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The influence of food intake on the development of structural and functional adaptation following ileal resection in the rat[1]

H. MENGE[2], M. GRÄFE, H. LORENZ-MEYER, AND E. O. RIECKEN

From the Medizinische Universitäts-Klinik, Marburg-an-der-Lahn, West Germany

SUMMARY The present study was undertaken to determine the influence of hyperphagia on the adaptive changes occurring in the rat jejunal mucosa as a result of intestinal resection. One group of resected rats was subjected to pair feeding with a sham-operated population, whilst another group was nourished ad libitum.

The animals which ate ad libitum developed hypertrophy of the mucosa which was accompanied by increased glucose absorption *in vivo* without changes in enzyme levels. These alterations were much less pronounced in the pair-fed group of resected animals, a finding that indicates that the adaptive changes are at least partially influenced by increased luminal nutrition.

Resection of a proximal or distal part of the small bowel provokes a marked hypertrophy of the mucosa of the remaining intestinal segment, which is accompanied by an increase in its absorptive capacity *in vivo*. Much attention has been directed to the role played by the increased intraluminal nutrition, accentuated by the onset of hyperphagia in such animals, in the development of this adaptation (Booth, Evans, Menzies, and Street, 1959; Dowling, 1974). In addition to much indirect evidence in favour of the hypothesis that luminal nutrition is essential for the maintenance of mucosal structure and function, we have recently provided a direct indication of the importance of the intestinal contents, when we demonstrated that the introduction of glucose into an excluded self-emptying blind loop partially reversed the atrophy provoked by the process of exclusion from continuity (Menge, Werner, Lorenz-Meyer, and Riecken, 1975). The present study was undertaken to explore under pair-fed and free-fed conditions the behaviour of the intestinal mucosa following resection so that the influence of food consumption, and hence of the luminal nutrition, on the adaptive changes in the mucosa could be directly investigated.

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[2]Present address: Hôpital Cantonal Universitaire, Département de Chirurgie Expérimentale, Lausanne

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Methods

Female Wistar rats weighing 170-190 g were employed. They were initially fed ad libitum with ground Altromin rat chow and tap water.

OPERATIVE TECHNIQUE

A resection of approximately 60% of the distal small intestine (IR) was performed under ether anaesthesia on 14 rats, and continuity of the gut was restored by end-to-end anastomosis. A further nine rats underwent a sham operation, whereby the intestine was cut and re-anastomosed without resection.

POSTOPERATIVE PROCEDURES

Following the operation, the rats were transferred to metabolic cages which permitted an exact evaluation of the daily food consumption. For the first three days after the operation, the animals were nourished simply with a sugared salt solution. Thereafter, nine of the ileal resected animals were provided only with the quantity of solid food that the paired controls had consumed on the preceding day. The food intake and the body weight of each animal of these two groups were measured daily. The remaining five ileal resected animals received their food ad libitum. On the 32nd postoperative day the intestines were examined.

LABORATORY INVESTIGATIONS

Determinations of glucose absorption *in vivo* and measurements of disaccharidase and dipeptidase activities in mucosal homogenates, as well as histological and morphometric examinations, were performed exactly as in the accompanying paper (Menge *et al*, 1975). In addition histochemistry of the mucosa was carried out as described previously (Menge, Bloch, Schaumlöffel, and Riecken, 1970). Quantitative evaluation was performed using a Leitz CMPV II microdensitometer: the results were corrected for the incubation time and the thickness of the samples, and were expressed as extinction · $min^{-1} \cdot \mu^{-1}$.

STATISTICAL EVALUATION

Throughout, the results were analysed by means of the Wilcoxon test.

Results

BODY WEIGHT

The sham-operated control rats gained weight immediately after the operation, whereas the pair-fed ileal resected animals maintained constant weight for six days. Thereafter, the weights rose in parallel (fig 1). Despite the fact that there was no

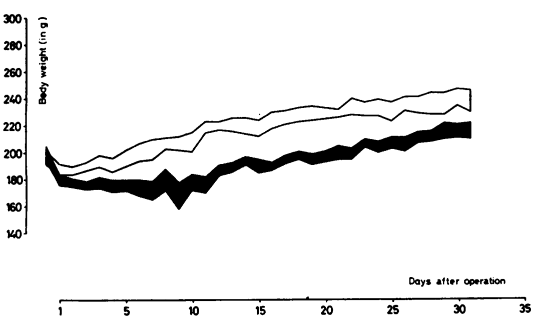

Fig 1 *Body weight of sham-operated control rats and pair-fed resected animals. Space between two thin lines represents means ± SEM of controls, whilst shaded area represents means ± SEM of operated animals.*

difference in weights at the beginning of the experiment, the pair-fed ileal-resected rats had significantly lower body weights than the sham-operated controls at the end of the experiment. In contrast, the free-fed ileal-resected animals weighed the same as the controls (table I).

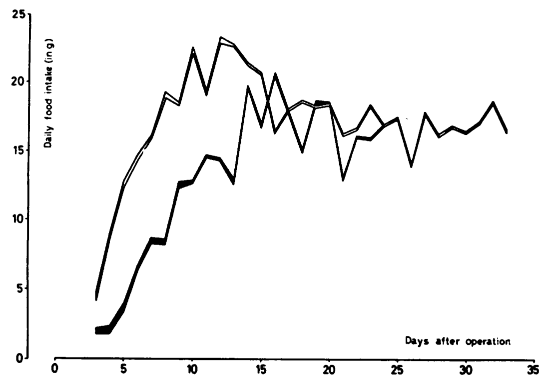

Fig 2 *Daily food consumption of sham-operated rats and pair-fed resected animals. Explanation as in figure 1.*

FOOD INTAKE

The amount of food consumed by the sham-operated rats rose constantly until the seventh postoperative day, then fell off for the next five days, at which stage it stabilized (fig 2). The IR animals consumed an increasing amount for the first seven days, but this quantity was always considerably less than that of the controls. For the next 15 days, the pair-fed ileal-resected rats ate approximately the same quantity as the sham-operated animals, though there often remained a small quantity of food in the cages. However, from the beginning of the fourth postoperative week, the animals obviously required more food than the controls, since the quantity offered was rapidly devoured and no traces remained.

HISTOLOGY AND MORPHOMETRY

There was no apparent difference in the mucosal structure of the control and pair-fed ileal-resected animals. The free-fed ileal-resected rats possessed evidently hypertrophic mucosae. Comparison of the morphometric parameters of the pair-fed ileal-resected animals with the controls revealed a tendency towards increased villus height, crypt length, villus width and epithelial cell height, but in no case did the difference reach the 5% probability threshold

Sham-operated Rats ($n = 9$)	*Rats with Ileal Resection*		*Comparison (Wilcoxon Test)*	
	Pair-fed ($n = 9$)	*Free-fed* ($n = 9$)	*Pair-fed:Controls*	*Free-fed:Pair-fed*
236 ± 6·4	216 ± 4·5	234 ± 11·5	$2\alpha < 0{\cdot}01$	$2\alpha > 0{\cdot}05$

Table I *Body weight in grams at end of experiment*[1]

[1]Results (in this and subsequent tables) expressed as means ± SEM of number of samples stated.

Mucosal Structure (in μ)	*Sham-operated Rats (n = 9)*	*Rats with Ileal Resection*		*Comparison (Wilcoxon Test)*	
		Pair-fed (n = 9)	*Free-fed (n = 5)*	*Pair:fed: Controls*	*Free-fed:Pair-fed*
Villus height	423 ± 11	455 ± 14	556 ± 28	2α >0·05	2α <0·01
Crypt length	185 ± 4	196 ± 5	240 ± 15	2α >0·05	2α <0·01
Villus height / Crypt length	2·3 ± 0·1	2·3 ± 0·1	2·3 ± 0·1	2α >0·05	2α >0·05
Villus width	93 ± 1·7	98 ± 2·6	114 ± 2·9	2α >0·05	2α <0·01
Epithelial cell height	26·7 ± 0·5	28·1 ± 0·6	32·0 ± 0·6	2α >0·05	2α <0·01
Muscle layer	61 ± 4	57 ± 2	91 ± 13	2α >0·05	2α <0·01

Table II *Morphometric evaluation*

Sham-operated Animals (n = 9)	*Rats with Ileal Resection*		*Comparison (Wilcoxon Test)*	
	Pair-fed (n = 9)	*Free-fed (n = 5)*	*Pair-fed:Controls*	*Free-fed:Pair-fed*
1·60 ± 0·07	1·88 ± 0·04	2·44 ± 0·15	2α <0·01	2α <0·01

Table III *Glucose absorption*[1]

[1]Determined *in vivo* with a perfusion technique, expressed in mg · cm intestine^{-1} · h^{-1}.

Enzyme Activity Studied (U/g protein)	*Sham-operated Rats (n = 9)*	*Rats with Ileal Resection*		*Comparison (Wilcoxon Test)*	
		Pair-fed (n = 9)	*Free-fed (n = 5)*	*Pair-fed:Controls*	*Free-fed:Pair-fed*
Maltase	262 ± 22	274 ± 19	239 ± 9	2α >0·05	2α >0·05
Lactase	23·7 ± 3·0	19·8 ± 2·7	18·7 ± 1·9	2α >0·05	2α >0·05
L-methionyl-glycine-dipeptidase	445 ± 34	546 ± 49	587 ± 46	2α >0·05	2α >0·05
Glycyl-L-leucine-dipeptidase	1856 ± 142	2677 ± 209	2616 ± 291	2α >0·01	2α >0·05
L-phenylalanyl-glycine-dipeptidase	189 ± 8	193 ± 8	170 ± 12	2α >0·05	2α > 0·05
L-phenylalanyl-L-proline-dipeptidase	374 ± 24	362 ± 19	321 ± 17	2α >0·06	2α > 0·05

Table IV *Biochemical determinations of dipeptidase and dissacharidase activities*

(table II). In contrast, the free-fed ileal-resected rats developed much taller and wider villi, deeper crypts, larger epithelial cells and thicker muscular layers.

GLUCOSE ABSORPTION

Glucose absorption was significantly increased in both groups of ileal-resected animals (table III), but the rise was much larger in the free-fed rats.

BIOCHEMICAL FINDINGS

The specific activities of maltase and lactase were the same in the three populations, when expressed in terms of the protein content of the homogenate (table IV). There was an increase in glycyl-L-leucine dipeptidase activity in both ileal-resected groups, but this was not accompanied by corresponding rises in the specific activities of the other dipeptidases examined (table IV).

QUANTITATIVE HISTOCHEMISTRY

Microdensitometric evaluation disclosed no significant differences in the activities of alkaline phosphatase, non-specific esterase or leucine aminopeptidase in the individual epithelial cells of the three populations (table V).

Discussion

In an attempt to explore the influence of nutritional factors on the adaptation of the remaining segment of intestine following resection, it was essential to remove a distal segment, since excision of the proximal bowel would automatically bring the distal intestine into contact with a richer diet. This was performed, however, in the knowledge that the adaptive changes in the proximal intestine following distal resection are much more modest than the alterations in distal segments subsequent to proximal resection (Booth *et al*, 1959).

Enzyme Activity Studied ($E{\cdot}min^{-1} \cdot \mu^{-1}) \cdot 10^3$	*Sham-operated Rats* (*n* = 8)	*Rats with Ileal Resection*		*Comparison* (*Wilcoxon Test*)	
		Pair-fed (*n* = 8)	*Free-fed* (*n* = 5)	*Pair-fed:Controls*	*Free fed:Pair-fed*
Alkaline phosphatase	3·9 ± 0·2	4·6 ± 0·3	3·8 ± 0·7	$2\alpha > 0{\cdot}05$	$2\alpha > 0{\cdot}05$
Non-specific esterase	10·9 ± 0·7	11·6 ± 0·7	10·7 ± 0·8	$2\alpha > 0{\cdot}05$	$2\alpha > 0{\cdot}05$
Leucine aminopeptidase	7·8 ± 0·5	9·1 ± 0·5	11·6 ± 1·8	$2\alpha > 0{\cdot}05$	$2\alpha > 0{\cdot}05$

Table V *Quantitative histochemistry of the intestinal epithelium*

The mucosal hypertrophy in the free-fed IR rats corresponds to that described by other investigators (Booth *et al*, 1959; Dowling and Booth, 1967). The ratio, villus height:crypt length, was unchanged, indicating that no zonal transformation of the mucosa occurred (Riecken and Menge, 1974). The enzymological results also agree with the findings of Gleeson, Dowling, and Peters (1972), who reported that there was no change in the specific activity of a variety of different mucosal enzymes, though there was an increase in their levels when expressed per unit length of intestine. Our histochemical results, which represent a factor not previously investigated in the context of intestinal resection, confirm the absence of changes in enzyme activities at the cellular level. These results indicate that the stimulation of absorptive capacity, observed both *in vivo* (Bury, 1972; Dowling, 1974) and *in vitro* (Robinson, Haroud, Luisier, Winistörfer, and Mirkovitch, 1974), is in fact a consequence of the increase in the number of absorbing cells and therefore of the absorptive surface, rather than an augmentation in the activity of the individual cells. This would suggest that hyperplasia occurs, as shown by Gleeson *et al* (1972) with DNA measurements, alongside the hypertrophy of the individual cells which we have demonstrated morphometrically.

In comparison with the free-fed animals, the pair-fed rats developed very little mucosal hypertrophy: the glucose absorptive capacity was only slightly increased, and the changes in morphometric parameters, although showing a tendency towards hypertrophy, did not attain statistical significance. These findings strongly indicate that mucosal hypertrophy is caused largely by increased intraluminal nutrition. Indeed, hyperphagia appears to play an important role in the development of the hypertrophy which is established at a stage when the free-fed rats eat considerably more than the control animals. The fact that hyperphagia *per se* induces mucosal hypertrophy has been suggested by our studies on alloxan diabetes in rats, where a good correlation between villus height and food intake was observed (Lorenz-Meyer, Gottesbüren, Menge, Bloch, and Riecken, 1974), Furthermore, hyperphagia, as a result of intermittent starvation, has been reported to induce an enlargement of mucosal structure and an increase in absorptive capacity (Fábry, Kujalová, and Petrásek, 1959).

The slight changes occurring in the pair-fed group require comment: it is possible that they are initiated by intermittent starvation (Fábry *et al*, 1959), since these rats devoured their food immediately it was provided and were thus, by definition, starved for the rest of the day. On the other hand, further factors may be involved, as suggested by other investigators that hypertrophy can develop within two weeks of the resection (Dowling and Booth, 1967; Bury, 1972), that is to say, before the animals have started to increase their daily food consumption (fig 2). Thus if further factors are involved in the adaptive changes occurring after resection, no indication as to their nature can be gleaned from the present experiments.

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