Promoting intestinal adaptation

Intestinal adaptation is the process by which the intestine responds to loss of surface area in order to maximize functional capacity. Recent studies suggest that the process can be accelerated and augmented by a combination of nutritional and non-nutritional interventions.

Short bowel syndrome is the leading cause of intestinal failure in the UK. The management of patients with short bowel syndrome must focus on the provision of supportive care with parenteral nutrition, but should also aim to encourage the remaining bowel to adapt to the loss of mucosal surface area. This process of intestinal adaptation includes both anatomical and functional changes which together increase the absorptive capacity of the remaining intestine and result in reduced parenteral requirements. In patients with a borderline length of residual intestine, adaptation may allow complete weaning from parenteral nutrition with avoidance of the associated complications. This article will briefly examine current understanding of the mechanisms behind intestinal adaptation, much of which derives from animal models, and will explore the therapeutic approaches aimed at accelerating and enhancing the process.

Mechanisms of intestinal adaptation

Extensive small intestinal resection results in marked structural and functional change in the residual intestine, with a significant increase in intestinal mass seen in rodent and canine models over a period of weeks postoperatively. Macroscopically, there is thickening of the small intestinal wall, predominantly as a result of mucosal hyperplasia, and dilatation and lengthening of the remaining intestine. Microscopically, small intestinal villi become elongated and there is deepening of the crypts (Williamson, 1978). Histological studies indicate an upregulation of both cell proliferation and apoptosis, and a shift in the balance between the two resulting in villous hypertrophy. The net effect of these changes is an increase in intestinal surface area which results in increased absorption of water, electrolytes and nutrients. Intestinal absorption is further augmented by upregulation of luminal transport proteins such as the Na+/glucose cotransporter (Hines et al, 1994).

Compared to animal models, there is less evidence of dramatic anatomical changes occurring in humans after loss of small intestinal length. However, studies in humans have shown a degree of intestinal lengthening and dilatation and there is evidence of increased mucosal cell proliferation and turnover resulting in villous lengthening. There is also functional evidence of adaptation as demonstrated by the ability of some patients with short bowel syndrome to be weaned off parenteral nutrition. The ability to become independent from parenteral feeding has been demonstrated to be dependent on the length of remaining small bowel and the presence of a colon in continuity, but to be rare if parenteral nutrition has been administered for >2 years (Messing et al, 1999).

An important difference between animal models and human subjects is the exact anatomy remaining after resection. In animal models of extensive small bowel resection a segment of jejunum is usually removed leaving ileum and colon in continuity. However, in humans, ileum is commonly lost and the most frequent post-resection anatomical variations are either an end-jejunostomy or a jejunocolic anastomosis. Studies in animals suggest that ileum has a much greater capacity for adaptive change, both anatomical and functional, than jejunum (Dowling and Booth, 1967). Human data suggest that there is very little structural adaptation in patients with an end jejunostomy; in patients with a jejunocolic anastomosis data are inconclusive with some studies demonstrating mucosal hyperplasia and others not.

Promoting adaptation

Theoretically, intestinal adaptation can be manipulated in a number of ways. The process of adaptation can be accelerated so that maximal adaptation occurs faster. Alternatively, the process of adaptation may be augmented so that a greater degree of adaptation occurs and functional capacity of the remnant small intestine is increased beyond the limits of what is normally achievable. Interventions aimed at promoting intestinal adaptation are commonly split into those which are nutritionally based and those which are non-nutritional. Nutritional manipulation generally aims to accelerate and maximize adaptation, while non-nutritional interventions, such as administration of exogenous growth factors, may allow further augmentation of the natural adaptive process.

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Nutritional interventions

The importance of enteral nutrients to intestinal morphology and function can be seen when subjects are fasted. In rodents, there is rapid loss of intestinal mucosal weight despite provision of adequate nutrients parenterally. Similarly, in humans who are kept nil by mouth for 3 weeks and fed parenterally, mucosal thickness is reduced by 20% compared to baseline (Buchman et al, 1995) and in children receiving long-term parenteral nutrition there is a significantly reduced rate of mucosal proliferation (Rossi et al, 1993). The anatomical changes associated with total parenteral nutrition are accompanied by functional changes including reduced brush border hydrolase activity and reduced concentrations of membrane transport proteins. The combined effect of these anatomical and functional changes is a significant reduction of intestinal digestive and absorptive capacity.

Experiments in animals have demonstrated that exposure to luminal nutrients is a critical stimulus to intestinal adaptation. In animals fed parenterally after small intestinal resection, the adaptive response is significantly attenuated (Feldman et al, 1976). There has been considerable interest in whether specific nutrients or types of nutrient can accelerate or enhance the adaptive response and a list of those implicated is shown in *Table 1*. Complex nutrients appear to provide a greater stimulus for adaptation than elemental and partially digested diets. This has led to the concept that intestinal adaptation is related to the 'functional workload' of the remaining intestine (Tappenden, 2006), possibly mediated by effects of these complex nutrients on production of pancreato-biliary secretions and release of growth factors such as those described later in this review.

Fatty acids and triglycerides

Soluble fibres, such as pectin, are important in patients with residual colon in continuity with the small intestine, as fermentation by colonic bacteria leads to production of short-chain fatty acids (SCFAs). SCFAs can provide an important source of calories and also prevent atrophy of the colonic mucosa. SCFAs have also been shown to enhance the small intestinal adaptive response and to increase the production of small intestinal transport proteins (Grey et al, 1984). Enteral, but not parenteral, lipid has been shown to enhance the adaptive response (Sukhotnik et al, 2004). While stimulatory effects appear greatest with free fatty acids, long-chain triglycerides also appear to have a beneficial role, possibly as a result of the provision of polyunsaturated fatty acids involved in cytokine synthesis, including arachadonic acid, eicosapentanoic acid and docosahexanoic acid.

Table 1. Nutrients that may stimulate the adaptive response

Soluble fibres
Long-chain triglycerides
Short-chain fatty acids
Glutamine
Arginine

Glutamine and arginine

Glutamine is a vital energy source for enterocytes while arginine is believed to be important in the maintenance of the intestinal barrier. In rodents, restriction of glutamine in animals fed parenterally results in rapid mucosal atrophy which is, in part, attenuated if glutamine is included in the intravenous feeds. Similarly, in pigs, inclusion of glutamine in parenteral feeds reduces the degree of mucosal atrophy in animals kept nil by mouth. In rat models of extensive small bowel resection, parenteral glutamine supplementation has been shown to improve the adaptive response (Tamada et al, 1993). However, data from humans have failed to show a similar effect and benefits of glutamine supplementation have only been seen in patients also receiving exogenous growth hormone. Arginine restriction, as with glutamine restriction, has a deleterious effect after massive small bowel resection in animal models. However, studies of arginine supplementation have failed to demonstrate a consistent benefit, with some even suggesting negative effects (Sukhotnik et al, 2003).

Non-nutritional interventions

Animal studies have identified a large number of naturally occurring humoral factors that are involved in the adaptive response (*Table 2, Figure 1*) (Cisler and Buchman, 2005). Experimental supplementation of these growth factors following intestinal resection enhances intestinal growth by increasing crypt cell proliferation and suppressing apoptosis. Intestinal function is further enhanced as a result of increased expression and activity of brush border enzymes. Several growth factors also enhance intestinal barrier function and pro-

Table 2. Growth factors shown to promote intestinal adaptation

Growth hormone
Glucagon-like peptide 2
Insulin-like growth factor 1
Epidermal growth factor
Hepatocyte growth factor
Transforming growth factor α
Keratinocyte growth factor
Neurotensin
Leptin

mote mucosal healing following ischaemic or inflammatory injury. Often these factors have been studied in isolation but it is becoming increasingly apparent that many of them act in concert. Several growth factors (e.g. epidermal growth factor (EGF), glucagon-like peptide 2 (GLP-2), growth hormone (GH), keratinocyte growth factor (KGF), and insulin-like growth factor 1 (IGF-1)) have been shown to have synergistic effects on mucosal growth. Some growth factors (e.g. EGF and transforming growth factor (TGF-α)) bind to the same receptors, while others growth factors (e.g. IGF-1) act primarily as downstream mediators. To date, clinical data in humans are limited to the effects of GH, GLP-2 and EGF. Unsurprisingly it has not always been possible to replicate findings from animal models.

Growth hormone

GH is secreted into the blood by the anterior pituitary gland and has growth stimulating effects on a wide variety of tissues. The intestinotrophic effects of GH are largely mediated through IGF-1, which is produced in the liver and also locally in mesenchymal cells of the lamina propria. GH is the only growth factor currently holding a Food and Drug Administration licence for the treatment of intestinal failure. However, evidence supporting its efficacy remains inconsistent, and positive effects on nutrient absorption and body weight have not been shown in all studies. In addition, no published trials have demonstrated an increase in fat absorption.

Comparison between published studies is hampered by the fact that trial protocols vary considerably with respect to patient populations, treatment protocols and outcome measures. These concerns have led to calls for caution in using GH as standard therapy (Scolapio, 2006). Nevertheless, results from the most recent prospective, double-blind, randomized, placebo-controlled trial of 41 parenteral nutrition dependent adults, appears to strengthen the argument that clinical benefits may be achieved in selected patients (Byrne et al, 2005). Following a 2-week stabilization period, 4-week treatment with GH and an optimized diet achieved a significant reduction in parenteral requirements compared with treatment with glutamine and diet alone. Combination treatment with GH and glutamine achieved added benefit. In the latter group, a significant reduction in parenteral requirements remained 3 months after cessation of treatment (Byrne et al, 2005).

Glucagon-like peptide-2

While many growth factors act systemically, GLP-2 stands out as exerting effects largely confined to the intestine and especially the small bowel. GLP-2 is a 33 amino acid peptide secreted from enteroendocrine L-cells in the distal small intestine and colon. Its release is stimulated by a variety of enteral nutrients, particularly carbohydrates, SCFAs, triglycerides and bile acids. Short bowel patients with an end-jejunostomy, who are known to have poor intestinal adaptation, have a reduced postprandial GLP-2 response (Jeppesen et al, 1999). A small uncontrolled pilot study of native GLP-2 in this patient group demonstrated that subcutaneous treatment for 35 days significantly enhanced fluid absorption and also led to modest improvements in energy absorption (Jeppesen et al, 2001). The positive effect on fluid absorption was almost doubled in an uncontrolled 21-day study of the long-acting GLP-2 analogue teduglutide (Jeppesen et al, 2005). This study also demonstrated significant increases in intestinal villous height and crypt depth, although effects on energy and macronutrient absorption remained comparatively minor (Jeppesen et al, 2005). The promising results of these pilot studies have paved the way for a phase three multicentre trial to evaluate the efficacy and safety of long-term treatment with teduglutide, which is currently underway.

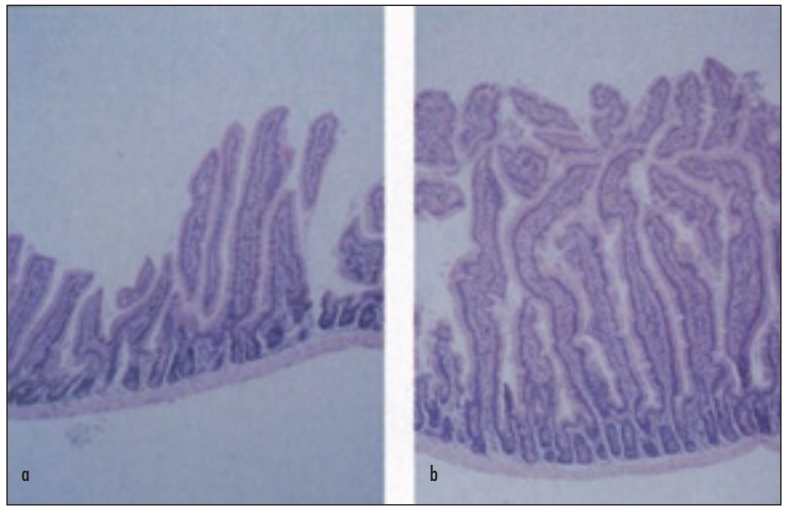

Figure 1. Effect of glucagon-like peptide-2 on murine small intestine. a. Normal murine small intestine. b. After 10 days of glucagon-like peptide-2 administration.

Epidermal growth factor

The EGF family comprises a number of peptides including EGF, TGF-α and heparin binding epidermal-like growth factor (HBEGF), which all share a common receptor. Animal models have shown that intestinal EGF receptor expression and activity is increased after resection and that intestinal adaptation is impaired in animals with defective receptors. EGF, a 53 amino acid peptide, is produced in submandibular glands, Brunner's glands, and is also present in colostrum and breast milk. The optimum route of delivery has not yet been established but a small uncontrolled pilot study demonstrated that enteral administration of EGF improved carbohydrate absorption and increased tolerance of enteral feeds in paediatric patients with short bowel syndrome (Sigalet et al, 2005).

Safety

More research is needed in order to determine optimum timing, dosing and route of administration of the

various growth factors and it is likely that maximal effects will be seen with combined nutritional and non-nutritional therapy. Long-term safety and cost effectiveness must also be taken into consideration. In particular, the use of growth factor therapy in humans raises the possibility of unwanted cell proliferation, potentially leading to carcinomatous tissue transformation in and outside the gastrointestinal tract. This is particularly relevant as many of the effects of exogenous growth factors are limited to the time of drug administration and patients may therefore be committed to lifelong treatment.

Conclusions

Enteral feeding appears to be a vital stimulus to intestinal adaptation and ongoing research will hopefully identify specific nutrients that will maximize the process. Nutritional factors like glutamine and SCFAs probably exert some if not all of their growth-promoting effects via the stimulation of growth factor release. An increasing understanding of the mechanism of action of these growth factors, particularly GH and GLP-2, has led to cautious optimism that growth factor supplementation in humans may be able to enhance the adaptive response beyond what is normally possible. **BJHM**

Figure 1 *is reproduced from Drucker et al (1996), by kind permission of the National Academy of Sciences, USA.*

Conflict of interest: Dr Wallis and Dr Gabe are involved in patient recruitment for an ongoing multinational trial of teduglutide administration in short bowel syndrome.

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KEY POINTS

- Following the loss of intestinal length, the remaining bowel undergoes a process of adaptation in order to maximize functional capacity.
- Enteral nutrition is a potent stimulus for intestinal adaptation and should be actively encouraged.
- Complex nutrients, such as soluble fibres and triglycerides, appear to have a greater beneficial effect than elemental and partially digested diets.
- Various growth factors have been shown to accelerate and augment the adaptive process in animal models.
- Growth hormone is licensed for use in short bowel syndrome in the USA although data supporting a significant effect on adaptation in humans are inconclusive.
- Glucagon-like peptide 2 has been shown to have a beneficial effect in pilot studies and larger trials using a long-acting analogue are ongoing.
- Future clinical trials are likely to employ combinations of growth factors in concert with nutritional interventions.