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Hyperenteroglucagonaemia and small intestinal mucosal growth after colonic perfusion of glucose in rats

B M MIAZZA, M Y T AL-MUKHTAR, M SALMERON, M A GHATEI, M FELCE-DACHEZ, A FILALI, R VILLET, N A WRIGHT, S R BLOOM, AND J-C RAMBAUD

From the Research Unit on Pathophysiology of Digestion (INSERM U54) Hôpital Saint-Lazare, Paris, France, Departments of Medicine and Histopathology, Royal Postgraduate Medical School, London, United Kingdom, Departments of Pathology and of Surgery, Hôpital Lariboisière, Paris, France

SUMMARY Beside intraluminal factors, humoral agents play an important role in intestinal adaptation. Enteroglucagon, the mucosal concentration of which is maximal in the terminal ileum and colon, is the strongest candidate for the role of small intestinal mucosal growth factor. The present experiment was designed to study the role of colonic enteroglucagon in stimulatiing mucosal growth in rats with a normal small intestine. After eight days of glucose large bowel perfusion, enteroglucagon plasma concentrations were 120·7±SEM 9·2 pmol/l, *versus* 60·1±6·8 in mannitol perfused control rats ($p<0·001$). Gastrin, cholecystokinin, neurotensin, pancreatic glucagon, and insulin plasma concentrations were unchanged. Crypt cell proliferation, measured by the vincristine metaphase arrest technique, increased significantly in the small intestine of glucose perfused animals ($p<0·005$–$0·001$) in comparison with the controls. This resulted in a greater mucosal mass in both proximal and distal small bowel: mucosal wet weight, DNA, protein and αD-glucosidase per unit length intestine were all significantly higher ($p<0·05$–$0·001$) than in mannitol perfused rats. Our data, therefore, support the hypothesis that enteroglucagon is an enterotrophic factor and stress the possible role of the colon in the regulation of small bowel trophicity.

The large bowel mucosa is rich in endocrine cells.[1–5] It is tempting to speculate as to whether these cells, triggered by unabsorbed nutrients, participate in a feed-back control of upper gastrointestinal functions. Acute intracolonic infusion of some nutrients does induce inhibition of gastric[6 7] and pancreatic exocrine[8] secretions. Another possible role for the colon as an endocrine organ could be a trophic action on the small intestine. Indeed, colonic mucosa has, after the ileum, the highest content of glucagon-like immunoreactivity both in man[9] and in rats,[10] and enteroglucagon is currently the strongest candidate as a small intestinal mucosal growth factor (enterotrophin).[11 12] Moreover, in rats with 50% and 90% ileal resection, which induces a mild but significant structural and functional adaptation of the residual proximal small intestine,[13] enteroglucagon is significantly increased both in blood and in colonic mucosa.[13] In this model, small intestinal absorption is impaired, and a direct effect of a compensatory increase in food intake on the stimulation of mucosal growth of the residual small bowel has been suggested.[14]

The present experiment was an attempt to study further the role of colonic enteroglucagon as an enterotrophin by using an experimental model which maintains small intestinal integrity. Glucose perfusion of the large bowel was used to trigger enteroglucagon release, as it has been shown to induce hyperenteroglucagonemia in man.[6]

Address for correspondence: Dr Jean-Claude Rambaud, Unité de Recherches sur la Physiopathologie de la Digestion, Inserm U54 – Hôpital Saint-Lazare 107bis, rue du faubourg Saint-Denis 75475 Paris CEDEX 10, France.

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Methods

STUDY DESIGN

Male SPF wistar rats weighing 250–300 g were used. After a short laparotomy under pentobarbital anaesthesia (Nembutal Abbott, 4 mg/100 g body weight), a vinyl tube (Portex Ltd) (id 1·0, od 2·0

mm) was inserted into the caecum. Its proximal end was pulled subcutaneously to the interscapular area, where it was connected to the perfusion system, attached to the rat by a dorsal harness. Solutions were infused at a flow rate of 1·8 ml/h by a constant peristaltic pump (Neotechnique, France). The animals could move freely in individual cages and had free access to food and water. Cages had a wire netting bottom allowing the passage of stools and urine to an underlying tray.

Non-fasted rats were killed after eight days of continuous intracaecal perfusion of 10% glucose (osmolality 555 mOsm/kg) (n=10). The resultant changes in plasma concentrations of several peptides, in intestinal cell proliferation (Crypt cell production rats = CCPR) and in small intestinal structure and function (see below) were compared with those found in 10% mannitol (osmolality 550 mOsm/kg) (n=8) perfused control animals.

In all rats, 4–6 ml blood were taken by cardiac puncture in heparinised tubes, containing also 0·2 ml aprotinin (Iniprol, Laboratoires Choay, France). The plasma was then separated by centrifugation and stored at −70°C until assay. At 0900 on the day they were killed, 10 glucose and eight mannitol perfused rats received vincristine sulphate (Oncovin, Lilly) at a dose of 1 mg/kg by intraperitoneal injection. The first rat in each group was killed 30 minutes after vincristine administration, the remaining animals were killed at 15 minute intervals thereafter. The whole intestinal tract, and the liver, pancreas and kidneys were then removed. The intestine was stripped of its mesentery and its contents washed out with ice cold isotonic saline. Six 2 cm samples were taken for CCPR measurement at sites 10, 25, 50, 75, and 90% of the small bowel length (measured between the pylorus and the ileocaecal valve) and in the distal colon (3 cm above the rectum); two rats in the glucose group were subsequently discarded because of inaccurate vincristine injection. Two samples (adjacent to sites 10% and 75%) were also taken for morphometry and fixed in Bouin's solution. Approximately 10 cm segments of jejunum (lying between sites 10 and 25%) and of ileum (75 to 90% of gut length) were sectioned and measured under 5 g tension. The mucosa was then scraped, weighed, and deep frozen (−70°C). Pancreases were carefully dissected free and weighed, as were livers and kidneys.

In order to establish that the colonic perfusate did not reflux into the small intestine, five animals were infused with either 10% glucose or 10% mannitol, containing a non-absorbable water soluble marker (^{14}C-polyethylene glycol (PEG-^{14}C), MW 4000, 10 μCi/l). The radioactivity of the total caecal content was measured by scintillation counting and compared with that found in 10 cm segments of distal ileum and proximal jejunum. Results showed that the radioactivity in the small intestine was 1–2 orders of magnitude less than in the caecum ($p<0·001$). Furthermore, there was no significant difference between jejunal and ileal radioactivity. The presence of significant amount of ^{14}C-PEG in the small bowel was very likely caused by coprophagia, which could not be totally avoided, because all animals had diarrhoeic stools soiling the wire netting floor of the cages. In agreement with these findings, the appearance of small intestinal contents was normal in all control and experimental animals, in contrast with the watery appearance of the colonic contents.

HORMONAL STUDY

Pancreatic glucagon and enteroglucagon were measured using two different antibodies to porcine pancreatic glucagon.[15] Total (gut and pancreatic) glucagon immunoreactivity was measured first using an antibody reacting with the N-terminal region of both peptides. Pancreatic glucagon was measured separately with a specific antibody to the C-terminal portion of the peptide. Enteroglucagon plasma concentrations were then obtained by substracting pancreatic from total glucagon immunoreactivity. Gastrin and cholecystokinin were measured using two antiserea.[16] One was directed to the C-terminal region, fully and equally cross reacting with both CCK and gastrin, the other was specific for the C-terminal region of the molecular form of gastrin G17. Cholecystokinin plasma concentrations were then obtained by subtracting G17 from total CCK plus gastrin immunoreactivity. Neurotensin[17] and insulin[18] were also measured by specific radioimmunoassays.

CRYPT CELL PRODUCTION RATE (CCPR)

Tissues were fixed in Carnoy's fluid for four hours and then transferred to 70% ethanol. After rehydration, followed by hydrolysis in HCl for six minutes at 60°C, the samples were stained with Feulgen's reagent. The crypts were individually dissected under the microscope. Vincristine-blocked metaphases were then counted in 10 crypts per sample. The mean metaphase counts were plotted against time after administration of the blocking agent. The crypt cell production rate per hour for each sampling site and in each group was given by the slope of the regression line fitted by the method of least squares.[19]

BIOCHEMICAL DATA

Small intestinal mucosa was homogenised in ice cold isotonic saline (Ultra-Turrax homogeniser, Janke

and Kunkel, FGR). After appropriate dilution, α-D-glucosidase activity was assayed fluorometrically,[20] DNA was measured according to Prasad *et al*[21] and protein was estimated by the method of Lowry *et al*.[22]

MORPHOMETRY

Tissues were stained with haematoxylin and eosin for the measurements of villus height, crypt depth, and total mucosal thickness. The results were the mean reading of 10 well orientated villi and crypts in each section and expressed in microns.

STATISTICAL ANALYSIS

Results are expressed as mean values ± SEM. The significance of the differences between mean values was tested by paired or unpaired Student's *t* test, as appropriate.

Results

BODY, PANCREAS, LIVER, AND KIDNEY WEIGHTS

These results are shown in the Table. After eight days of continuous colonic perfusion, all animals appeared healthy. There were small and statistically non-significant variations in body weight in both glucose and mannitol rats. Glucose perfusion provoked no change in the weight of pancreas, liver and kidneys, in comparison with mannitol perfused animals.

HORMONES

Non-fasting plasma concentrations of enteroglucagon, gastrin, cholecystokinin, and insulin are shown in Figure 1. After glucose perfusion, enteroglucagon plasma concentrations were significantly higher ($p<0.001$) than in the controls. In contrast, gastrin, cholecystokinin, pancreatic glucagon, neurotensin, and insulin plasma concentrations were not significantly influenced by colonic perfusion of glucose. Pancreatic glucagon and neurotensin results were less than 5 and 3 pmol/l respectively, and not significantly different between controls and glucose rats; therefore they are not shown on Figure 1.

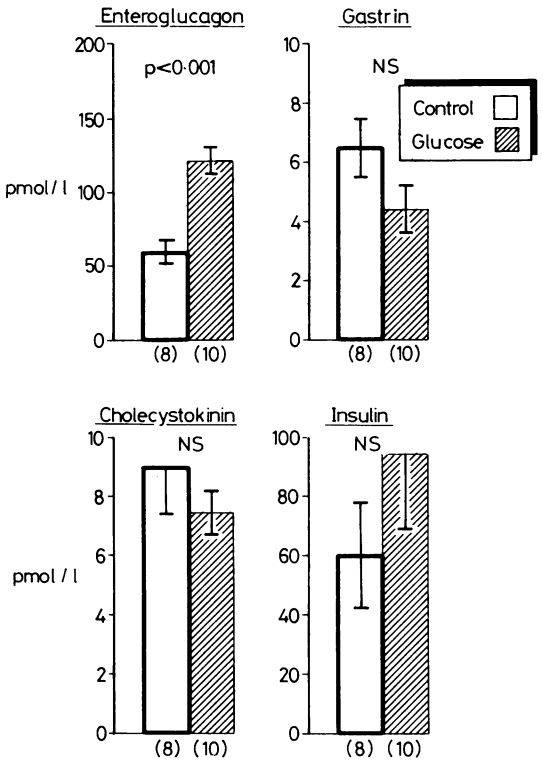

Fig. 1 *Plasma concentrations of enteroglucagon, gastrin, CCK and insulin in controls and glucose perfused rats. Number of animals in each group is indicated at the base of each column. NS denotes no significant difference.*

Table *Total body, pancreas, liver and kidney weights before and after 8 days of mannitol (n=8) or glucose (n=10) large bowel perfusion*

	Mannitol		*Glucose*
Initial body weight (g)	276·3±5·5	ns	273·7±7·1
	↑		↑
	ns		ns
	↓		↓
Final body weight (g)	263·9±5·8	ns	278·7±5·2
Pancreas (g)	1·19±0·04	ns	1·13±0·04
Liver (g)	11·2±0·2	ns	10·4±0·3
Kidneys (g)	2·1±0·1	ns	2·1±0·1

Results are mean±SEM; ns denotes no statistically significant differences.

CRYPT CELL PRODUCTION RATE (CCPR)

Data for CCPR per hour in five sites of the small intestine and in the distal colon are shown in Figure 2. Crypt cell production rate per hour increased significantly ($p<0.005$–0.001) in sites one to four after glucose perfusion, whereas the differences did not reach statistical significance in the most distal site of the small bowel (terminal ileum) nor in the colon.

SMALL INTESTINAL STRUCTURE AND FUNCTION

After eight days colonic perfusion of glucose, small intestinal mass increased significantly in both jejunum and ileum (Fig. 3). Mucosal wet weight, DNA and protein content per unit length of

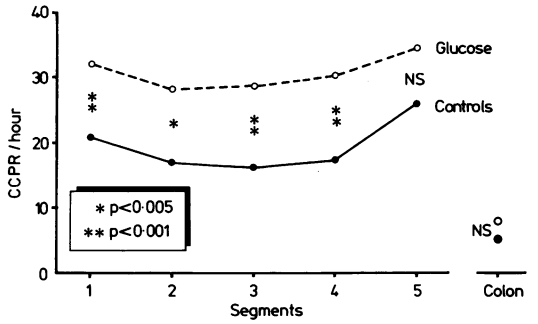

Fig. 2 *CCPR/h in five different small intestinal segments and the colon for eight animals in each group. Segments 1–5 correspond to sites distant of 10, 25, 50, 75 and 90% of total small bowel length measured from the pylorus.*

intestine were all greater ($p<0·05$–$0·001$) than in controls. The activity of α-D-glucosidase, expressed per unit length of small bowel, increased significantly ($p<0·05$–$0·02$) in both proximal and distal intestine (Fig. 4). When the results were expressed per milligram DNA, α-D-glucosidase activity was significantly greater in the ileum ($p<0·05$) but not in the jejunum (Fig. 4). Results of quantitative histology are shown in Figure 5. Despite a trend towards longer villi, deeper crypts and a thicker mucosa, particularly in the ileum, none of these differences reached statistical significance.

Discussion

Besides the role of luminal nutrition and pancreatico-biliary secretions,[11] there is good evidence that hormonal factors play a role in intestinal adaptation. Direct evidence for a humoral control was found in cross circulation experiments:[23 24] small bowel resection stimulated a hyperplastic response not only in resected animals, but also in the unoperated partners of the parabiotic pairs. Similar results were observed after jejunectomy,[25] jejunal exclusion,[12] ileal infusion of 30% dextrose[26] and during lactation[27] in intestinal segments completely isolated from the topical action of nutrients and pancreatico-biliary secretions.

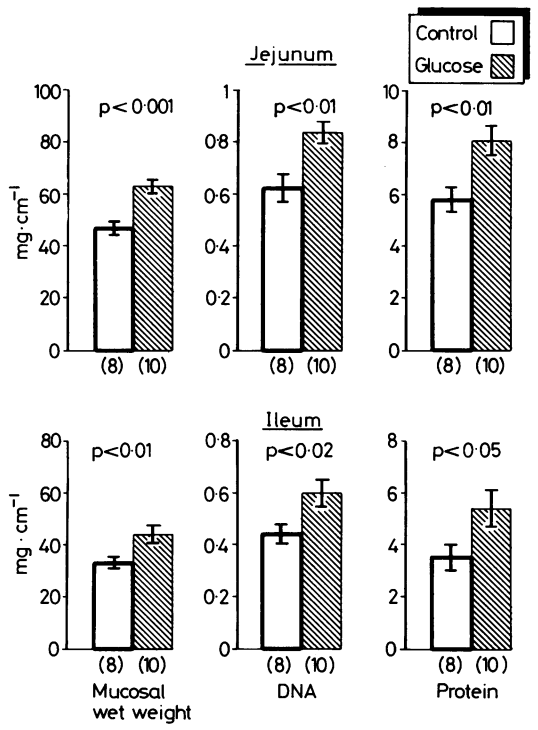

Fig. 3 *Mucosal wet weight, DNA and protein (mg/cm) in jejunum and ileum.*

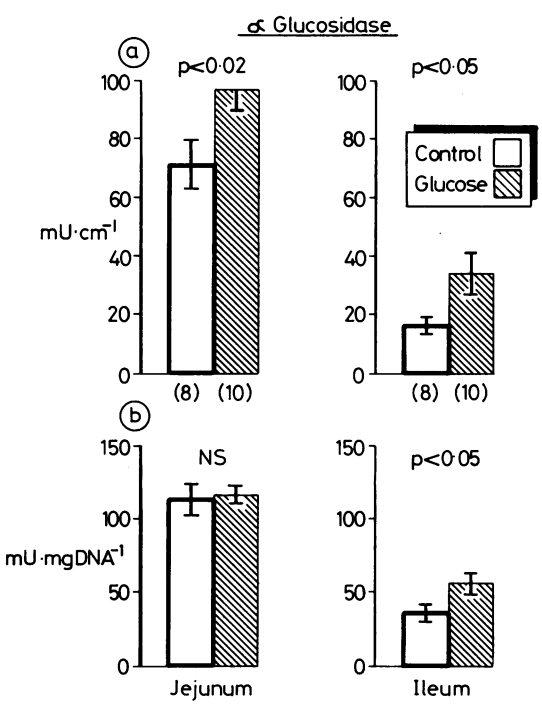

Fig. 4 *D-glucosidase activity in jejunum and ileum. Panel a: α-D-glucosidase activity per cm intestine. Panel b: α-D-glucosidase activity per mg DNA.*

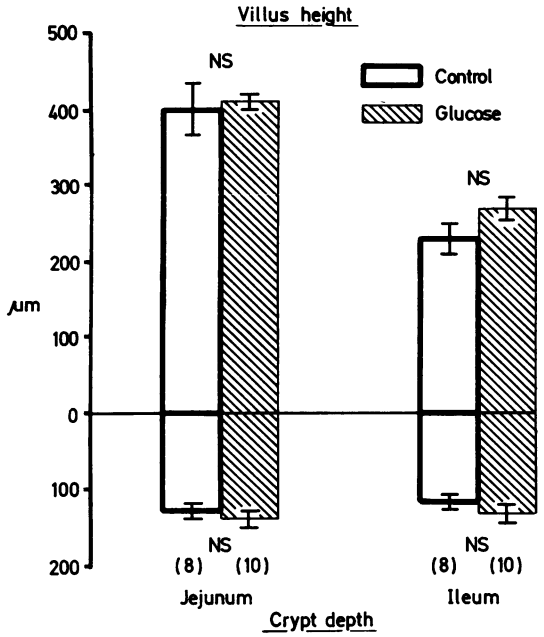

Fig. 5 *Quantitative histology in jejunum and ileum showing villus height above, and crypt depth below the horizontal axis.*

The potential role of some hormones has been investigated. Gastrin can be trophic to the duodenum,[28] but not to the rest of the small intestine.[28 29] The administration of cholecystokinin plus secretin prevented the mucosal hypoplasia of total parenteral nutrition both in dogs[30] and rats.[31] An indirect action, however, mediated through the secretions of liver and pancreas, is more likely than a direct enterotrophic effect.[32] Several recent studies[13 33–38] have shown that in various situations where intestinal adaptation occurs, circulating enteroglucagon concentrations are raised.

The present experiment was an attempt to study further the possible role of colonic enteroglucagon as a mucosal growth factor, in an animal model which maintained small bowel integrity. We stimulated enteroglucagon release from its endocrine cells by perfusing the colon with a glucose solution. Our working hypothesis was that if enteroglucagon is enterotrophic, we should be able to show changes in cellular proliferation and possibly in mucosal mass in the small intestine, at a distance, and therefore without contact with the colonic perfusate. This is indeed what we found.

In agreement with the findings of a previous study in man,[6] colonic perfusion of glucose provoked a two-fold increase in enteroglucagon blood levels compared with mannitol controls. The possibility of a reflux of glucose in the distal intestine, which is rich in enteroglucagon cells,[13] was excluded by inspection of small and large bowel contents and by experiments in which PEG-^{14}C was added to the colonic perfusion solution. As enteroglucagon was measured only eight days after starting the perfusion, it could be argued that it was not released by the colon but by the hyperplastic small bowel. Against this hypothesis is the fact that the small intestinal hormone cholecystokinin was not increased. Of course, we cannot exclude the possibility that glucose may have released other colonic regulatory peptides or amines such as serotonin, vasoactive intestinal peptide, somatostatin,[1 2 4] pancreatic polypeptide,[5] and peptide YY which is especially abundant in the rat large bowel mucosa.[3] None of these substances have been considered until now as a putative enterotrophic factor.

Crypt cell production rate and indices of mucosal mass (mucosal wet weight, DNA and protein per unit length of intestine) were increased by large bowel glucose perfusion, when compared with mannitol treated controls. The increase in CCPR was not statistically significant in the most distal small intestine site. This last finding is further evidence against reflux of glucose into the distal ileum, as an intraluminal glucose load at this site should have induced mucosal growth. It is noteworthy that the effect of large bowel glucose perfusion seems specific for the small intestine, because colonic CCPR was unaffected and no change was found in the weight of pancreas, liver and kidneys; however, the stomach was not studied. The absence of effect on pancreatic weight support the suggestion that enteroglucagon does not mediate the pancreatic hyperplasia observed after transposition of the proximal jejunum between the stomach and the duodenum.[38]

A similar pattern of results was found for α-D-glucosidase activity, when expressed per unit length intestine. Changes in enzyme specific activity, however, could only be detected in the ileum. The results for quantitative histology were somewhat disappointing. Despite the tendency towards greater values after colonic glucose perfusion, none of the values were significantly different. This was caused in part by the large scatter of the results in both experimental and control groups, but also probably by the inaccuracy of this technique in detecting small alterations.[39] Indeed, it must be stressed that the changes in mucosal mass after large bowel perfusion of glucose were relatively small – approximately 30% increases above the control values. In this respect our results are similar to those observed

after ileal resection[40] whereas the ileal hyperplasia induced by proximal small intestinal resection is much more marked.[11] As the rise in enteroglucagon plasma concentrations is equivalent in both types of resection,[13] the greater enterotrophic action of jejunectomy could be accounted for by differences in luminal factors. We did not measure food intake in our study. Hyperphagia was very unlikely, however, because body weight did not significantly vary in both experimental and control animals. Moreover a putative hyperphagia secondary to diarrhoea should have happened in both mannitol and glucose rats, and thus cannot explain the difference in small bowel mucosa growth between the two animal groups. The absence of weight gain during the perfusion period was in fact probably because of decreased ingesta, secondary either to the stress of experimental conditions, or perhaps to a specific inhibition of appetite by the colonic – glucose and mannitol perfusion.

Finally, the present experiment indicates that the colon is capable of influencing not only gastric[6 7] and pancreatic[8] functions, but also epithelial cell renewal in the small intestine. Whether this is a physiological function remains to be established, as glucose is not delivered in significant amounts to the normal colon. Preliminary experiments have also shown that twice daily starch or oleic acid instillation in the rat colon for eight days induces an increase in jejunal mucosal weight (unpublished), though the amounts administered were markedly higher than those probably entering the colon during normal feeding.

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