclusively demonstrated. Remnant small bowel lengthening and dilatation has been noted in patients with SBS, suggesting morphologic mechanisms in human intestinal adaptation[44]. However, the mucosal adaptation typical in rodent models is not seen in the human adaptive response[45,46]. Indeed, several studies have shown that no increases in villous height or crypt depth were detected among patients who underwent intestinal resection, as compared to healthy controls[42,47].

With the existence of various relevant anatomical, physiological and biochemical differences between the human and rodent gastrointestinal tracts[48], and a conspicuous lack of comparable human studies, the clinical adequacy of the rat as a model of intestinal adaptation remains to be determined. Although the morphological and functional changes that occur in the rodent following massive small bowel resection have been well characterized[23,49], direct evidence for similar changes in humans is lacking. Accordingly, caution must be used when attempting to extrapolate findings from rodent studies to the human population. An alternative model, the neonatal piglet, has been used in short bowel studies[50-52]. The neonatal pig has recently been used to determine the effects of IGF-1 and dietary manipulations in an intestinal resection model[53,54]. The degree to which the results obtained using this model reflect human findings has yet to be determined, and the rodent remains a popular model for studies of intestinal adaptation.

DIETARY REGULATION

The topic of the dietary regulation of intestinal gene expression has been reviewed[31,55]. Dietary constituents provide continual environmental signals that elicit the expression of a host of genes that influence intestinal adaptation[56]. Every day, enterocytes are exposed to different nutrients that vary according to the nutrient intake of the host. For this reason, the intestine must be able to

adapt to variations in the dietary load and composition[31,57]. The intestine, like many other biological and engineered systems, is quantitatively matched to prevailing peak loads with modest reserve capacities. Indeed, physiological capacities are optimal and most economical if they ascribe to the adage "enough, but not too much"[57]. Therefore, intestinal enzymes and transporters are characterized by a "safety factor", a parameter that represents the ratio of its capacity to the load placed on it[58]. The maintenance of this reserve capacity is biosynthetically costly, but is necessary given the unpredictable nature of dietary contents.

Parenteral vs enteral nutrition

Small bowel atrophy is well characterized in rodent models using total parenteral nutrition[59-61]. Not surprisingly, the presence of luminal nutrients also contributes greatly to the adaptive process. Intestinal adaptation following massive small bowel resection is limited, but not entirely abolished in the absence of luminal nutrition[62]. The following sections detail the effects of the type and amount of various luminal nutrients on the adaptive process.

Lipids

Dietary fat content influences the uptake of hexoses and lipids into rabbit jejunum following ileal resection[16]. More recently, using a rat model of SBS, Sukhotnik *et al* (2003) demonstrated that early feeding of a high fat diet increased lipid absorptive capacity of the intestinal remnant[63]. The main mechanisms of this effect may be an acceleration of structural intestinal adaptation, resulting in an increased number of enterocytes. However, at the molecular and cellular level, a high fat diet decreased mucosal mRNA levels of the lipid binding protein FAT/CD36 and decreased oleic acid uptake by isolated enterocytes. This is in contrast to what is seen with the liver fatty acid binding protein (L-FABP), a cytosolic lipid binding protein. Mice that were chronically fed a diet enriched in sunflower oil had increased the liver fatty acid binding protein (L-FABP) mRNA levels in their small intestine[64]. The effect was specific to this gene, as the intestinal fatty acid binding protein (I-FABP) was unaffected.

Not only the amount of fat, but also the type of dietary fat may influence intestinal function. Keelan *et al* (1996) tested the hypothesis that the intestinal morphology and uptake of nutrients after resection of the distal half of the small intestine in rats responds to alterations in the dietary content of saturated (SFA) and polyunsaturated (PUFA) fatty acids[65]. Adult female Sprague-Dawley rats were subjected to a sham operation or to the surgical resection of the distal half of the small intestine. The animals were fed chow for 3 wk, then either chow or isocaloric semisynthetic SFA or PUFA diets for a further 2 wk. The *in vitro* jejunal uptake of glucose was twice as high in animals that had undergone resection and were fed SFA than in those fed PUFA. It was suggested that SFA was necessary in the diet to ensure that adequate adaptation takes place.

Thiesen and colleagues examined the effect of dietary lipids on lipid uptake in rats post-resection. Intestinal resection had no effect on the mRNA expression of early response genes (ERGs), proglucagon, or the ileal lipid binding protein (ILBP), but was associated with reduced jejunal mRNA for ornithine decarboxylase (ODC) and for the liver fatty acid binding protein (L-FABP)[66]. These resection-associated changes in gene expression were not linked with alterations in the intestinal uptake of long chain fatty acids or cholesterol. In animals undergoing intestinal resection and fed SFA or given control vehicle, there was a reduction in jejunal proglucagon mRNA expression as compared to those animals fed chow or PUFA. ODC mRNA expression in the jejunum of resected animals was reduced. Thus, dietary lipids modify the uptake of lipids in resected animals, and ODC and proglucagon may be involved in this adaptive response[67].

The way by which dietary lipids alter gene expression and consequently change membrane composition and/or nutrient transport may be through the activation of peroxisome proliferator-activated receptors (PPAR), hepatic nuclear factor-4 (HNF-4), nuclear factor κ B (NFκB), and sterol response element binding proteins 1c (SREBP1c)[56]. By binding to these transcriptional factors, dietary lipids affect the rate of transcription and consequently the protein synthesis of nutrient transporters[65,68]. It is also known that PPARs belong to the superfamily of receptors that include the glucocorticosteroid receptor (GR)[69]. When the locally acting glucocorticosteroid (GC) budesonide was administered concomitantly with SFA diet, the jejunal uptake of glucose was increased but the ileal uptake of fructose was reduced[70].

It has been suggested that dietary lipids participate in signal transduction involving the activation of second messengers, such as cAMP, Ca^{2+} and diacylglycerol, thereby changing the mRNA expression[71]. Studies with glycosphingolipid have revealed the importance of these lipids and their metabolites in signaling pathways via the tyrosine kinase-linked receptors, a signal system mediated by protein kinase C (PKC), mitogen activated protein kinase (MAPK), other kinases, as well as mediated by the cytosolic Ca^{2+} concentration[72]. More recently, additional new signals involved in the adaptive intestinal response 3 days after a 50% intestinal resection have been identified by cDNA microarray analysis, such as small proline-rich protein 2, involved in wound healing; glutathione reductase, a gene involved in intestinal apoptosis; NF-2 family members, also involved in apoptosis; etoposide-induced p53-mediated apoptosis; basic Kruppe-like factor, a transcription factor that activates the promoter for IGF-1; and prothymosin-α, involved in cell proliferation[73,74]. These observations of altered expression of signals are useful to generate hypotheses that can be tested in future studies to establish whether these signals represent a primary or a secondary event.

The glycospingolipid, phospholipid, cholesterol and fatty acid composition of plasma membranes may be modified in mammalian cells[75]. For example, Keelan et al. (1990) demonstrated that alterations in dietary fatty acid saturation influence intestinal BBM phospholipid fatty acid composition in rats[76]. The investigators proposed that the previously reported diet-associated changes in active and passive intestinal transport are due at least in part to these alterations in the fatty acid composition in BBM phospho-

lipids. A diet enriched with SFA is associated with increases in the saturation of BBM phospholipid fatty acids, while a diet enriched with PUFA is associated with an increase in the unsaturation of BBM phospholipid fatty acids[3,4]. The degree of fatty acid unsaturation or saturation, as well as the cholesterol and ganglioside/glycosphingolipid content, are factors that influence the fluidity of the BBM[77,78]. Changes in the fluidity of the BBM may alter the permeation of molecules and nutrients through this barrier, as well as the conformation of binding sites on transporter proteins such as SGLT1 and GLUT5[79]. For example, alterations in BBM fluidity influence the passive uptake of lipids, as well as the carrier-mediated D-glucose uptake[79,80]. While enhancement of fluidity increases the uptake of lipids, fluidization of BBM from enterocytes located on the villous tip decreases the uptake of D-glucose to levels seen in the BBM from enterocytes located on the crypts[81]. The explanation for the effect of BBM fluidity on glucose uptake is unknown, but represents a potentially important post-translational process.

The lipid composition of cell membranes alters the passive permeability properties and transporter activity across the membrane[75]. The altered membrane lipid composition may act in part by changing the viscosity or fluidity of the membrane, including the microenvironment surrounding the transporter. Meddings (1989) compared *in vivo* membrane lipid permeability within the same intestinal region, under conditions where membrane physical properties were radically altered by feeding rats an inhibitor of cholesterol synthesis[82]. Marked reductions in membrane fluidity were observed due to the replacement of membrane cholesterol with its precursor 7-dehydrocholesterol. Associated with these alterations was a pronounced reduction in membrane lipid permeability. Therefore, BBM membrane lipid permeability*, in vivo*, appears to be correlated with the physical properties of the bilayer.

Recently, two types of specialized microdomains in the BBM have been identified: lipid rafts and caveolae. These regions are important in signal transduction as well as lipid and protein trafficking[83-85]. They are enriched in saturated fatty acids, cholesterol and gangliosides[84-86]. Feeding rats a diet enriched with gangliosides increases jejunal glucose uptake[87]. Feeding a ganglioside-rich diet increases the ganglioside content and decreases the cholesterol content in the intestinal mucosa, plasma, retina and brain[88]. Similar changes in the lipid composition of intestinal microdomains, or lipid rafts, occur following ganglioside feeding[89]. Although SGLT1 has been localized to these microdomains in renal epithelial cells[90], it is not known if sugar transporters reside in intestinal BBM microdomains. If this is the case, local changes in membrane fatty acids may affect the activity of transporter by altering the configuration of the protein, potentially exposing or masking the transporter binding sites and thereby modifying nutrient uptake. In addition, gangliosides may influence intestinal sugar transport *via* their effect on pro-inflammatory mediators, many of which are known to influence intestinal sugar transport[91-93]. For example, in rats challenged with lipopolysaccharide, ganglioside feeding reduced the production of intestinal platelet activating factor, PGE2, LTB4, as well as reduced plasma levels of IL-1β and TNF-α[94].

Carbohydrates

Dietary carbohydrate may induce the intestinal adaptive response by increasing the abundance of hexose transporters to facilitate a higher rate of sugar absorption[11]. In a murine model, intestinal glucose uptake was directly correlated with the dietary carbohydrate load[31,39,95]. The effect of dietary carbohydrate on nutrient transporter abundance has been reported in several animal models. For instance, the abundance of SGLT-1 in BBM and GLUT2 in the BLM were elevated in animals fed a high carbohydrate diet and associated with this enhanced level of protein was an increase in glucose absorption[19,96,97]. As well, the GLUT5 transporter abundance was elevated with enhanced dietary fructose, leading to increased fructose uptake[98].

The initiation of the dietary glucose-induced adaptive response occurs in the intestinal crypts, where the transport capacities of the nutrient transporters are programmed[39,40,95,97]. In this mouse model, phlorizin binding was utilized as a means of measuring the glucose transporter site density. Changing the murine diet from a high to a low carbohydrate regimen reduced the amount of glucose transporter, as estimated from the density of phlorizin binding. The alteration in the density of phlorizin binding was first observed in the crypt cells, and over a three-day period was subsequently seen in the villous tip cells. This suggests that the crypt enterocytes respond to the high carbohydrate diet to increase their phloridzin binding; those cells then migrate up the villous over the next three days, contributing to the process of enhancing glucose uptake.

The enterocytes may adapt to the high carbohydrate diet by increasing the crypt cell turnover rate, enhancing the enterocyte migration rate, as well as by reprogramming the capability of nutrient transporters in the crypts to accommodate to the requirement for higher monosaccharide transporters[97].

Animals fed a glucose-enriched diet have an increased glucose uptake, resulting from up-regulation of both BBM and BLM glucose transporters[19,96,99]. The precocious introduction of dietary fructose causes enhanced expression of fructose transporters and fructose transport earlier during development, without changing glucose uptake[97]. The substrates glucose and fructose are both specific in terms of up-regulation of their corresponding transporters, SGLT1 and GLUT5. Therefore, increasing the sugar composition of the diet results in increases in the transport of these nutrients. In contrast, increases in essential amino acids or other substances that are potentially toxic at high levels (such as iron, calcium or phosphorous) are associated with no change, or even reductions in transport[38,100].

Furthermore, in many cases other nutrients may be equal or even more potent inducers of the transporter than its specific substrate. For example, young animals fed a diet enriched with polyunsaturated fatty acids (PUFA) have a decline in glucose uptake, as compared to animals fed a saturated fatty acid (SFA) enriched diet[70,101,102]. Similarly, Vine *et al* (2002) studied the effect of various fatty acids on the passive and active transport properties of rat jejunum, and found that an SFA-enriched diet increased Na^+-dependent glucose uptake when compared to a diet

enriched with n6 PUFA[103]. In contrast, in aged rats, glucose uptake is increased by PUFA and not by SFA[36].

Dietary fiber also modulates intestinal nutrient uptake. For example, a diet enriched with fermentable fiber increased glucose uptake and GLUT2 transporter abundance in dogs[104]. *In vitro* studies, in which rat intestinal tissue was incubated with β-glucan isolated from barley or oats, show reductions in the uptake of stearic and linoleic acids (Drozdowski *et al*, 2005, unpublished observations). Furthermore, many studies have investigated the effect of TPN supplemented with short chain fatty acids, the products of fiber fermentation. Increases in glucose uptake, GLUT2 mRNA and protein, and intestinal morphology were seen in normal rats as well as in rats following intestinal resection[105-108].

Protein

Dietary protein also has an impact on the intestinal morphology and active amino acid transport[40,109,110]. Both *in vitro*[110] and *in vivo*[109] rat experiments have shown that a high protein diet increases amino acid uptake in the jejunum. An alteration in the amount of dietary protein induces reversible adaptation of the non-essential amino acid transport rate[111]. Feeding a high protein diet to mice induces a 77%-81% increment in the uptake of non-essential amino acids[40], yet only a 32%-61% increase for essential amino acids. On the other hand, a protein-deficient regimen reduces uptake of non-essential amino acids, such as aspartate and proline, and maintains or increases uptake for essential amino acids and alanine. Thus, the nature of the adaptive response depends upon the type of amino acid and the needs of the animal.

Glutamine is a key metabolic fuel for enterocytes, mediating cellular nucleic acid synthesis and proliferation. Parenterally fed rats demonstrate decreased atrophy of the intestinal mucosa following glutamine supplementation[112]. Glutamine administration also normalizes the reduced levels of intestinal adaptation in rats receiving total parenteral nutrition (TPN) following intestinal resection[113]. It is noteworthy that some studies of oral glutamine supplementation in the rat have failed to document more than temporary mucosal proliferation[114]. This indicates that mechanistic differences that are intrinsic to the method of glutamine administration may exist, and suggests that these may be significant in regulating the adaptive response.

Other amino acids may inhibit intestinal adaptation. Sukhotnik *et al* (2005) examined the effects of the parenteral administration of the nitric oxide precursor arginine to rats following 75% small bowel resection[115]. Arginine supplementation was associated with lower cell proliferation indexes and greater enterocyte apoptosis. This observation led the investigators to conclude that arginine inhibits structural intestinal adaptation.

Polyamines

Polyamines are found in all eukaryotic cells[116], and they play an important role in growth and differentiation[117]. Polyamines are obtained either from the diet, or via synthesis from ornithine[118]. Uda *et al* (2002) demonstrated that luminal perfusions of polyamines rapidly (in less than 5 min) enhance intestinal glucose uptake in rats, and increase BBM SGLT1 protein[119].

Polyamine synthesis or uptake may be an important event that initiates the adaptive hyperplasia seen in the intestinal remnant after partial small bowel resection. Enteral diets supplemented with ornithine alpha-ketoglutarate (OKG), a precursor for arginine, glutamine and polyamines, enhances intestinal adaptation in models of intestinal resection[120,121]. Indeed, studies by both Tappenden *et al*[122] and Thiesen *et al*[66] suggest that ornithine decarboxylase (ODC), a key enzyme in polyamine synthesis, may mediate the adaptive process in rats that is stimulated by the administration of either glucocorticosteroids or short chain fatty acids to rats following intestinal resection.

The role of polyamines in the adaptation of the intestine during development has also been studied. Wild *et al* (2005, unpublished observations) showed that in postnatal rats, oral spermidine treatment resulted in the precocious expression of the intestinal sugar transporters (SGLT1, GLUT2 and GLUT5), as well as ODC. This led the investigators to conclude that oral polyamines induce precocious maturation of sugar transporters, which may be mediated by alterations in ODC gene expression.

HORMONAL REGULATION

Glucocorticosteroids

In a model of extensive intestinal resection (50% enterectomy), the proximal and distal intestinal remnants were adequate to assess the morphology and function at these sites[11,112]. The glucocorticosteroid prednisone had no effect on the intestinal uptake of glucose or fructose in these resected animals[70]. In contrast, the locally acting steroid budesonide increased by over 120% the value of the jejunal Vmax for the uptake of glucose, and increased by over 150% the ileal uptake of fructose. The protein abundance and mRNA expression of SGLT1, GLUT5, GLUT2 and Na+/K+ APTase α 1 and β 1 cannot explain the enhancing effect of budesonide on glucose and fructose uptake. Budesonide, prednisone and dexamethasone reduced the jejunal expression of the early response gene c-jun. In resected animals, the abundance of the mRNA of ODC in the jejunum was reduced, and glucocorticosteroids (GC) reduced the jejunal expression of the mRNA of proglucagon. These data suggest that the enhancing influence of GC on sugar uptake in resected animals may be achieved by post-translational processes involving signalling with c-jun, ODC and proglucagon, or other as yet unknown signals.

In contrast, the uptake of D-fructose by GLUT5 was similarly increased with budesonide and with prednisone. The increases in the uptake of fructose were not due to variations in the weight of the intestinal mucosa, food intake, or in GLUT5 protein or mRNA expression. There were no steroid-associated changes in mRNA expression of c-myc, c-jun, c-fos, of proglucagon, or of selected cytokines. However, the abundance of ileal ODC mRNA was increased with prednisone. Giving budesonide or prednisone to post- weaning rats for four weeks in doses equivalent to those used in clinical practice increases

fructose but not glucose uptake. This enhanced uptake of fructose was likely regulated by post-translational processes[70].

Growth hormone

Growth hormone (GH) has been suggested as possessing pro-adaptive properties[123]. In rats and piglets, GH administration results in an increase in small bowel length and function per unit length[124]. Hypophysectomized rats undergo mucosal hypoplasia of the small bowel, as well as a reduced adaptive response following resection that is restored by GH[125]. In contrast, transgenic mice expressing elevated levels of GH show hypertrophy of the small intestine[124]. IGF-1 expression in the small bowel is regulated by GH and is believed to induce enterotrophic effects following resection[113,126]. In a rat model of SBS, acute IGF-1 treatment of TPN fed rats produced sustained jejunal hyperplasia, and facilitated weaning from parenteral to enteral nutrition[127]. GH administration to normal rats has been reported to have positive effects on mucosal growth and intestinal adaptation following massive resection[128], although contradictory data exists[129,130]. Human and rabbit studies have indicated that increased nutrient transport activity devoid of morphologic changes may be the method of GH-induced intestinal adaptation[131].

GH administration has been shown to inhibit the liberation of glutamine from muscle during catabolic states in humans[132], suggesting a possible role for combined GH and glutamine provision in adaptive bowel enhancement. Trials investigating any such synergism in the rat have yielded conflicting results. Some studies have failed to demonstrate an additive effect of GH and glutamine in the enhancement of post-resection intestinal adaptation[133], while others have documented a positive synergistic effect[134].

The mechanisms of action by which GH and/or glutamine may enhance the human adaptive process cannot be clearly surmised from the existing rodent data. Many studies have inherent deficits in terms of nutrient controls that could have contributed to the conflicting outcomes which have been described. The trophic effects of enteral nutrition on the adaptation process are well known[3]. Studies evaluating the contribution of non-specific, nutrient-derived augmentation of the adaptation process, as well as the mechanisms of any such nutrient factor interactions, may be useful in defining more accurate and therapeutically applicable results.

Animal studies have confirmed the enhancing effect of GH on nutrient absorption[123,124]. For example, GH has been shown to enhance the absorption of amino acids using *ex vivo* human BBM vesicles[134]. An intestinal mucosal GH receptor has been described in rats and humans[135], and GH promotes cell differentiation and clonal expansion of these differentiated cells[136].

The use of growth hormone in human clinical studies has been investigated. It has been suggested that the efficacy of GH and/or glutamine therapy in the adaptive response of the small bowel may be based mainly upon the clinical status of the patient (for example, the presence of a portion of the colon in continuity with the remaining resected small intestine)[137]. Evaluation of the effect of such variables in the rat may facilitate further understanding of the pathology and physiology of the bowel adaptation process, as well as more clearly defining positive predictive indicators of the bowel's ability to be rehabilitated. Furthermore, existing human data has indicated that the administration of high concentrations of GH can actually increase patient morbidity and mortality[138], demonstrating a primary need for equivalent clinical research in the testing of these factors.

In home parenteral nutrition (HPN)-dependent patients with SBS, the use of high dose recombinant human GH (0.4 mg/kg per day) in controlled[138,139] and uncontrolled studies[140] has led to variable results. These patients were given glutamine supplements by mouth or parenterally, and their diet was modified. In the randomized and placebo-controlled study of Scolapio *et al*[139], the subjects ingested a standardized 1500 kcal/d diet, which is clearly different from the hyperphagic diet consumed by many SBS patients[140], and which may contribute to the physiological adaptation that occurs in the remaining intestine after extensive resection. It is unclear whether glutamine is beneficial for the adaptive response in humans, and in rat models of SBS, it is unclear whether glutamine supplementation is efficacious for the adaptive process[2,141]. Furthermore, both a hyperphagic diet and the absence of malnutrition are needed for humans to achieve optimal intestinal adaptation[44,142].

When HPN-dependent patients with SBS were provided a usual *ad libitum* hyperphagic diet, and given low doses of GH (0.05 mg/kg per day) for three weeks, there was significant improvement in the intestinal absorption of energy (15% ± 5%), nitrogen (14% ± 6%) and carbohydrate (10% ± 4%)[143]. The increased food absorption represented 37% ± 16% of total parenteral energy delivery. Body weight, lean body mass, D-xylose absorption, insulin-like growth factor 1, and insulin-like growth factor binding protein 3 increased, whereas uptake of GH binding protein decreased. During treatment with GH, improvement in net intestinal absorption compared with placebo was 427 ± 87 kcal/d, representing 19% ± 8% of the total energy expenditure required to obtain energy balance equilibrium in patients with SBS[140].

A review of the literature in this area by Matarese *et al*[144] noted that there were differences in gastrointestinal (GI) anatomy, dietary compliance, nutritional status, presence of mucosal disease, and diagnosis both within and between the studies. They concluded that "*administering recombinant human growth hormone alone or together with glutamine with or without a modified diet may be of benefit when the appropriate patients are selected for treatment*".

Insulin-like growth factor 1

Insulin-like growth factor 1 (IGF-1) also proved to be efficient in increasing intestinal adaptation following resection in rats. IGF-1 treatment following 70% jejuno-ileal resection attenuated fat and amino acid malabsorption[145] and increased total gut weight by up to 21%. The IGF-1 receptor was increased in the jejunum and

colon due to resection. Resection also increased circulating IGF-binding proteins (IGFBP). IGF-1 treatment had no effect on IGF-1 mRNA or IGF-1 receptor density, but increased IGFBP5 in the jejunum. This increase in IGFBP5 was correlated with jejunal growth after IGF-1 treatment[146].

More recently, a study was conducted to determine the effect of IGF-1 on enterocyte kinetics following intestinal resection[147]. IGF-I treatment in resected rats significantly increased jejunal mucosal mass by 20% and mucosal concentrations of protein and DNA by 36% and 33%, respectively, above the response to resection alone. These changes reflected an increase in enterocyte proliferation and an expansion of the proliferative compartment in the crypt. No further decrease in enterocyte apoptosis and increase in enterocyte migration were observed.

IGF-I treatment may also facilitate weaning from parenteral to enteral nutrition. After a 60% jejunoileal resection plus cecectomy, rats treated with recombinant human IGF-I (3 mg/kg body weight) or control vehicle were maintained exclusively with TPN for 4 d and were then transitioned to oral feeding. TPN and IGF-I were stopped 7 d after resection and rats were maintained with oral feeding for 10 more days. Acute IGF-I treatment induced sustained jejunal hyperplasia, as demonstrated from the presence of greater concentrations of both jejunal mucosal protein and DNA, and was associated with the maintenance of a greater body weight and serum IGF-I concentrations[127].

A study was done using male transgenic mice with targeted smooth muscle IGF-1 overexpression[148]. These animals and non-transgenic littermates underwent 50% proximal small bowel resection. The results showed that growth factor over-expression led to a unique mucosal response characterized by a persistent increase in remnant intestinal length and an increase in mucosal surface area. Therefore, IGF-1 signaling from within the muscle layer may be important in resection-induced intestinal adaptation.

Epidermal growth factor

Epidermal growth factor (EGF) up-regulates intestinal nutrient transport[149]. This effect is mediated by PKC and PI3K[150] and involves the redistribution of SGLT1 from microsomal pools to the BBM[151]. After massive intestinal resection, endogenous EGF is increased in the saliva and is decreased in the urine[152]. EGF stimulates intestinal adaptation after intestinal resection: the BBM surface area and the total absorptive area increased until d 10, and EGF treatment induced a further increase in BBM surface area[153]. In a study by O'Brien and colleagues[154], mice underwent a 50% small bowel resection or sham operation, and were then given orally an epidermal growth factor receptor (EGFR) inhibitor (ZD1839, 50 mg/kg per day) or control vehicle for 3 d. ZD1839 prevented EGFR activation, as well as the normal postresection increases in ileal wet weight, villus height, and crypt depth. Enterocyte proliferation was reduced two-fold in the resection group by ZD1839. These results more directly confirm the requirement of a functional EGFR as a mediator of the postresection adaptation response. Interestingly, previous work has demonstrated that the EGFR is predominantly located on the BLM of enterocytes[155], but after small bowel resection the EGFR shows redistribution from the BLM to the BBM, with no change in the total amount of EGFR[156]. It is not known how this redistribution occurs. This is an important point, since modification of this process may represent a useful means to accelerate the intestinal adaptive process.

In a study by Knott *et al*[157], laser capture microdissection (LCM) microscopy was used to elucidate the specific cellular compartment(s) responsible for postresection changes in EGFR expression. Mice underwent a 50% proximal resection or sham operation, and after three days frozen sections were taken from the remnant ileum. Individual cells from the villi, crypt, muscularis and mesenchymal compartments were isolated. EGFR mRNA expression for each cell compartment was quantified using real-time reverse transcription polymerase chain reaction (RT-PCR). EGFR expression was increased two-fold in the crypt after resection, directly correlating with the zone of cell proliferation. This supports the hypothesis that EGFR signaling is crucial for the mitogenic stimulus for adaptation. The additional finding of increased EGFR expression in the muscular compartment is novel, and may imply a role for EGFR in the muscular hyperplasia seen after massive small bowel resection. As noted previously, it is of interest that the muscle layer also appears to play a role in the adaptive response to IGF-1[148].

The treatment of resected rats with EGF has been studied. In a study by Sham *et al*[158], male juvenile rats underwent either transection or ileocecal resection leaving a 20-cm jejunal remnant. Resected animals were treated orally with placebo or recombinant human EGF. Resected EGF-treated animals lost significantly less weight than those in the transection group, absorbed significantly more 3-0 methylglucose, and had reduced intestinal permeability as determined by the lactulose/mannitol ratio. Work by Chung *et al*[159] using rabbits showed that intestinal resection altered SGLT1 mRNA and protein expression along the crypt-villous axis, with expression being highest in the mid-villous region. Oral EGF normalized SGLT1 expression, resulting in a gradient of increasing expression from the base of the villus to the villous tip.

More recently, Nakai and colleagues[160] investigated the role of EGF in stimulating intestinal adaptation following small bowel transplantation. Treatment of rats with EGF (intraperitoneally for three days) following intestinal transplantation resulted in increased glucose absorption, SGLT1 abundance and the villous height and crypt depth in the graft. This has not yet been studied in humans.

Keratinocyte growth factor

In a study by Yang *et al*[161], adult C57BL/6J mice were randomized to a 55% mid-small bowel resection, resection with keratinocyte growth factor (KGF) administration (SBSKGF), or a sham-operated (control) group, and were killed at d 7. Ussing chamber studies showed that KGF increased the net transepithelial absorption of 3-O-methyl glucose as well as sodium-coupled alanine absorption, but

had no effect on epithelial permeability barrier function. Epithelial cells were separated along the crypt-villous axis with LCM, and epithelial KGF receptor (KGFR) mRNA abundance was studied using real time RT-PCR. KGF up-regulated KGFR mRNA abundance, predominately in the crypt and the lower portion of the villus.

Leptin

Leptin plays an important role in the regulation of body fat and satiety (reviewed in[162]). Leptin reduces food intake[163] and leptin-deficient mice develop obesity[164]. Leptin may be a potential growth factor for the normal rat small intestine. The effect of 14 d of parenteral leptin administration (2 μg/kg per day) to rats following 80% small bowel resection was studied. Leptin was associated with a 44% increase in galactose absorption and a 14% increase in GLUT-5 abundance, but with no change in DNA content or in SGLT abundance. These findings suggest that leptin may potentially be clinically useful in patients with impaired intestinal function[165].

Ghrelin

Ghrelin is a gastric hormone that is released in response to enteral nutrients. It has an opposite effect when compared to leptin, as it stimulates food intake[166]. The role of ghrelin in intestinal adaptation is unknown.

Glucagon-like peptide 2

Animal studies have demonstrated a potential role for GLP-2 in the adaptive response following intestinal resection[147]. Several investigators have demonstrated increases in plasma GLP-2 levels following intestinal resection in rats[167-169]. In a study by Dahly *et al*[147], rats were subjected to 70% midjejunoileal resection or ileal transection, and were maintained with TPN or oral feeding. Resection-induced adaptive growth in TPN- and orally-fed rats was associated with a significant positive correlation between increases in plasma bioactive GLP-2 and proglucagon mRNA abundance in the colon of TPN-fed rats and in the ileum of orally fed rats. While these increases were transient in the TPN-fed group, luminal nutrients produced a sustained increase detected at 3 and 7 d post-resection. These data support a significant role for endogenous GLP-2 in the adaptive response to mid-small bowel resection in both TPN and orally fed rats[147].

Recently, further correlations between post-resection GLP-2 levels, morphological indices, crypt cell proliferation rates and nutrient absorption have been made[170]. In this study, an inverse correlation was found between post-prandial GLP-2 levels and fat or protein absorption as assessed by a 48 h balance study. These results, along with data obtained from studies showing that GLP-2 immunoneutralization inhibits post-resection adaptation[171], further implicate GLP-2 as a post-resection mediator of adaptation.

GLP-2 administration in rats increases the adaptive response to massive intestinal resection[172]. In this study, Sprague-Dawley rats were divided into two groups, with a 75% mid-jejunum-ileum resection and a sham operated groups. Animals were treated with 0.1 μg/g GLP-2 analog (protease resistant human GLP-2) or placebo given subcutaneously twice daily for 21 d. The total weight of the rats and the mucosal mass per centimeter were compared between the groups. Administration of this peptide or its analogs was associated with an increase of the mucosal mass in the proximal jejunum and terminal ileum. The absorption and urinary excretion of oral D-xylose is proportional to intestinal mucosal surface area and transit time. While resection reduced D-xylose excretion and GLP-2 restored D-xylose excretion to levels above control values within 21 d of administration. This indicates that GLP-2 has a positive effect on intestinal morphology and absorptive function following resection.

More recently, Martin *et al*[173] investigated the effects of GLP-2 in a TPN-supported model of experimental short bowel syndrome. Juvenile Sprague-Dawley rats underwent a 90% small intestinal resection and were randomized to three groups: enteral diet and intravenous saline infusion, TPN only, and TPN plus 10 μg/kg per hour^{GLP-2}. TPN plus GLP-2 treatment resulted in increased bowel and body weight, villus height, intestinal mucosal surface area, and crypt cell proliferation. Intestinal permeability tests showed that GLP-2 reduced the lactulose-mannitol ratio indicating that GLP-2 lowered intestinal permeability when compared with the TPN alone. GLP-2 increased serum GLP-2 levels and intestinal SGLT-1 protein abundance compared with either TPN or enteral groups. This study demonstrates that GLP-2 is capable of stimulating intestinal adaptation in the absence of enteral feeding,

Because a number of hormones and growth factors have been shown to influence intestinal function, Washizawa *et al*[174] compared the effects of GLP-2, GH and KGF on markers of gut adaptation following massive small bowel resection (MSBR). KGF increased goblet cell numbers and TTF3, a cytoprotective trefoil peptide, in the small bowel and the colon. They also observed that while both GH and KGF increased colonic mucosal growth, GLP-2 exerted superior trophic effects on jejunal growth. GLP-2 also increased the glutathione/glutathione disulfide ratio, resulting in improved mucosal glutathione redox status throughout the bowel. Because of the differential effects of GLP-2, GH and KGF on gut adaptation following MSBR, the authors conclude that a combination of these agents may be most beneficial.

A pilot study to determine the efficacy of GLP-2 in patients with SBS has been completed. A non-placebo controlled study was conducted in 8 patients with SBS with an end-enterostomy type of anastomasis (6 had Crohn's disease and 4 were not receiving HPN)[175]. Treatment with GLP-2 (400 μg subcutaneously twice a day for 35 d) increased intestinal absorption of energy, body weight, and lean body mass. Crypt depth and villous height were also increased in 5 and 6 patients, respectively.

A review by Jeppesen[176] on the role of GLP-2 in the treatment of SBS concludes that *"Currently, hormonal therapy in short-bowel patients should be considered experimental and it is only recommended in research studies. The optimal duration and concentration requirements for GLP-2 to induce beneficial effects on intestinal secretion, motility, morphology and most importantly absorption, are not known. Optimal dosage and administration of this new treatment to short-bowel patients may eventually result in long-term improvements in nutritional status and independence of*

parenteral nutrition in a larger fraction of short-bowel patients".

SIGNALS OF INTESTINAL ADAPTATION

A number of studies have investigated the signals involved in intestinal adaptation using animal models of intestinal resection. Dodson *et al*[177] identified three subsets of genes that were up-regulated by constructing a cDNA library from the remnant ileum of resected rats. This library was screened, and subtractive hybridization was used to identify genes that were induced following resection. These included genes involved with regulating the absorption and metabolism of nutrients. For example, L-FABP, apolipoprotein A-IV, cellular retinal binding protein II and ileal lipid binding protein were identified as genes that were induced following 70% intestinal resection in rats. Genes involved in cell cycle regulation were also identified. For example, phosphorylation and dephosphorylation are important regulators of the cell cycle, and PP1δ, a subunit of a serine/threonine phosphatase was indeed up-regulated. Grp78, a member of the heat shock protein family was also increased. Grp78 resides in the ER and acts as a chaperone during protein assembly and transport. It may also have a protective role, and prevent apoptosis as a way of promoting the proliferative response following intestinal resection[178,179].

Rubin *et al*[180] further characterized the molecular and cellular mechanisms following 70% resection in rats. An immediate early gene, PC4/TIS7, was markedly increased soon after resection, with levels returning back to normal by one week post-resection. Although the function of this protein is unknown, it may be related to cytodifferentiation as it is expressed only in the villus and not in the crypts.

Erwin *et al*[74] used cDNA microarrays to gain insight into the mechanism of intestinal adaptation. Mice underwent a 50% intestinal resection and three days afterwards RNA was extracted from the remnant ileum. Multiple genes were induced, and they divided these into four categories: (1) Apoptosis, DNA synthesis, repair and recombination (10 genes); (2) Oncogenes, tumor suppressors, cell cycle regulators (3 genes); (3) Stress response, ion channels and transport (4 genes); (4) Transcription factors and general DNA-binding proteins (1 gene). Many of the genes (ODC, c-neu, glucose-related protein, IGFBP-4) that were identified agreed with the results of other studies of intestinal resection. For example, ODC was increased in this study, and this agrees with previous findings that showed ODC to be involved in the adaptive process[66,122,181]. Some new factors were also identified including glutathione reductase (involved in apoptosis), Basic Kruppel-like factor (transcriptional regulator that activates the IGF promoter), prothymosin-α (associated with increased cell proliferation), and eteposide induced p53 responsive mRNA (stress response protein involved in p53 mediated apoptosis).

Stern *et al*[73] performed a similar analysis of gene expression following 50% intestinal resection in rats. The gene with the largest increase was identified as *sprr2*, a novel gene unknown previously to be involved in intestinal adaptation. EGF administration post-resection further increased *sprr2* expression and enhanced the adaptive response. This protein plays a role in the terminal differentiation of stratified squamous epithelium. Its role in the intestinal epithelium is unclear and warrants further investigation.

Finally, a variety of other signals have been described as possibly playing a role in the process of intestinal adaptation. These include prostanoids[182], uncoupling proteins[183], peroxisome proliferation-activated receptor α (PPARα)[184], transforming growth factor-α[185], SPARC (secreted protein, acidic and rich in cystine[186], Bcl-2[187], endothelin-1[188], erythropoietin[189], the GATA family of zinc finger transcription factors[190], hepatocyte growth factor[191], the early response genes (ERG)[192], PC4/TIS7[180] and epimorphin[193]. More recently, augmented Wnt signaling has been shown to enhance the adaptive response to massive small bowel resection[194]. Several of these signals may be useful to modify in a clinical setting to enhance the intestinal adaptive response.

Microarray technology is a powerful tool that is constantly developing into a more sophisticated technique of identifying novel genes involved in physiological processes. Intestinal adaptation awaits further characterization by hypothesis-testing studies. From the information that is available at this time, it is clear that genes regulating the cell cycle, proliferation, differentiation and apoptosis are important components of the adaptive process.

CONCLUSION

The process of intestinal adaptation is complex and multifaceted. Although a number of trophic nutrients and non-nutritive factors have been identified in animal studies, successful and reproducible clinical trials are lacking. However, the functional adaptation of segmental bowel grafts has been studied. Benedetti *et al* (2001) reported a case study in which a segmental graft from a living donor demonstrated preogressive functional adaptation, as assessed by water and D-xylose absorption as well as fecal fat studies[195]. Morphological adaptation has been documented in three patients following successful intestinal transplantation[196]. In fact, more than 50% increases in villous height and absorptive surface area were seen at 6 mo, suggesting that functional changes in intestinal function are associated with morphological changes. Therefore, while human data is limited there is evidence indicating that the adapative process occurs. Still, additional human studies are required before the clinical implications of the animal data can truly be established. Understanding the mechanisms underlying the adaptive process in humans may direct research toward strategies that maximize intestinal function and impart a true clinical benefit to patients with short bowel syndrome.

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