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Crypt cell production rate, enterocyte turnover time and appearance of transport along the jejunal villus of the rat

A.B.R. Thomson [a,*], C.I. Cheeseman [b], M. Keelan [a], R. Fedorak [a], M.T. Clandinin [c]

[a] *Nutrition and Metabolism Research Group, Division of Gastroenterology, Department of Medicine, 519 Robert Newton Research Building, University of Alberta, Edmonton, Alberta, Canada T6G 2C2*

[b] *Nutrition and Metabolism Research Group, Department of Physiology, University of Alberta, Edmonton, Alberta, Canada T6G 2C2*

[c] *Department of Medicine and Foods & Nutrition, University of Alberta, Edmonton, Alberta, Canada T6G 2C2*

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Abstract

Intestinal nutrient absorption is subject to adaptation with, for example, diabetes, diet lipid variations (isocaloric semisynthetic diets enriched with saturated (S) or polyunsaturated (P) fatty acids), ileal resection and abdominal irradiation. These models were used in rats to assess dynamic morphology and distribution of amino acid transporter along the villus. The enterocyte migration rate (EMR) was measured using [^{3}H]thymidine; the vincristine metaphase arrest technique was used to determine the crypt cell production rate (CCPR); quantitative autoradiography was used to assess the time and age of enterocytes when the uptake of 1 and 20 mM [^{3}H]leucine and [^{3}H]lysine was initiated along the villus. The enhanced jejunal uptake of nutrients which occurs after a 50% distal enterectomy was associated with a fall in EMR and CCPR, yet the enhanced nutrient uptake which occurs in diabetes is not associated with any alteration in EMR, CCPR, enterocyte transport pool (ETP), i.e., the length of the enterocyte column along with the villus containing amino acid transporter) or expression of transporter along the villus. The reduced uptake of nutrients in rats fed P as compared with S was associated with increased rather than decreased ETP and age of the enterocytes at the tip of the villus. The reduced nutrient uptake which occurs 3 days after abdominal irradiation was associated with increased EMR and CCPR, and reduced ETP and age of enterocytes of the tip of the villus. However, 14 days after irradiation when nutrient transport remains reduced, these parameters have returned to normal. Thus, alterations in nutrient transport may be associated with changes in the dynamic morphology of the intestine, but the two processes are not necessarily interdependent. We speculate that the changes in the dynamic morphology of the intestine, and the changes of amino acid transport which occurs in these models of intestinal adaptation, are independently controlled.

Key words: Abdominal radiation; Absorption; Adaptation; Crypt cell production rate; Diabetes; Enterocyte turnover time; Intestinal resection; (Jejunum)

1. Introduction

Enterocytes formed in the intestinal crypt migrate up the villus and are sloughed from the villus tip. This takes about two days in the rat, and during this time the enterocyte gains digestive enzymes such as lactase and sucrase and as well as transporters for amino acids and glucose [1]. De novo sucrase synthesis can occur during enterocyte migration, and the turnover time for the enzymes in the brush-border membrane (BBM) responsible for carbohydrate and dipeptide digestion is about 6 h, much shorter than the life of the enterocyte itself [2,3]. The turnover time of transporter in the cell membrane is unknown, but three points warrant emphasis: firstly, the glucose transporter in the basolateral membrane can be up-regulated after only 4 h of hyperglycemia [4]. Secondly, accumulation of ^{3}H-labelled leucine or lysine in the intestinal villus appears when the enterocyte is approx. 32 h of age and occupies the top third of the villus [5–7]. This appearance of transporter in the upper portion of the villus is not observed in young animals [8], and the induction of transporter by a low protein diet is determined by the age of the enterocyte and not just by its location along the villus

* Corresponding author. Fax: + 1 (403) 4927964.

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[9]. It is unknown whether this induction of transporter at a given enterocyte age rather than position along the villus is a general phenomenon. Thirdly, variations in the carbohydrate content of the diet of mice change the intestinal absorption of glucose as the result of alterations in the transport capability of cells in the crypts, rather than as the result of any modification of carrier properties in enterocytes lining the upper portions of the villus [10–12]. The enhanced ileal uptake of glucose in streptozotocin-diabetic rats may be due in part to the 'recruitment' of glucose transport in the lower portions of the villus of diabetic animals [13]. It remains to be established whether this recruitment phenomenon occurs in other models of intestinal adaptation such as following abdominal irradiation, following ileal resection or with the isocaloric manipulation of the type of lipid in the diet. In addition, it is unknown what is the nature of the interrelationship between crypt cell production rate (CCPR), enterocyte migration rate (EMR), the age of the enterocyte or its position along the villus when amino acid transporter function first appears. Accordingly, we measured CCPR, EMR and [^{3}H]leucine and [^{3}H]lysine uptake along the villus in several models of intestinal adaptation: in diabetic intestine, in the jejunum following ileal resection, following abdominal irradiation, and in the jejunum of rats fed isocaloric semisynthetic diets high in saturated or polyunsaturated fatty acids.

2. Methods and materials

Animals

We choose four groups of animals in which previous studies had demonstrated alterations in the jejunal uptake of nutrients. Four groups of rats (Sprague-Dawley) were studied to assess the effect of diabetes, dietary fatty acid composition, ileal resection and irradiation on crypt cell production rate (CCPR). In the first group, six animals were rendered hyperglycemic (blood glucose over 275 mg/dl, and under 375 mg/dl) by the intravenous injection of streptozotocin (65 mg/kg body weight) and six animals were injected with saline to serve as non-diabetic controls [14]. Diabetic and control animals were studied 14 days post-injection. In the second group, eight rats were fed for two weeks on a semisynthetic nutritionally adequate diet rich in saturated fatty acids, and eight animals were fed an isocaloric diet rich in polyunsaturated fatty acids. The composition of these diets has been published [15]. In the third group, six animals were subjected to laparotomy and resection of the distal 50% of their small intestine, while 6 animals were subjected to laparotomy and transection to serve as controls [16]. Resected and control animals were studied six weeks after surgery. They were fed ad libitum, and their weights were similar at the time of experimentation. They were allowed 6 weeks to recover, to gain weight normally, but still to have alterations in nutrient uptake. In the fourth group, six animals served as controls while 18 animals were exposed to 600 cGy external abdominal irradiation; a subset of six animals were studied three, seven and 14 days post-irradiation [17]. The animals were allowed ad libitum access to food and water until the morning of the experiments. The details of these models have been published [14–17]. These models were chosen since the intestinal uptake of nutrients is increased in diabetes and following an ileal resection, and is decreased after abdominal radiation and with feeding a polyunsaturated diet.

Materials

L-[4,5-^{3}H]Leucine (120 Ci/mmol), L-[4,5-^{3}H]lysine (96 Ci/mmol) and [*methyl*-^{3}H]thymidine (25 Ci/mmol) were obtained from Amersham International, Amersham. Amino acids and Grade I glutaraldehyde were supplied by Sigma, St. Louis, MO. NTB2 nuclear track emulsion was from Eastman Kodak, Rochester, NY.

Crypt cell production rate (CCPR)

Vincristine was the stathmokinetic agent of choice for the metaphase arrest technique since in the small intestine it does not affect the flux of cells into or out of DNA synthesis as measured by double labelling methods [18]. In addition, vincristine is available almost immediately after injection, unlike other stathmokinetic agents [19]. The optimal dose is the lowest that will arrest all metaphases and prevent anaphase escape over the experimental period selected for a specific tissue [20]. The adult Sprague-Dawley rats were given vincristine sulfate (0.5 mg/kg body weight) by intraperitoneal injection and were killed 2.5 h post-injection by the injection of Euthanyl® (pentobarbital), 500 mg/kg body weight. The optimal dose of vincristine was determined by dose–response curves and found to be 0.50 mg/kg body weight for the small intestine of Sprague-Dawley rats (data not shown). The optimal collection period was determined by linearity studies to be 2.5 h after intraperitoneal injection.

Tissue sections from proximal small intestine (jejunum) were fixed in Bouin's, dehydrated, embedded in paraffin, cut, and stained with hematoxylin and eosin. Slides were randomized so that the total and mitotic cells were counted 'blind'. Approx. 1000 cells were counted for each site. Each section contained approx. 150 crypt cells. The number of mitotic cells was expressed as percent metaphases, and reflected the CCPR. All data ares expressed as means ± standard error (S.E.). Significant differences ($P < 0.05$) between two groups were determined by the unpaired Student's *t*-test.

Autoradiography

The technique previously described by Cheeseman [5] was employed. The middle fifth (jejunum) of the small intestine was removed from the rats under anesthesia after flushing out the luminal contents with saline at room temperature. The tissue was opened up along the antimesenteric border and mounted with the mucosal surface uppermost, over stainless steel pins on a lucite block. The serosal surface was kept moist with a piece of filter paper soaked in saline. This block was then clamped to a second one with 12 identical ports which each exposed a disk of mucosa of 0.2 cm^2 surface area (area equivalent to serosal surface, with no correction made for villi). Each port could be rapidly filled or emptied by suction, and the bulk phase could be rapidly stirred with a small propeller to reduce the effect of intestinal unstirred water layers. The entire apparatus was maintained at 37°C. The mounted tissue was preincubated for 10 min to allow it to equilibrate. Then two chambers at a time were drained and the radiolabelled solution was added containing either 1 or 20 mM leucine or lysine and a minimum of 100 μCi/ml of [^{3}H]leucine or [^{3}H]lysine. The incubations lasted 45 s, during which the bulk phase was stirred at 900 rpm. The ports were then drained and immediately filled with fixative (4% glutaraldehyde, 2% sucrose in phosphate-buffered saline (pH 7.3)). This fixative was left in contact with the tissue until all 12 ports had been incubated. The tissue was then punched out of the transport chamber and kept in fixative for 30 min. After washing in phosphate-buffered saline overnight to remove the glutaraldehyde, the tissue was fixed in glycomethacrylate. Sections (10 μm) were coated with NTB2 nuclear track emulsion and left to expose in the dark at 4°C for 14–21 days.

Microdensitometry

Scanning microdensitometry of unstained sections of the autoradiographs was carried out at a final magnification of ×400 using a Vickers M85 microdensitometer. Scanning of autoradiographic pictures was performed on villi at a wavelength of 650 nm and in discrete 30 μm steps along the villi. All optical density readings were converted to a percentage of the maximum density for each villus which was invariably at the villus tip. Values for the 30 μm steps were averaged for the villi and analysed and expressed as a mean ± S.E. Curves were analysed for changes in slope; where a change of greater than 100% was found this was defined locus of change in expression of the amino acid carrier.

Measurement of enterocyte migration rates

Animals were injected intraperitoneally with [^{3}H] thymidine (1 μCi/g body weight) and were killed 10, 18, 26, 34 or 42 h later. The tissue was then processed

Table 1
Morphology, enterocyte migration rate, crypt cell production rate and expression of transporter along the jejunal villus

Condition	Villus height	EMR (μm/h)	Initial expression of transporter along the villus		Tip age (h)	CCPR (% metaphase)	ETP (μm)
			initial expression distance (μm)	age (h)			
Diabetes							
Control	432 ± 10	9	232 ± 26	35 ± 2	55	11.9 ± 0.8	188
Diabetic	496 ± 11	8	233 ± 26	38 ± 3	63	10.8 ± 1.0	187
Diet							
P diet	640 ±	12	255 ± 15	23 ± 14	53	14.5 ± 0.6	385
S diet	560 ±	13	240 ± 15	25 ± 15	44 [a]	14.7 ± 0.8	320 [a]
Resection							
Control	530 ±	16	255 ± 10	18 ± 0.7	37	14.2 ± 0.8	305
Resected	480 ±	12 [b]	248 ± 26	18 ± 1.9	40	7.0 ± 1.4 [b]	232
Irradiation [d]							
Control	420 ± 18	10	180 ± 7	34 ± 1.3	56	11.7 ± 0.3	240
3 days	290 ± 32	15 [c]	90 [c]	18 [c]	37 [c]	21.3 ± 1.3 [c]	210 [c]
7 days	405 ± 17	10	120 [c]	26 [c]	57	11.1 ± 1.1	300 [c]
14 days	390 ± 14	10	210	35	57	9.6 ± 1.5	210

EMR, enterocyte migration rate (μm/h); CCPR, crypt cell production rate (% metaphase); ETP, enterocyte transport pool (length of villus expressing amino acid transport, μm).

[a] $P < 0.05$, saturated versus polyunsaturated diet.

[b] $P < 0.05$, resected versus control.

[c] $P < 0.05$, irradiated versus control.

[d] The data for villus height, EMR and initial expression of transporter along the villus have been published for the irradiation group [21]. The results for initial expression of transporter from this group is from pooled data and values for ± S.E. are not available.

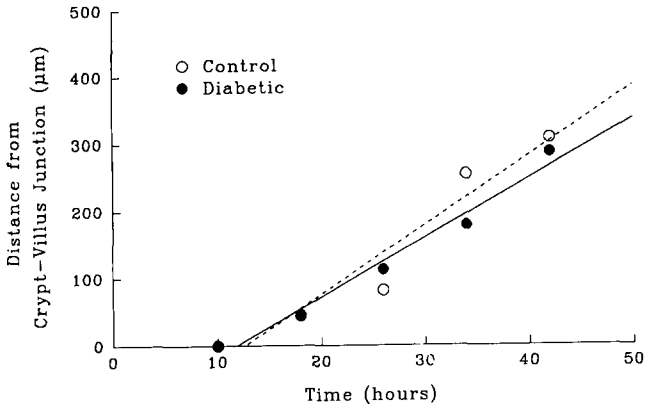

Fig. 1. Cell migration rates along intestinal villi in control and diabetic rats. Animals were injected IP with 1 μCi/g body weight of [^{3}H]thymidine and killed 10, 18, 26, 34 or 42 h later. Mid-intestine was fixed, sectioned, processed for autoradiography and the distance of the silver grain front from the crypt-villus junction was measured. Data shown are the mean values from between 11 and 29 villi obtained from four animals. The lines were fitted by linear regression analysis. The horizontal paired lines indicate the top of the villi (approx. 420 μm).

for autoradiography as described above. The distance of the silver grain front from the crypt-villus junction was measured using a micrometer eyepiece on a microscope. This gave values of the enterocyte migration rate (EMR) in μm/h.

3. Results

Diabetes mellitus

Two weeks of diabetes had no effect on the jejunal villus height or on the enterocyte migration rate (EMR) (Table 1 and Fig. 1). Consequently the data for autoradiography of the tissue was plotted using only distance along the villi, and not the age of the cells. Figs. 2 and 3 show the distribution of radiolabeled [^{3}H]leucine density for the intestinal epithelial cells in control and diabetic animals, as measured with 1 and 20 mM L-leucine and 1 and 20 mM L-lysine. Both amino acids showed the same distribution for both concentrations, and there was no difference between control and diabetic animals. The initial distance along the villus where uptake increased significantly corresponds to a cell age of 34–36 h out of the crypt. The majority of substrate was found in the top 150–180 μm of the villi. The distribution of radiolabeled [^{3}H]leucine along the villi showed the same pattern of distribution as has been reported previously [1,5,7]. The length of the villus containing transporter (ETP, enterocyte transport pool) was also similar in diabetic and in control rats; i.e., both leucine and lysine were taken up by the same tip region of the villi and diabetes had no effect on this pattern. Furthermore, the EMR was similar in diabetic and control rats (8–9 μm/h), the villus heights were similar, and the cells were a similar age at the villus tips (55–63 h). The crypt cell production rate (CCPR) in the jejunum and ileum was also unaffected by diabetes (Table 1). Thus, the previously reported increased jejunal uptake of nutrients in diabetic rats [14] is not explained by alterations in EMR, CCPR, or ETP.

Changes in diet lipid content

The jejunal EMR was similar in rats fed the isocaloric semisynthetic diets enriched with saturated (S) or polyunsaturated (P) fatty acids (Table 1 and Fig. 4): the slopes of the two lines were identical, (12.1 ± 0.5 and 12.6 ± 0.6 h respectively). Both lines have a correlation coefficient of 0.998. Thus, the data for autoradiography of the tissue has been plotted using only distance along the villi. The diets had no effect on CCPR in the jejunum or ileum (Table 1). The diets

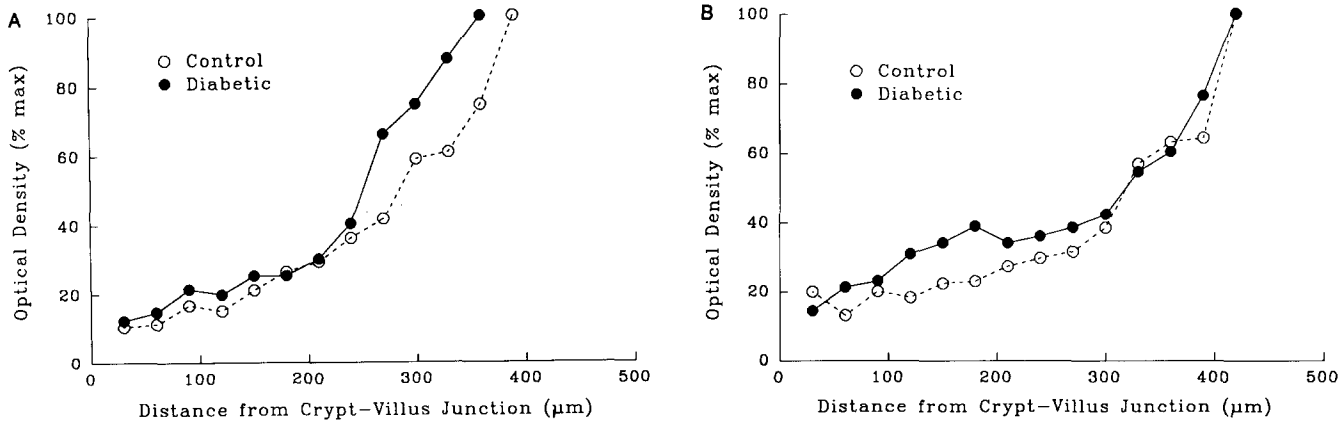

Fig. 2. The distribution of silver grain density along the villi of control and diabetic rats. Mid-intestine (lower jejunum) was incubated with 1 mM (A) or 20 mM (B) L-leucine, outlined in Methods and materials. Silver grain density is expressed as a percentage of the maximum. Each data point represents the mean value obtained from 13 villi in three rats.

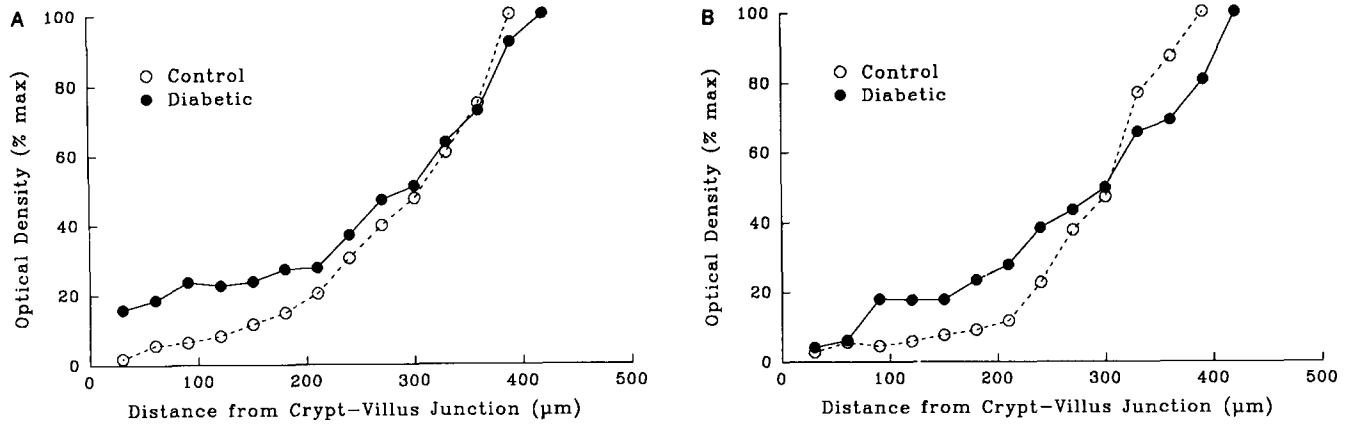

Fig. 3. Distribution of silver grain density along the villi of control and diabetic rats as obtained for L-lysine uptake. Mid-intestine (lower jejunum) was incubated with 1 mM (A) or 20 mM (B) L-lysine as described in Methods and materials. Silver grain density is expressed as a percentage of the maximum. Points are the mean values of 15 villi from three animals.

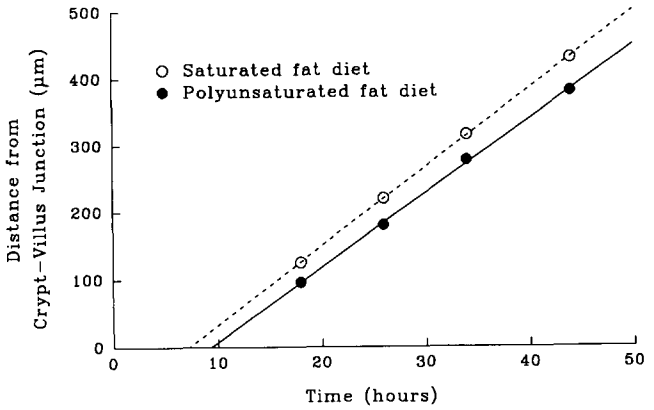

Fig. 4. Cell migration rates along intestinal villi in rats fed isocaloric semisynthetic diets high in saturated or polyunsaturated fatty acids. The lines were fitted by linear regression analysis.

also had no effect on the position and hence age of when cells expressed transport for either leucine or lysine (Fig. 5). For lysine this corresponds to about 28 h or 240 μm from the villus base (Fig. 6) and for leucine, 270 μm or 33 h. The EMR was similar on both diets, but the villus height was higher (640 versus 560 μm) and the age of the villus cells was greater (53 versus 44 h) in rats fed the P as compared with S (Table 1). As a result, a greater length of villus was available for transport of amino acids in the P as compared with S (385 versus 320 μm, respectively). Thus, the greater uptake of nutrients in rats fed S as compared with P [12] was associated with lower villus height, ETP and age of the enterocytes at the tip of the villus.

Ileal resection

The height of the jejunal villus was similar but the EMR was slower ($P < 0.05$) in resected than in control rats (Table 1). The CCPR was reduced by about 50% (14.2 versus 7.0% metaphase in control and resected rats, respectively), but the age and position of the

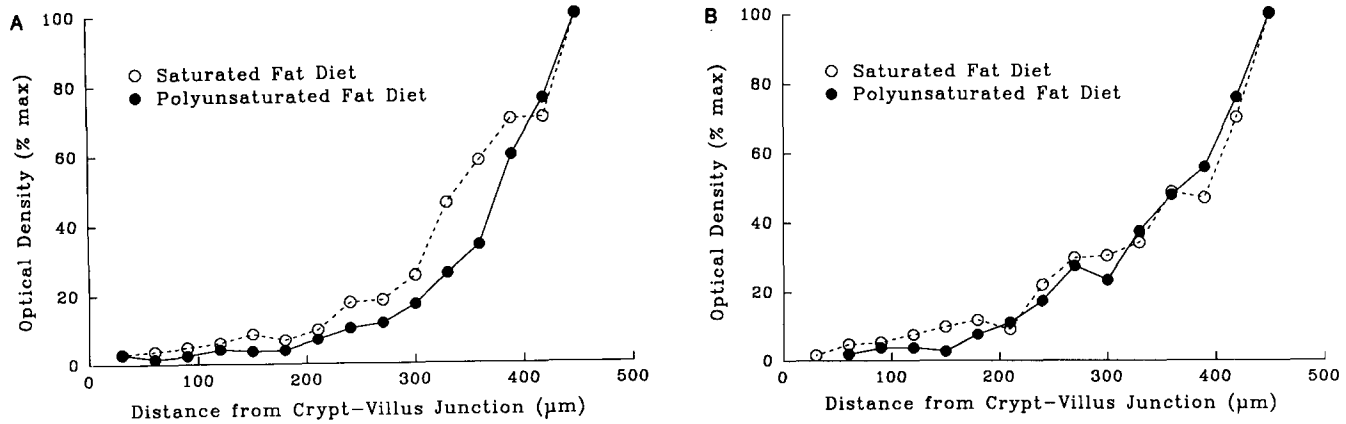

Fig. 5. The distribution of silver grain density along the villi of rats fed isocaloric semisynthetic diets high in saturated or polyunsaturated fatty acids. Mid-intestine (lower jejunum) was incubated with 1 mM L-leucine (A) or 1 mM L-lysine (B) as described in Methods and materials. Silver grain density is expressed as a percentage of the maximum.

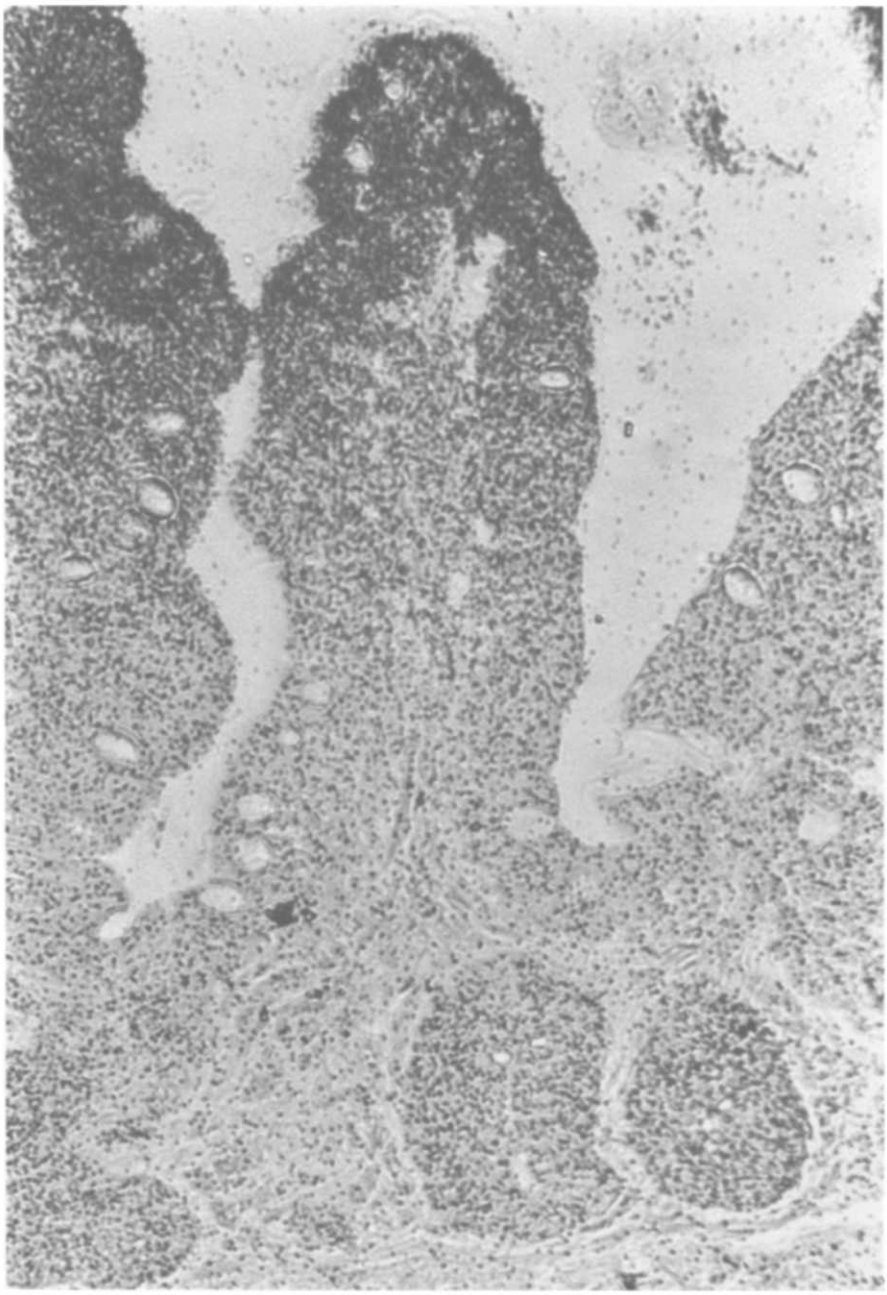

Fig. 6. Autoradiogram of jejunal villus showing the distribution of radioactive lysine taken up by enterocytes. A sheet of jejunum was incubated with 1 mM L-lysine labelled with tritium for 90 s while the mucosal medium was rapidly stirred to minimize unstirred water layers. The tissue was then rapidly fixed with glutaraldehyde before sections were mounted on glass slides. These slides were dipped in photographic emulsion and exposed for 7 to 14 days before being developed. Silver grain density was then determined using a scanning microdensitometer (see Methods and materials).

enterocytes transporting leucine and lysine was similar in both groups. The length of the villus containing transporter was similar in control and resected rats (290 and 270 μm, respectively). Thus, the increased uptake of nutrients into the jejunum of animals subjected to a 50% distal enteroectomy [16] was associated with reduced EMR and CCPR, without any alteration in ETP or the age of the enterocytes.

Abdominal irradiation

Three days after abdominal irradiation the jejunal villus height fell, EMR and CCPR increased, and transporter was expressed when the cells were younger and closer to the crypts (Table 1). By 14 days after abdominal radiation, villus height, EMR, CCPR, ETP, expression of transporter along the villus, and age of the enterocytes at the tip of the villus had returned to

normal, yet under identical conditions nutrient uptake remained suppressed.

4. Discussion

Adaptation in the intestine involves both morphological and functional changes [21]. These include alteration in the isoforms of glucose carriers [22–24], alterations in the lipid composition of the brush-border membrane [14], and changes in membrane fluidity [25]. Adaptive responses of the intestine which result in an altered transport capacity could result from a variety of mechanisms. For example, the individual cells could transport more or less substrate by altering the maximal transport rate (V_{max}) or the Michaelis constant (K_m) of the transporter protein. Alternatively, the total number of transporting cells could be changed without any alteration of the V_{max} or K_m in each enterocyte. This latter effect might result from either an alteration in the height of the villi (which would give more or fewer epithelial cells), or the rate of enterocyte migration might change, giving more or less time for the enterocytes along the villus to mature and express their transport capacity, thereby changing the total number of transporting enterocytes (i.e., the size of the enterocyte transport pool without necessarily altering the total number of enterocytes or the height of the villus).

We choose to study four groups of animals in which previous studies have demonstrated increased (diabetes, resection) or decreased (abdominal irradiation, feeding a polyunsaturated fatty acid diet) nutrient uptake [14–17]. It is clear from these data that no single mechanism explains the known alterations of nutrient uptake described in diabetes, diet lipid manipulation, ileal resection or abdominal irradiation [14–17,21,26]. For example, feeding a diet enriched in saturated fatty acids (P) increases glucose uptake in the jejunum [15], yet there is a decreased height of the villi, and a decreased time for the cells to reach the villus tip, and a decreased ETP (enterocyte transport pool, ie the length of the villus containing amino acid transporter), without a change in the EMR or the CCPR (Table 1). Therefore, diet-induced changes in amino acid uptake cannot be explained by an alteration in the size of the enterocyte transport pool, or the age of the cells along the villus. In contrast, three days after irradiation, villus height falls, ETP falls, and the age of the cells on the villus falls, yet nutrient uptake also falls [17]. At least in these two models then, the less mature cells resulted in a shorter length of the villus expressing amino acid transport, yet the direction of altered nutrient uptake was not necessarily decreased.

In some studies, there may be an increase in villus height, particularly in the ileum of diabetic rats [13]. In this study, and in this group of rats, diabetes did not alter the jejunal villus height, enterocyte migration up the villi, the age of the enterocytes at the tip of the villi, the CCPR, or the expression of amino acid transporter along the villus. And yet, with mild diabetes (fasting blood glucose greater than 275 mg/dl, highest level 375 mg/dl), glucose and lipid uptake is increased [14]. Recruitment of glucose transporter in the ileum has been suggested from autoradiographic studies using [^{3}H]phlorizin [13], but this does not occur in the jejunum [27]. Amino acids are taken by sodium-dependent transport systems which are most active in the mature intestinal epithelial cells covering the upper third of the villi [1,5,6]. Our data suggests that recruitment does not occur, since the size of the enterocyte transport pool (the length of villus expressing amino acid transport) does not change (Table 1). It is possible that the alterations in nutrient transport are signalled to the intestinal crypt cells, which must then migrate up the villus before greater uptake is expressed [10–12]; this possibility was not specifically addressed in this study.

With resection and abdominal irradiation there were parallel changes in CCPR and EMR: 3 days after abdominal irradiation, CCPR increased from 11.7 to 21.3, and EMR increased from 10 to 15 mm/h (Table 1). The opposite occurred with resection: a slowing of EMR from 16 to 12 mm/h but a halving of CCPR from 14.2 to 7.0. As CCPR rises and EMR rises, 3 days after abdominal irradiation, the height of the villus tends to fall, the age of the enterocytes on the villus falls, and the size of the enterocyte transport pool falls (Table 1). However, this sequence is not necessarily followed in reverse, since the fall in CCPR and EMR with resection does not significantly alter villus height, enterocyte age or the size of the enterocyte transport pool. Thus, a change in CCPR or EMR does not necessarily alter the size of the enterocyte transport pool or the age of the enterocytes along the villus. It is speculated therefore that the changes in the dynamic morphology of the intestine and the changes of amino acid transport which occur in these models of intestinal adaptation, are independently controlled.

It is unknown what controls villus height: with the production of more cells emerging from the crypts at the villi, the villi might lengthen, unless EMR quickens, in which case the villi might shorten. These two potentially counteracting changes occur three days after abdominal irradiation, suggesting that here the EMR has the dominant effect. However, EMR falls after ileal resection without an accompanying fall in CCPR, and villus height remains unchanged. Thus, there is likely a complex interaction between each of these parameters, and an alteration in dynamic morphology is not necessarily associated with a change in the height of the villi or in the transport function. This comparison of a series of different conditions therefore emphasizes the

multiplicity of factors which are involved in the adaptation of the small intestine. All of the various potential components of a response must be considered before the adaptation to a given stimulus or condition can be fully understood.

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