

INTESTINAL ADAPTATION AND AMINO ACID TRANSPORT FOLLOWING MASSIVE ENTERECTOMY

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1. ABSTRACT

Morphological and physiological adaptation in residual small intestine occurs after massive enterectomy and is influenced significantly by different growth factors and hormones. The mechanism of adaptation occurs through hypertrophy and hyperplasia as well as nutrient transporter changes. These transporters are classified into different classes dependent on its biological properties. The adaptation process evolves over time and different nutrient absorption profiles occur at different postoperative stages. There is an initial decrease in amino acid transport after resection followed by a return to approximately normal levels. Glucose also follows a similar pattern of changes but returns to normal later than amino acids. The time course of these changes are different for different animals with rat adaptation being much faster than rabbit. Growth hormone (GH) induces increased amino acid transport during this adaptation period, however, appears not to affect small intestine hypertrophy or hyperplasia. The increase in transport occurs via an increase in transport numbers rather than affinity. Epidermal growth factor (EGF) also increases amino acid transport in postoperative animals. Its advantage is it is orally stable when given with a protease inhibitor. EGF also reverses the down-regulating effects of the somatostatin analogue Octreotide (SMS) post resection. EGF in combination with GH has additive effects. However, the effects of the growth factors are site specific. GH and EGF combination therapy significantly increased alanine and arginine transport in distal small bowel after 70 % enterectomy but not in the proximal small bowel. The same combination increases leucine and glutamine transport in the proximal small intestine only. Understanding the specific changes that occur with these therapies may

improve quality of life for patients and also reduce that need for total parenteral nutrition.

2. INTRODUCTION

Short bowel syndrome (SBS) is a devastating clinical condition which results from the surgical removal of small bowel for intestinal volvulus, ischemic bowel, inflammatory bowel disease, or abdominal trauma (1, 2). It is defined by a set of clinical symptoms and signs which include intractable diarrhea, steatorrhea, weight loss, dehydration, malnutrition, and malabsorption of fats, vitamins, and other nutrients. These symptoms do not necessarily appear after a specific length of bowel is resected. Rather, differences in absorptive capacity leads to tolerance of a range of per cent bowel loss. Resections up to 50% are well tolerated without a need for long term nutritional supplementation. Up to 75% resection may be eventually tolerated after a period of adaptation. Mitigating factors include preservation of the ileocecal valve which can significantly increase transit time and thus absorption (3). Patients with larger resections may survive on total parenteral nutrition (TPN), yet complications such as hepatic dysfunction and sepsis leading to death may arise (4-7). Furthermore, the material cost of TPN is also great, with at least 5,000 patients nationally maintained on TPN at a cost of \$100,000 per patient per year.

Clinically, the scope of symptoms after massive enterectomy is not static. Dudrick *et al* described three distinct periods during which the remaining intestine attempts to compensate for the loss of surface area. The first period occurs during the initial two postoperative months. This is characterized by a clinical picture of fluid and electrolyte imbalance, adjustment of organ blood flow, and other acute operative responses. The second period is two months to two years. This is characterized by intestinal adaptation and the defining of maximum oral feeding tolerances for different food. Beyond two years, the body achieves maximum adaptation and develops a homeostasis

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(3). Both morphological and physiological changes coincide with clinical changes that occur, which have recently been clarified. Studies have examined nutrient transport at different time intervals postoperatively. Mucosal nutrient uptake occurs via functionally discrete transporters that are regulated by the availability of specific nutrients and the mediation of hormones and cytokines (8-14). Although compensatory hypertrophy and hyperplasia are well-described (3), recent interest has arisen in the actual transport of nutrients from the lumen across the enterocytes and into the circulation. Many growth factors affect the changes that ensue (15-17). This review will discuss how the bowel adjusts physiologically after massive enterectomy and how various growth factors can affect nutrient transport during this adaptation period. Specifically, the role of human growth hormone (hGH), epidermal growth factor (EGF), and Octreotide (SMS) will be examined.

3. AMINO ACID TRANSPORTERS

For amino acids to reach the portal venous system and liver, some form of transport must occur across enterocytes. A classification system has been made to help clarify the varieties of transporters noted. Christensen *et al* described the importance to integrate both substrate transported as well as biological properties in naming the systems. These include system A, ASC, B, B⁰⁺, and y⁺ (18).

Inherent to a nutrient transporter, is its ability to uptake a variety of amino acids with differing affinity for each given specific transporter class. The amino acid must cross both the brush border membrane into the enterocyte and the basolateral membrane into circulation. Transporters are reversible in their action, and it is a dynamic balance that allows for a concentration gradient of amino acid from lumen to circulation. This influx and efflux also allows for the enterocyte to retain amino acids for its own nutritive purposes (19, 20).

In terms of studies of specific transporters, many papers deal with isolating, identifying, and characterizing specific proteins involved. For example, a sodium-dependent neutral L-alpha-amino acid transporter was purified and identified as part of system B in rabbit small intestine (21). However, not much is currently known regarding how specific transporters are expressed by cells of enterocytes during times of stress and pathology. Ultimately, it is important to understand how therapy for short gut syndrome will impact different transporter systems. This can identify which therapies are most effective at increasing amino acid and other nutrient transport from intestinal lumen to the circulation.

4. ADAPTATION

Physiologically, one would expect the small intestine to upregulate the capacity of nutrient absorption to compensate for the loss of surface area. This process may occur secondary to an increase in enterocyte numbers in the form of hyperplasia and hypertrophy, increasing the

absorption in the residual intestine by as much as fourfold (3). The key is whether each individual enterocyte undergoes adaptation to increase its efficiency in nutrient uptake. This may occur by increasing transporter affinity or by increasing the number of transporters. Thus far, most studies show an increase in transporter numbers rather than increasing individual transporter carrying capacity, which would imply a protein conformational shift.

Not all amino acids are created equal. Although long considered non-essential, glutamine plays a central role as the primary oxidative fuel for dividing enterocytes (22-24). Glutamine may be considered an essential amino acid in times of stress (25). Klimberg *et al* demonstrated the beneficial effects of enteral glutamine in decreasing intestinal related complications after whole abdominal radiation. Rats receiving supplemental glutamine after irradiation had a lower incidence of bloody diarrhea, bowel perforation, and increased mucosa villous height compared to rats that received isonitrogenous amounts of glycine (26). Souba *et al* demonstrated that the gut switches from an organ of glutamine release to that of uptake after enterectomy (27). Thus, glutamine as a component of enteral diets may be a key factor in SBS recovery and eventual tolerance of enteral nutrition. Because of this importance, many studies examine the changes in glutamine transport during the convalescence period.

After massive small intestine resections, glutamine and other amino acid transport evolves over weeks to months. In adult Sprague-Dawley rats, net glutamine flux across enterocytes declined to 12% from a normal of approximately 22% in the immediate postoperative period. However, by one week, glutamine extraction increased to 31% with a concomitant decrease in glutaminase activity. These changes returned to baseline levels by three weeks (28). Sarac *et al* defined sequential alterations in gut mucosal amino acid and glucose transport after 70% jejunal-ileo resection in rabbits. There were no changes in transport at one week for glutamine, alanine, leucine, and glucose. Transport was significantly decreased at one month and returned to normal for all except for glucose at three months post operatively. Mucosal and villous height and total wall thickness also underwent changes. At one week, there were no differences. However, at one month, the mucosal and villous height were significantly increased. Despite decreased transport, both heights returned to normal at 3 months post operatively (29).

The above studies suggest that the adaptation Dudrick *et al* described occurs at the molecular level (3). The time scale differs for different animal models. Rats adapt more quickly when compared to rabbits. In both models, a transient drop in nutrient transport is seen with a eventual return to baseline (28, 29). The importance of such observations is that at times of downregulation, it may be possible to provide anabolic growth factors to help accelerate eventual adaptation. We will examine certain candidates that may be of clinical use. What is important is understanding the time course of adaptation in humans to optimize any treatment.

5. GROWTH HORMONE

Human growth hormone (hGH) is a single chain polypeptide of 191 amino acids with multiple anabolic effects, including increased amino acid transport in small bowel. Other systemic effects include improved nitrogen retention, reduced hepatic urea production, and diminished renal urea excretion (30). If hGH can be used clinically to help enhance amino acid transport during adaptation, it is conceivable that patients can be weaned from TPN sooner. The variables to assess growth hormone effectiveness would include small bowel hypertrophy and hyperplasia, amino acid transport, IGF-I serum levels, and molecular expression of transporters.

The intestinal mucosa is a target for hGH. Byrne *et al* used a combination of recombinant hGH and a glutamine-enriched modified low fat and high fiber diet to further enhance gut adaptation and enteral nutrient absorption in maximally adapted long-term home-TPN-dependent SBS patients. Yet, the mechanisms of each specific intervention are not known (31). Villous hyperplasia did not consistently occur after postoperative administration of growth hormone (GH) in rats subjected to 80% resection. After 7 days, mucosa weight of all resected animals, whether or not given GH, were increased when compared to sham operated animals. However, no difference in mucosa weight between the short bowel animals and short bowel animals given GH existed. Thus, GH had no effect above and beyond bowel resection itself. Animals with 80% resection administered GH did experience a body weight gain, however, compared to animals who only underwent the 80% resection (32, 33). It is unclear whether total body weight is related to improved lean body mass, which is more important in assessing nutrition than changes related to fluid retention. In this model, GH acts through mechanisms other than increasing cellularity.

In New Zealand White rabbits, transport of glutamine and leucine were increased by 33% and 39% respectively, in hGH-treated versus saline-treated small bowel resection groups. This upregulation was due to an increase in transport numbers and not a change in transport affinity (figure 1)(33). This phenomenon was also demonstrated in small bowel from human patients who were given hGH prior to small bowel resection. In the human studies, only higher doses of hGH (0.2 mg/kg) were effective. Jejunum and ileum behaved in a similar fashion (34). Because hGH may work through the IGF-I pathway, serum IGF-I levels were examined (35). Ziegler *et al* showed an increase in IGF-I mRNA expression in IGF-I treated rat ileum one week after 80% resection. IGF-I was given subcutaneously (36). However, IGF-I serum levels in rabbits and rats do not correlate well to this increase in transport activity (32, 33). Thus, IGF-I does not appear to be the pathway through which hGH affects transport activity.

Human growth hormone clearly is able to upregulate nutrient transport in the adaptive period. Its

specific action appears to be upregulation of nutrient transporter numbers and not by other mechanisms (33, 34). However, the human small intestine is not homogeneous along its length. It consists of the duodenum, jejunum, and ileum each with different functions and absorption of nutrients. Previous articles all treat the small intestine as a single entity. It is likely that growth factors may affect different segments of the bowel differently. This will be important in tailoring therapy for individual patients depending on the type of residual bowel.

6. EPIDERMAL GROWTH FACTOR AND COMBINATION THERAPY

Epidermal growth factor (EGF) is a 53 amino acid, 6 kD polypeptide secreted by the salivary glands and Brunner's glands of the duodenum (37). It induces cellular effects by binding a 170 kD glycoprotein, activating an intrinsic tyrosine kinase mechanism (38, 39). EGF is also found in mammalian milk and saliva thus suggesting a role in intestinal epithelial proliferation (40). Certain clinical effects of EGF have been documented alone as well as in combination with Octreotide and hGH. The EGF receptor (EGF-R) has been localized to the basolateral and not the brush border membrane in both rats and humans (41, 42). This may suggest a role for luminal EGF only during periods of stress or injury. That is, the basolateral side may become exposed to luminal contents secondary to breakdown of intestinal mucosal, such as that due to trauma. Also, this is important when considering the route of EGF administration.

After massive small bowel resection, intraperitoneal or subcutaneous infusion of EGF has been shown to enhance small bowel adaptation. Sodium-glucose cotransporter (SGLT1) expression, as measured by Western blot analysis, was significantly increased. This effect did not occur for all transport molecules, however, such as sucrase and Na⁺/K⁺ ATPase, where resection alone increased the expression even without EGF. Only in the case of SGLT1 did EGF increase expression above that of the untreated resection group. The clinical application of this is unclear. EGF had no effect on sham operated animals suggesting a priming effect for EGF by massive enterectomy (43). Morphologically, it was shown that mucosal height and crypt depth of ileum and small bowel length were significantly increased after massive enterectomy in EGF treated groups. No significant differences were seen in villous height between small bowel resection groups given saline and small bowel resection groups given EGF. EGF had minimal effects in sham operated animals (44).

Glutamine transport also seems to be affected by EGF. In rats treated with three doses of subcutaneous EGF, transport of glutamine and alanine increased (with more than a doubling of glutamine transport). Kinetic studies showed that the transporter increased in number rather than affinity. Concomitant, glucose transport decreased by 50 %, suggesting the central role of amino acids in the adaptive period (45). This study demonstrated

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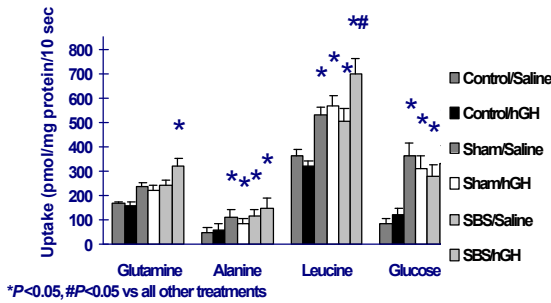


Figure 1: Effects of human growth hormone on amino acids and glucose transport in short bowel rabbit BBMVs

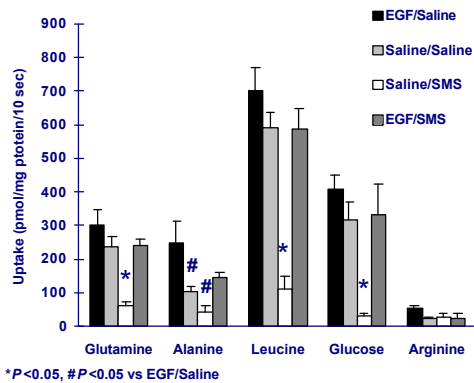


Figure 2: Effects of EGF and SMS on amino acids and glucose transport in short bowel rabbit BBMVs

that EGF did have effects on amino acid transport in animals even without massive small bowel resection.

Further studies isolated distal versus proximal small bowel in the setting of massive enterectomy and growth factors. Combinations of factors had been employed to explore whether synergistic effects may exist in these situations. In rabbits, subcutaneous agents were given for seven days, one week after 70 % enterectomies. Treatment groups included hGH alone, EGF alone, and hGH in combination with EGF. Glucose, glutamine, and leucine transport were all increased in only the proximal small bowel with combination therapy of hGH and EGF. No effects were noted when EGF was given alone. Alanine and arginine transport were noted to be elevated in the distal small bowel after combination therapy as well. Again, individual therapy did not seem to be effective. This clearly shows the growth factors can behave in an additive, site-specific, nutrient-dependent fashion (46).

Using an everted mucosal sleeve technique on intact intestinal segments, Swaniker *et al* demonstrated a steady increase in glutamine uptake from three weeks post operatively to six weeks in rabbits given EGF for seven

days (47, 48). This study did not separately interpret distal versus proximal small bowel transport. Mucosal dry weight consistently increased at both three and six weeks. What is interesting is that Swaniker *et al* did notice a difference in glutamine transport when EGF was given right after surgery (48). Iannoli *et al* did not see such a difference when EGF administration was delayed for seven days (46). This implies the timing of EGF therapy may be critical. Therapy may be altered depending on what segment of bowel is resected.

EGF was also studied in combination with Octreotide, a somatostatin analog known to suppress pancreatic and gastric secretions (49). Octreotide is routinely used in SBS patients to reduce diarrhea (50-52). Somatostatin reduced nutrient transport after 70% enterectomy while concomitant EGF reversed this effect (figure 2) (53). Liu *et al* also demonstrated that EGF in combination with Octreotide significantly increased transporter expression above animals given Octreotide alone after 80% enterectomy (54). These findings warrant caution in the clinical use of Octreotide as transport upregulation may be inhibited.

An advantage of EGF is it may be orally stable when combined with protease inhibitors (55, 56). Ornithine decarboxylase activity (ODC) and mucosal DNA content increased after fasting rats were given infusions of EGF into distal jejunum. This effect was not unique to EGF, as refeeding also produced similar increases in ODC activity and DNA content. In the case of ODC only, however, EGF did increase activity above that of refed rats not treated with EGF. EGF seems to play a role in preventing the starvation induced effects but does not in all situations further the improvements seen in refeeding the rats (57). In another study, rabbits given luminal EGF in isolated intestinal loops had significant increases in glucose and proline uptake in brush border membrane vesicles prepared from the loops (58).

Recently, microvillous height and overall surface area were studied in EGF treated rabbits after 70% enterectomy. Although villous height was not increased, microvillous height and surface area was. This hypertrophy may be helpful in increasing absorption (59). Thus, EGF may play an important role in pathological states but its relevance in normal healthy states may be minimal. Most studies have concentrated on the effects of subcutaneous administration. It would be interesting to see if such effects can be reliably replicated with use of oral therapy. This may impact the cost of any potential therapy as well as compliance of patients.

7. PERSPECTIVES

Patients with SBS require long term individual therapy. Careful attention must be paid to metabolic and nutritional requirements (3). Ultimately, volitional oral nutrition is the goal. There is no doubt that the small bowel can adapt after enterectomy. Certain growth factors do effect this adaptation favorably for patients (31, 34, 43, 44,

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46, 48). Unlocking the potential of the small bowel, however, will require insight to specific details such as timing, duration, and section of bowel resected. Our work confirms that the intestine is not homogeneous and different operations can cause very different spectrum of malabsorption profiles (46). Thus, understanding molecular details will allow the clinician to fine tune therapy in hopes of optimizing results of these abnormalities.

Questions that remain include the expression of transporters and growth factor receptors in enterocyte both after surgery and in response to treatment. So far, hGH and EGF are only two of many growth factors which may affect the bowel (39). The effects of other agents may significantly impact treatment as we have seen that combination therapy does have its own distinctive actions (46, 53, 54). Regardless, the eventual aim is to convert more patients to enteral nutrition. With an understanding of where, when, and how these molecular changes occur, treatment can be more specific to each patient's individual needs. This achieves two goals: patient health and cost containment.

8. ACKNOWLEDGMENT

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