Enteral supplementation with ornithine α ketoglutarate improves the early adaptive response to resection

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Abstract

***Background*—Polyamine synthesis or uptake, or both, might be an important event that initiates the adaptive hyperplasia seen in the intestinal remnant after partial small bowel resection.**

***Aim*—The ability of an enteral diet supplemented with the ornithine salt: ornithine α ketoglutarate (OKG), a precursor for polyamine synthesis, to modulate the adaptive response of the remnant ileum after jejunectomy was evaluated.**

***Methods*—Adult Wistar rats underwent a resection of the proximal 50% of the small intestine. Controls underwent a single transection. The rats were fed intragastrically with a nutritive mixture supplemented either with casein hydrolysate or with OKG (1 g/kg). The isoenergetic and isonitrogeneous diets was given continuously for seven days.**

***Results*—Villus and crypt hyperplasia was observed in the remnant ileum compared with transected controls. OKG supplementation started after resection a further increase in villus height. After resection, OKG supplementation increased significantly the putrescine content and the amount of ornithine decarboxylase mRNA. A twofold to threefold increase of sucrase activity was measured in the resected animals compared with the transected rats. In contrast, the amount of sucrase mRNA was significantly lower in the ileum of the resected rats and OKG supplementation initiated a further drop in the amount of sucrase mRNA without pronounced changes in enzyme activity.**

***Conclusions*—The adaptive hypertrophy seen after resection can be accelerated by supplementing the diet with ornithine (OKG) a precursor of polyamine synthesis. In the remnant ileum, the reduced amount of sucrase mRNA, despite the increased level of sucrase activity, suggests a post-translational control of sucrase expression.**

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Keywords: jejunectomy, intestinal adaptation, putrescine, sucrase, ornithine decarboxylase, intragastric feeding.

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After partial small bowel resection, the remnant intestine undergoes compensatory structural and functional changes characterised by villi hyperplasia, increased crypt cell proliferation, and increased migration rate of enterocytes along the villi, which combine to produce improved digestive capacities.[1–4] Many studies have shown that enteral feeding can stimulate the adaptive response of the remaining intestine and that the extent of intestinal response depends on the content of the diet.[5–9] Although the events governing the adaptive response to resection are poorly understood, numerous factors are known to stimulate epithelial cell proliferation and differentiation and may potentially have a therapeutic role in the treatment of short bowel syndrome.[8 10–12] In this regard, several studies have suggested that polyamine synthesis or uptake, or both, might be an important intracellular event, which initiates the adaptive hyperplasia seen in the intestinal remnant after partial small bowel resection.[13–16] Indeed, the polyamines (putrescine, spermidine, spermine) modulate RNA polymerase activity and stimulate RNA, DNA, protein, synthesis, cell division, and tissue growth.[15] The key of polyamines seems to be corroborated by the findings that the inhibition of mucosal ornithine decarboxylase (ODC) activity with the specific inhibitor difluoromethyl ornithine (DFMO) prevents intestinal adaptation after small bowel resection in rats.[16] Both enteral and intravenous putrescine and spermidine completely restore adaptive mucosal growth.[16] In addition, it has been reported that the inhibition of diamine oxidase, the polyamine degrading enzyme, by aminoguanidine treatment improved the adaptive response to intestinal resection.[17 18]

As an alternative, the stimulation of the endogenous synthesis of polyamines in the mucosa of the remnant intestine would represent another approach that may potentiate post-resectional gut adaptation. In this regard, a dietary supplementation with the amino acid ornithine, the direct precursor of putrescine, might represent an interesting candidate to improve the post-resectional adaptive process. The highly soluble ornithine salt: ornithine α ketoglutarate (OKG), is formed of two molecules of ornithine and one molecule of α ketoglutarate. It efficiently improves the nutritional status in protein depleted patients,[19] and has been successfully used enternally and intraveously in the treatment of surgical patients[20] as well as in burned and traumatised patients.[21 22] In healthy subjects, oral administration of OKG produces a transient increase in plasma concentrations of ornithine and a rapid increase in urea excretion, which suggests that the compound is metabolised extensively.[23] The

small intestine is a major site of metabolism for ornithine.[24] We have previously reported that an enteral supplementation with OKG given to healthy rats stimulates the decarboxylation of ornithine by ODC leading to an increased synthesis of putrescine in the intestinal mucosa.[25] The aim of this study was therefore to evaluate, in the rat, the ability of OKG given enterally to modulate adaptation of the remaining ileum after 50% resection of the small intestine.

Methods

Animals

The experiments were conducted according to the National Research Council Guide for use and care of laboratory animals with the authorisation (n°00573) of the French Ministry of Agriculture.

Male Wistar rats (n=28), weighing 400–430 g, were housed under standardised conditions (22°C, 60% relative humidity, 12 hours light and 12 hours dark cycle) and were randomly divided into two groups. The animals from the experimental group (n=14) underwent partial resection of the small intestine as follows. The rats were anaesthetised with an intraperitoneal injection of Ketamine (Sigma, UK) (0·5 mg/100 g body weight), the abdomen was opened through a midline incision. The length of the intestine was measured from the ligament of Treitz to the ileocaecal junction. The proximal 50% of the intestine was resected. The duodenum was anastomosed to the remaining ileum in continuity. Control rats (n=14) underwent anaesthesia, laparotomy, and a single transection at the middle of the jejunoileum followed by reanastomosis.

After surgery, the animals were starved for 24 hours and thereafter fed enterally via an intragastric catheter.[25] They received a nutritive mixture (Normoreal Na40, Laboratories Sodietal, France) containing (in terms of energy): 15% protein (50% casein and 50% soya protein), 55% carbohydrate (maltodextrin), and 30% soya oil. The enteral mixture was administered continuously at a flow rate of 3·4 ml/hour and provided a daily calorie intake of 82 kcal per rat. All animals had free access to drinking water.

The resected animals and the transected controls were given continuously for seven days the enteral mixture supplemented either with free aminoacids (casein acid hydrolysate, Sigma, UK, 1 g/kg per day, n=7) or with the ornithine salt (OKG, laboratories J Logeais, France, 1 g/kg per day, n=7).[25] The diets were isoenergetic and isonitrogenous, and contained the same amounts of electrolytes and vitamins.

One hour after the end of the enteral feeding period (seven days), a 20 cm segment corresponding to the terminal part of the ileum was collected under ether anaesthesia.

Histology

Intestinal samples corresponding to the first 2 cm of the collected intestinal segment were fixed in 10% formalin. The fixed samples were dehydrated in progressive concentrations of ethanol, cleared in xylene, and embedded in paraffin wax. Deparaffinised 5 μm sections were stained with haematoxylin and eosin. The villus length and crypt depth were measured with an image analyser. Only villi sectioned from their base to the top with a single epithelial layer at their tips and crypts, and a visible lumen along their entire depth were considered as suitable for quantitative evaluation.

Biochemistry

Immediately after collection the intestinal segment was flushed with ice cold 0·9% NaCl. The mucosa was scraped off with a glass slide, weighed, and frozen in liquid nitrogen.

Enzyme assays – samples of the mucosa were homogenised in mannitol (50 mM), TRIS 2 mM (pH 7·1). Brush border membranes were isolated from mucosal homogenates as described by Schmitz *et al.*[26] Sucrase activity was determined according to the method of Dahlqvist.[27] Enzyme activities were expressed either as specific activities in the purified brush border membranes (mU per mg of protein) or as total activities per segment (mU per cm of intestinal length). One unit of activity corresponds to one μmol of product formed per minute at 37°C.

Polyamines – aliquots of the mucosal samples were homogenised in 10 parts (w/v) of perchloric acid (200 mM), and the homogenates were centrifuged at 3000 *g* for 10 minutes after standing for 16 hours at +2°C. The clear supernatants were diluted with perchloric acid (200 mM) and 200 μl aliquots were applied on a reversed phase column for separation. The polyamines were determined by separation of the ion pairs formed with *n*-octanesulphonic acid, reaction of the column effluent with *o*-phtaladehyde/2-mercaptoethanol reagent, and monitoring of fluorescence intensity.[28]

RNA isolation and northern analysis – total cytoplasmic RNA from the ileal segment was extracted by acid guanidinium thiocyanate-phenol-chloroform extraction.[29] For northern blot analysis, aliquots (20 μg) of total RNA were separated by electrophoresis on 1% agarose, 17% formaldehyde gels, and transferred to nitrocellulose filters. The filters were hybridised to ^{32}P-labelled nucleotide probes for β actin[30] used as internal standard, sucrase-isomaltase[31] and ODC[32] according to standard procedures.[33] The filters were exposed to Kodak XAR-5 films using an intensifying screen. Specific mRNA was quantified by densitometric scanning of the bands. Correction for loading was performed by dividing the densitometries of these bands by the densitometries of the interal standard (β actin) used as reference.

Statistics

Data are reported as means (SEM). Statistical differences between groups were evaluated by one way analysis of variance and specific

Body weight changes and total mucosal wet weight of the intestinal segment (20 cm length)

Diet group	*Body weight changes (g)*	*Musocal weight (g)*
Transected rats		
Casein (7)	−11 (5)	0·77 (0·05)*
OKG (7)	−17 (2)	0·80 (0·06)*
Resected rats		
Casein (7)	−17 (2)	1·34 (0·06)†
OKG (7)	−20 (4)	1·33 (0·07)†

Transected and resected rats were fed an enteral diet supplemented with casein hydrolysate (1 g/kg per day) or with ornithine α ketoglutarate (OKG) (1 g/kg per day). Values are mean (SEM). The number of animals per group is in parentheses. *Compared with†, $p<0·01$.

differences were identified using Student-Newman-Keuls multiple comparisons test.

Results

As the Table shows, the body weight changes were not significantly different between the various groups. After seven days of enteral feeding the body weight loss of the transected and resected animals was very similar and did not exceed 5% of their initial weight. The mucosal weight of the ileum was increased by 65% in the resected animals when compared with the transected controls, the modifications in the composition of the enteral diet had no influence on those changes.

In the resected animals, after seven days of enteral feeding, villus hyperplasia and increased crypt depth was observed in the remnant ileum compared with the transected controls (Fig 1). In the resected animals, OKG supplementation caused a further increase in the height of the ileal villi without significant changes in crypt morphology compared with the resected rats receiving casein hydrolysate.

The putrescine, spermidine, and spermine content (Fig 2A) and the amount of ODC mRNA (Fig 2B) were significantly increased in the ileal mucosa after jejunectomy. OKG supplementation increased significantly the putrescine content and the amount of ODC mRNA in the mucosa of both transected controls and resected animals when compared with the corresponding rats receiving casein hydrolysate. OKG supplementation caused about a twofold increase in the amount of putrescine and in the expression of ODC mRNA in the ileal segment after jejunectomy when compared with resected animals receiving casein hydrolysate. However, under those conditions, the amount of the other polyamines: spermidine and spermine, were not increased.

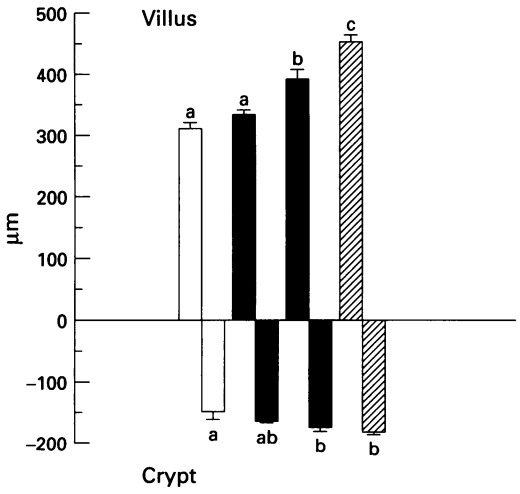

Figure 1: Villus height and crypt depth in transected and resected animals. Transected rats were fed enterally a diet supplemented with either casein hydrolysate (open column), or with ornithine α ketoglutarate salt (dotted column). Resected rats were fed enterally a diet supplemented with either casein hydrolysate (black column), or a diet supplemented with ornithine α ketoglutarate salt (hatched column). Values are means (SEM), n=7 per group. For villus or crypt, columns not sharing a common superscript differ significantly; p<0·05.

The total activity of sucrase, expressed per cm intestinal length, was significantly increased in the remaining ileum after jejunectomy after seven days of enteral feeding. Similarly, a twofold increase of the enzyme specific activity in the brush border membranes was also observed (Fig 3A). OKG supplementation did not modify the level of the total enzyme activity measured in the remaining intestinal segment after resection. At the cellular level, OKG supplementation caused a significant decrease in the level of specific activity measured in the brush border membrane of the enterocytes lining up the villi. Changes in the amount of sucrase mRNA (Fig 3B) did not parallel those seen at the level of enzyme activity. In contrast with the increased enzyme activity, the amount of the corresponding mRNA was significantly lower in the ileum of the resected animal compared with the transected controls. OKG supplementation led to a further significant decrease in the amount of the mRNA in the ileum. This effect was prominent in the mucosa of the remnant ileum of the resected animal despite the maintenance of high level of enzyme activity.

Discussion

Increased ODC expression and polyamine content play a crucial part in the adaptive response of the remnant intestine after resection.[13–16] This study shows that feeding rats with an enteral diet supplemented with OKG, a precursor of endogenous polyamine synthesis,[19 25] increases ODC expression, increases the putrescine content of the mucosa, and accelerates mucosal growth in the ileum after jejunectomy. However, the effect of OKG on polyamines was restricted to putrescine as neither spermidine, nor spermine were increased by the precursor administration. This specific effect of OKG supplementation on the putrescine content of the mucosa has also been observed in healthy animals and results from the balance existing between the two metabolic pathways that are activated by OKG treatment in the intestinal mucosa for polyamines: the decarboxylation of ornithine by ODC and the oxidative deamination of putrescine to γ aminobutyric acid.[25]

Intestinal adaptation after resection seems to depend on a number of factors. It has been shown that a potent nutrient independent stimulus for intestinal cell proliferation occurs within minutes after resection and that the first

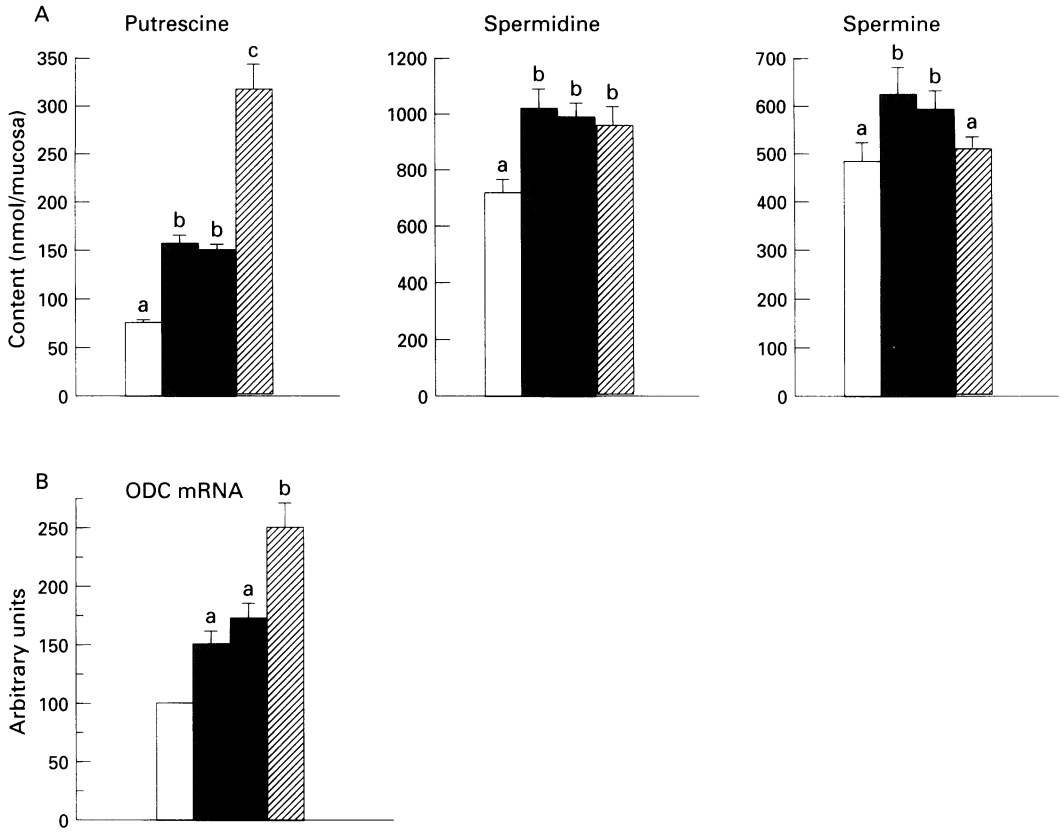

Figure 2: (A) Polyamine content of the ileal mucosa in transected and resected animals. Values are given in nmol/g wet weight (means (SEM), n=7 per group). For a given polyamine: columns not sharing a common superscript differ significantly; p<0·05.) (B) Relative amount of ODC mRNA in the ileal mucosa of transected and resected animals. The amount of mRNA measured in transected control rats were used as reference. The amount of mRNA was quantified by densitometric scanning of the bands. Correction for loading was performed by dividing the densitometries of these bands by the densitometries of the internal standard. Values are means (SEM), n=7 per group. Columns not sharing a common superscript differ significantly; p<0·05. Transected rats were fed enterally a diet supplemented with either casein hydrolysate (open column), or with ornithine α ketoglutarate salt (dotted column). Resected rats were fed enterally a diet supplemented with either casein hydrolysate (black column), or a diet supplemented with ornithine α ketoglutarate salt (hatched column).

targets of this stimulus are the crypt cells in the residual intestine.[4] However, other studies have shown the importance of luminal nutrients in the adaptive processes to resection.[34 35] In addition, this study suggests that the composition of the diet given enterally modulates the degree of adaptation, which is time dependent.[35] The early adaptive response to resection (that is, in the first week) seems dependent on changes in polyamine metabolism and leads to increased mucosal mass and hyperplasia. This effect seems at least partly related to mucosal exposure to nutrients,[5 6] as shown here with OKG supplementation. However, it is obvious that the complex mechanisms involved in the adaptive responses to resection are also dependent on several systemic or local factors.[12 36]

At a functional level, mucosal disaccharidases are reported as increased, unchanged or even decreased in the remnant intestine after resection; however, most studies suggest that the total activity of brush border enzymes increase in parallel to the increase in mucosal mass.[2 7 34 37 38] Our data show an increase in brush border sucrase activity in the resected animals that is concomitant with the increase in mucosal mass and hyperplasia of villus and crypt compartments. Resection induced in one week a twofold to threefold increase in sucrase total and specific activities in the remaining ileum, indicating increased digestive capacities for the ileal segment after resection.

The level of sucrase activity in the brush border membranes is often used as a biochemical marker of functional maturity of the enterocyte. However in the light of our data, the role of sucrase activity as a marker of enterocyte maturity becomes questionable. Indeed, after resection we report an early increase in both total and specific activity of sucrase despite a twofold decrease in the amount of sucrase mRNA in the remaining ileal mucosa. Several trends of evidence support the view of increased enterocyte immaturity in the remaining ileum after resection: hypertrophied villi with reduced life span, increased rate of crypt cell proliferation,[39] higher level of ODC expression, increased polyamine synthesis, and reduced expression of sucrase transcripts. To conciliate the increased enterocyte immaturity with the higher level of sucrase activity measured in the ileum after jejunectomy, the possiblity of a post-translational control of sucrase expression should be considered. The trigger to the post-resectional increase in sucrase activity is the sudden exposure of the ileal mucosa to carbohydrates that were previously absorbed upstream. These substrates, resulting from intraluminal hydrolysis of starch by pancreatic enzymes, may stabilise

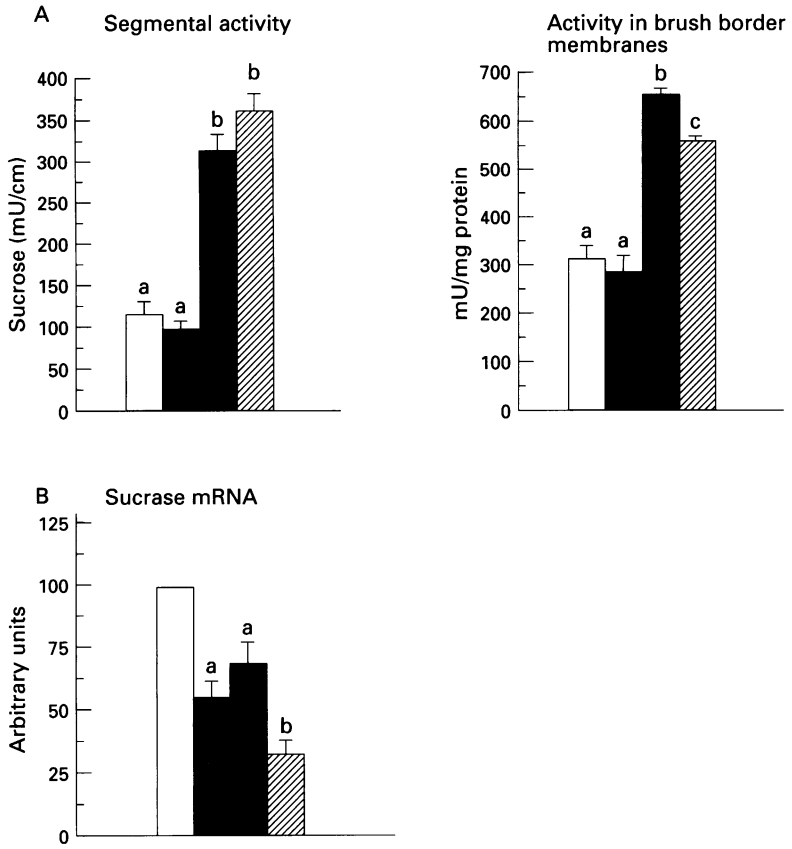

Figure 3: (A) Sucrase total activity in the mucosa per centimetre intestinal length and sucrase specific activity in isolated brush border membranes in the ileum of transected and resected rats. Results are means (SEM) of seven rats per group; columns not sharing a common superscript differ significantly; p<0·05.) (B) Relative amount of sucrase mRNA in the ileal mucosa of transected and resected animals. The amount of mRNA measured in transected control rats was used as reference. The amount of mRNA was quantified by densitometric scanning of the bands. Correction for loading was performed by dividing the densitometries of these bands by the densitometries of the internal standard. Values are means (SEM), n=7 per group. Columns not sharing a common superscript differ significantly; p<0·05.

the enzyme molecule (sucrase-isomaltase) in the brush border membrane and modify enzyme processing and consequently stimulate its activity. It must be emphasised that sucrase present an inherent low expression in the ileum under normal physiological conditions.[40] The enzymic response of the distal small bowel to proximal resection would be a result of increased luminal nutrition acting at the level of the enzyme molecule anchored in the brush border membrane, a process that is independent of the maturity status of the enterocytes lining up the villi. However trophic factors such as hormones, regulatory peptides or dietary polyamines[41] could also modulate structural and functional maturation alike. Indeed in this study we show that treatment with OKG, a precursor of putrescine synthesis, induced a drop in the expression of sucrase mRNA in the transected animal and exacerbated the drop of this transcript in the mucosa of the resected animal indicating clearly that other factors, independent of the composition of luminal nutrients could modulate the expression of sucrase.

In conclusion, early adaptational hypertrophy of the ileal mucosa after jejunectomy is highly dependent on polyamine metabolism and can be accelerated by supplementing the diet with a polyamine precursor like OKG. The adaptive hypertrophy results in an increase in villus height, crypt hyperplasia together with a reduced expression of sucrase mRNA associated with increased sucrase activity in the brush border membrane of the enterocytes. This 'paradoxal' increase in sucrase activity in the remaining ileum might be related to the exposure to substrates that are normally hydrolysed and absorbed upstream by the proximal part of the intestine, and which are controlling enzyme molecule processing and stability at the level of the brush border membranes. To improve better functional differentiation, nutrition might represent a way to promote a number of common adaptive responses that could counteract the effects of crypt hyperplasia and villus hypertrophy in the remnant intestine after resection.

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