Enteral nutrition and the small intestine

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It is now accepted that, whenever possible, nutritional support should be given enterally, reserving parenteral nutrition for patients with intestinal failure. This is partly because of the many problems associated with parenteral feeding, such as complications of central line insertion and metabolic derangements,1 but recently it has also been appreciated that enteral feeding may have a positive advantage over parenteral feeding by maintaining small intestinal mucosal structure and function. Thus it may improve intestinal recovery and adaptation after gastrointestinal surgery, especially after small bowel resection. In addition, maintaining the barrier function of the intestinal mucosa may be an important consequence of enteral nutrition, for, in the critically ill, early enteral feeding may reduce translocation of bacteria and endotoxin from the gut lumen into the portal circulation,2 thus decreasing the incidence of septicaemia.3

Recently, it has also been found that enteral nutrition influences the secretory function of the small intestine. In experimental animals starvation results in intestinal hypersecretion to neurotransmitters and secretagogues4-6 and such a response may contribute to the life threatening diarrhoea that can occur in patients with severe malnutrition.6 This review will focus, however, on the effects of enteral nutrition on small intestinal mucosal proliferation, with particular emphasis on the actions of individual nutrients.

Background
Most studies of small intestinal adaptation have been performed in experimental animals and of these the rat has been the most commonly used species. The experimental data reviewed here are derived from studies in laboratory rats, unless otherwise stated.

During starvation the small intestinal mucosa rapidly atrophies,7-9 with a reduction in cell proliferation being noted within hours of food withdrawal,10 and this occurs even when the overall nutritional state of the animal is maintained by total parenteral nutrition (TPN).11 12 Conversely, refeeding increases mucosal cell proliferation again, with even an initial rebound effect when cell proliferation increases above pre-starvation values.13

Studies in the dog as well as the rat have shown that luminal nutrients may stimulate this mucosal proliferation by a local direct action at their site of absorption.14 15 This direct effect, surprisingly, does not result from the use of the nutrients as sources of energy by mucosal cells, as, in rats, non-metabolisable absorbed substrates, such as galactose and 3-O-methyl-D-glucose, can also promote mucosal cell proliferation.16 17 This has led to the interesting concept that the 'workload' of absorption determines the proliferative response.16 17 Luminal nutrients may also stimulate mucosal cell proliferation indirectly by releasing an enterotrophic hormone from the distal small intestine and colon.18-21

The identity of such a hormone(s) remains uncertain, and although there is circumstantial evidence from studies in humans as well as animals in favour of enteroglucagon,22-28 some recent in vivo and in vitro data have questioned this hypothesis.25-28 A third mechanism by which luminal nutrients may increase mucosal cell proliferation is by stimulating release of pancreaticobiliary secretions, which are themselves trophic to the small intestinal mucosa.29-31

At the cellular level both direct and indirect enterotrophic effects of luminal nutrients seem to be mediated by induction of ornithine decarboxylase (ODC) and subsequent increases in cellular levels of polyamines.32-35

In vitro and in vivo studies suggest that induction of ODC occurs largely at the post-transcriptional level.36 37 In contrast with enteroglucagon synthesis, which results mainly from increased DNA transcription.38

Adaptive changes in small intestinal mucosal mass are generally accompanied by parallel changes in segmental absorptive function,39-43 but the magnitude of induction of individual transport processes can be selectively influenced by the specific nature of the nutrients within the lumen. Thus in rats receiving TPN, infusion of D-glucose, but not the unmetabolised 3-O-methyl-D-glucose, into the small intestine increases specific transport capacity for glucose,17 while substituting protein isocalorically for carbohydrate in the diet increases amino acid transport capacity and reduces the transport capacity for galactose.44

INTESTINAL ADAPTATION IN HUMANS

Although most studies of adaptation have been in experimental animals, available data in humans provide good evidence for functional adaptation in response to changes in food intake. Thus starvation or total parenteral nutrition cause a fall in brush border enzyme activity in humans.45 46 and reduced absorption...
of ingested mannitol and D-xylene.\textsuperscript{47, 48} The evidence, however, for structural adaptation of the human small intestine in response to food withdrawal is less clear. In patients who have previously had jejunooileal bypass operations for obesity, atrophy has been noted in the bypassed segment at a subsequent operation,\textsuperscript{49} but this finding has not been universal.\textsuperscript{50} Although a fall in protein content of jejunoileal biopsy specimens has been noted after a prolonged fast,\textsuperscript{49} standard histological examination of the biopsy specimens in such patients or in patients who have received TPN for a prolonged period has shown no evidence of mucosal atrophy.\textsuperscript{45, 46, 51}

Only small samples from a limited number of intestinal sites can be taken in humans and this may in part explain the relatively poor evidence for structural adaptation in response to changes in food intake. Recently an interesting method has been used to give an indirect measure of total levels of small intestinal mucosal mass in humans. This method has relied on displacement of the enzyme diamine oxidase from endothelial binding sites in the lamina propria by intravenous heparin. This enzyme is confined almost exclusively to the small bowel mucosa and the post-heparin plasma concentrations may therefore reflect levels of mucosal mass. In subjects receiving TPN there was a reduction of post-heparin plasma concentrations that was reversed on refeeding.\textsuperscript{52}

**Effects of individual nutrients on mucosal growth**

**CARBOHYDRATE AND AMINO ACIDS**

Weser \textit{et al}\textsuperscript{53} compared the effects of individual carbohydrates and found that disaccharides promote greater mucosal growth in rats than do isocaloric amounts of monosaccharides. This requires the hydrolysis of the disaccharide and absorption of its monosaccharide components, because the effect of sucrose on mucosal cell proliferation is largely abolished by the alpha glucosidase inhibitor, acarbose. Different hydrolysable disaccharides have similar effects on small intestinal mucosal mass,\textsuperscript{53} as do different monosaccharides,\textsuperscript{15, 17} but a mixture of amino acids stimulates mucosal growth and ODC concentrations more than an isocaloric amount of glucose.\textsuperscript{18, 54} Dietary supplementation with ornithine (as its alpha ketoglutarate salt) causes small intestinal mucosal growth, perhaps as a result of increased polyamine production,\textsuperscript{55} but other individually administered amino acids may also stimulate mucosal cell proliferation to varying degrees.\textsuperscript{56}

Attention has recently focused on the role of the amino acid glutamine in small intestinal growth. Glutamine is an important metabolic substrate for small intestinal mucosal cells\textsuperscript{57} and its deficiency causes mucosal atrophy.\textsuperscript{58} Glutamine is unstable in solution and so is often omitted from regimens for parenteral nutrition. This may in turn contribute to the mucosal atrophy associated with TPN, as supplementation with parenteral glutamine can reduce, though not completely reverse, the atrophy in animals.\textsuperscript{59} Glutamine is, therefore, essential for small intestinal epithelial cell growth and thus may have an important role in the diet of patients with small intestinal disease, as, at least in animals, inclusion of glutamine in the diet enhances mucosal proliferation after small bowel resection, or cryotherapy or radiation injury.\textsuperscript{46, 60} It is not clear, however, whether supplementing this amino acid above minimum requirements further enhances mucosal growth.

**DIETARY LIPIDS**

Initial reports raised the exciting possibility that dietary fat may exert a greater trophic stimulus to the small intestinal mucosa than other nutrients. Thus Morin \textit{et al}\textsuperscript{63} found that intragastric infusion of long chain triglycerides enhanced the adaptive response to partial small intestinal resection in the rat more than protein or carbohydrate. Long chain triglycerides, and subsequently it was shown that long chain free fatty acids have an even greater effect than long chain triglycerides.\textsuperscript{64} Nevertheless, although others have also shown a potent enterotrophic effect for long chain triglycerides,\textsuperscript{65–69} this has not been a universal finding. For example, Thomson \textit{et al}\textsuperscript{70} using a number of different measures of mucosal mass found little consistent evidence for an enhanced enterotrophic action of a high fat diet compared with laboratory chow, while in two other studies long chain triglycerides substituted for carbohydrate alone in the diet even seemed to cause jejunal mucosal atrophy.\textsuperscript{71, 72}

Recent findings suggest, however, that the method by which long chain triglycerides are given itself profoundly influences the proliferative response of the small intestinal mucosa, as boluses increase small intestinal mucosal mass and cell proliferation compared with the same daily dose of fat consumed more gradually as part of a mixed diet.\textsuperscript{73} This may be because bolus doses of fat enhance release of enteroluglagon from the distal small intestine and colon.\textsuperscript{73} In a mixed diet substituting long chain triglycerides for glucose does not affect the overall mucosal mass of the small intestine, but does change the distribution of mucosal mass along the small intestine.\textsuperscript{74} With increasing proportions of long chain triglycerides (and decreasing amounts of glucose) mucosal mass falls in the proximal small intestine and correspondingly rises in the mid small intestine.\textsuperscript{74} These changes may reflect differences in the sites of absorption of glucose and lipid, with mucosal cells proliferating locally in response to the ‘workload’ of absorption.\textsuperscript{15–17} This finding now also explains why some earlier studies have suggested that dietary fat causes mucosal atrophy in comparison with carbohydrate.\textsuperscript{71, 72} For in those studies mixed diets were used and measurements were confined to the jejunum and did not include the mid small intestine. By contrast with long chain triglycerides, medium
Chain triglycerides, which are more rapidly hydrolysed and absorbed,75 maximally stimulate mucosal proliferation in the proximal small intestine when given in mixed diets.76 77

Essential fatty acids may have an important role in mucosal proliferative responses, as deficiency of this dietary component attenuates the adaptive response of the small intestinal mucosa to partial small intestinal resection78 and also reduces the regenerative response of the mucosa to methotrexate induced injury.79 Such effects might result from decreases in mucosal concentrations of prostaglandins, which are products of essential fatty acid metabolism and are themselves trophic to the small intestinal mucosa.80 There is little evidence, however, that supplementing the omega 6 fatty acid, linoleic acid above minimum requirements is trophic to the small intestinal mucosa76 and a diet containing 10% by weight of safflower oil (rich in linoleic acid) does not enhance any parameters of mucosal mass during recovery from methotrexate induced mucosal injury over a diet containing 1% by weight safflower oil.79 The essential fatty acids, however, in fish oil (the omega 3 family) may have special properties. Thus, an oil rich in eicosapentaenoic acid improved mucosal recovery after methotrexate induced injury81 and also stimulated mucosal growth after partial small intestinal resection when compared with other long chain fatty acids.82

In the diseased or resected small bowel addition of long chain triglycerides to the diet might cause steatorrhoea. The more rapidly hydrolysed and absorbed medium and short chain triglycerides may be better tolerated when small intestinal absorptive capacity is reduced. It is thus of considerable interest that Kriple et al83 found that substituting short chain triglycerides for carbohydrate in a diet enhances the small intestinal adaptive response to distal small bowel resection. Direct infusion of short chain fatty acids into the ileum also stimulates mucosal cell proliferation both in the caecum and in the more proximal jejunum, perhaps by release of a trophic gut peptide.84 Interestingly, intravenously administered short chain fatty acids may stimulate small intestinal mucosal proliferation both in intact animals85 and after partial small intestinal resection.86

The nature of ingested fat may also influence the absorptive function of the small intestine, perhaps as result of changes in the nature of lipid incorporated into the cell membrane of the enterocyte. Thus Thomson et al have found that a number of specific intestinal transport properties can be varied according to the nature of ingested triglycerides,72 87 88 while Sagher et al89 showed that, compared with a diet rich in fully saturated fatty acids, a diet rich in polyunsaturated fat significantly improved jejunal absorption of water and electrolytes. This second study raises the possibility that changing the nature of ingested lipid may offer a simple means of improving absorptive function for water and electrolytes in acute diarrhoeal illnesses.

**DIETARY FIBRE**

Non-absorbable, inert bulk such as kaolin has no trophic effect on the small intestinal mucosa,90 91 but dietary fibre may provide a potent enterotropic stimulus. Ecknauer et al. showed that supplementing an elemental diet with alpha cellulose increases small intestinal weight and cell proliferation compared with the same elemental diet alone,92 and others have confirmed that dietary fibre is trophic to the small intestine and colon,93-95 with the increases in small intestinal cell proliferation being most notable distally.96

Dietary fibre can be fermented by lower gut bacteria to release short chain fatty acids97 and Goodlad et al91 showed that small intestinal and colonic mucosal proliferation was maximally increased by the most fermentable fibres and that the enterotropic effects were abolished in germ free animals.98 Short chain fatty acids may exert a direct trophic action on the colonic epithelium,99 perhaps because colonic enterocytes use them as a metabolic fuel.100 101 In addition, as already described, infusion of short chain fatty acids into the ileum can stimulate cell proliferation more proximally,102 perhaps by releasing a trophic gut peptide, in the studies of Goodlad et al.101 Enteroglucagon release was stimulated by the most fermentable fibre. The role of enteroglucagon was questioned, however, by the finding that concentrations of this hormone were high in fibre fed germ free animals,28 even though mucosal proliferation was not increased.98

The role of bacterial fermentation in mediating the enterotropic effect of dietary fibre has itself also been disputed. In two studies, the trophic effects of a number of different non-digestible polysaccharides showed little correlation with their fermentability by gut bacteria,27 102 and in rats fed increasing amounts of haricot beans there was no increase in duodenal or caecal cell proliferation, despite increases in short chain fatty acid production in the caecum.103 Johnson et al27 104 have suggested that the viscosity of the diet may be important as, in their studies, only the most viscous diets increased cell proliferation in the terminal ileum perhaps because these viscous polysaccharides delayed absorption of nutrients and increased their delivery to the terminal ileum. In keeping with this hypothesis, this group had subsequently produced evidence for synergism between the enterotropic effect of corn oil and a viscous non-starch polysaccharide, guar gum.105

While the stimulatory effects of dietary fibre on small intestinal mucosal proliferation may prove to be beneficial, it is interesting to speculate that, conversely, the therapeutic efficacy of elemental and polymeric diets in Crohn’s disease106-108 may result from the lack of fibre in these diets. In experimental animals such diets cause mucosal atrophy, especially in the ileum, and in relation to standard laboratory diets109 110, this effect could result from the absence of a trophic stimulus to the distal gut that is normally provided by dietary
fibre. It is therefore conceivable that the therapeutic efficacy of these enteral feeds in Crohn’s disease is related to such local ‘bowel rest’ in the distal gut.

Discussion

By stimulating mucosal cell proliferation, enteral nutrition may provide clinical advantages to patients after gastrointestinal surgery, particularly small bowel resection. In the rat and dog it has been shown that enteral nutrition is essential for stimulating adaptive hyperplasia in the remnant.112 After partial small intestinal resection, and so a diet that has a potent enterotropic action might provide great benefit in the short bowel syndrome. In our view, the data suggesting that short chain triglycerides and fatty acids are potent stimulants of mucosal growth hold great promise. The observed enterotropic effects of intravenously given short chain fatty acids and glutamine also suggest that supplementing parenteral fluid regimens with these nutrients may preserve small intestinal mucosal integrity and function in patients who cannot receive enteral nutrition.

It has also been proposed that maintenance of mucosal integrity may reduce bacterial translocation from the gut and so reduce the incidence of sepsis in critically ill and post-operative patients.2 A recent study in patients undergoing elective surgery has challenged this assertion by showing no increase in the incidence of bacterial translocation at the time of laparotomy in patients fed preoperatively by TPN compared with patients who were enterally fed.51 Comparatively fit patients undergoing elective surgery, however, may not be the most relevant group to study, as it is possible that the risk of bacterial translocation is in any case low in such patients. Any beneficial effect of enteral feeding might be more apparent in critically ill patients in whom the risk of bacterial translocation may be increased,2 perhaps as a consequence of mucosal damage resulting from impaired mucosal blood flow.2,113 Indeed, another recent study in patients who had suffered multi-system trauma showed that, compared with TPN, enteral feeding reduced the incidence of sepsis only in severely injured patients.114 Nevertheless, it is debatable whether the protective effects of enteral feeding in such patients are caused by maintenance of mucosal integrity in itself, or whether another mechanism, such as stimulation of local immune function,115 could be more important. Deitch has shown that there is a poor correlation between the incidence of translocation and parameters of mucosal mass in rats and mice receiving various enteral and parenteral feeds.116

Further research might be directed at assessing further the benefits of enterotropic dietary regimens in a clinical setting, with particular attention to the incidence of gut derived sepsis in the critically ill patient, to the efficacy of small intestinal adaptation after gastrointestinal surgery, and to amelioration of cytotoxic or radiation induced intestinal injury. Little is known about the molecular mechanisms that mediate the direct enterotropic actions of absorbed nutrients, and so research in this field may provide a method of further enhancing mucosal proliferative responses to enteral feeding and of adding to our knowledge of the factors that control epithelial cell growth.

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