Impaired meal stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure

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Abstract

Background—Glucagon-like peptide 2 (GLP-2) is a growth factor for the intestinal epithelium in rodents and may affect intestinal transit.

Aims—To study the GLP-2 response to nutrient ingestion in seven short bowel patients with intestinal failure and seven controls.

Methods—The patients and controls were admitted twice for two test meals after a night of fasting. Meal A was liquid (300 ml, 1.88 MJ); meal B was a regular breakfast (755 g, 3.92 MJ). Plasma samples were collected for 180 minutes; GLP-2 immunoreactivity was measured with an NH₂ terminal specific radioimmunoassay.

Results—Both meals elicited significant increases in plasma GLP-2 in controls. The magnitude and duration of the responses were dependent on the meal size: the maximum median (25–75%) increases after meal A and B were 24 (3–28) and 48 (33–56) pmol/l. Plasma GLP-2 returned to basal concentrations 180 minutes after meal A, but remained at 50% of peak values after meal B. In the patients neither meal significantly changed the GLP-2 concentration; the maximum median elevation after meal B was 5 (2–8) pmol/l. There were significant differences between patients and controls with respect to the GLP-2 responses to meals A and B.

Conclusion—Identification of GLP-2 as a tissue specific intestinal growth factor and demonstration of an impaired meal stimulated GLP-2 response in short bowel patients raises the possibility that GLP-2 administration may constitute a new therapeutic strategy, enhancing jejunal adaptation in ileum resected short bowel patients with intestinal failure.

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Keywords: short bowel syndrome; growth factors; intestinal adaptation, human

Recent work by Drucker *et al* has shown that glucagon-like peptide 2 (GLP-2) may act as a growth factor for the intestinal epithelium in rodents.¹ Identification of this novel tissue specific intestinal growth factor raises the possibility that GLP-2 administration may constitute a new therapeutic strategy for patients with intestinal failure. Evidence exists that GLP-2 may also serve as one of the ileal brake hormones.² GLP-2 is liberated through a post-

translational processing of proglucagon in the intestinal L cells and in pancreatic A cells where GLP-2 is contained within the sequence of the major proglucagon derived fragment, a large protein that contains the sequences of both GLP-1 and GLP-2.^{3,4} In the intestine, at least four distinct proglucagon derived peptides (PGDPs) are liberated through the tissue specific post-translational processing of proglucagon: glicentin, oxyntomodulin, GLP-1, and GLP-2.^{3,5} The significance of PGDPs in intestinal epithelial growth has been suggested previously,^{6,7} but due to the failure of many investigators to discriminate between individual PGDPs, the intestinotrophic effects have only recently been assigned to GLP-2. GLP-2 is produced throughout the small and large bowel in the proglucagon expressing L cells, which are located predominantly in the distal ileum.⁸ GLP-2 may act locally in a paracrine manner or as a humoral growth factor.

The specialised epithelial cells of the small intestine constitute a functionally important organ for nutrient absorption, immune function, and regulation of fluid and electrolyte balance. Diseases that interrupt the integrity of the small bowel epithelium, through inflammation, infiltration, surgical resection, or ischaemia may cause intestinal failure. Intestinal failure is defined as the reduction in functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients.⁹ Prior to attempting to assess the therapeutic benefit of GLP-2 treatment in patients with intestinal failure, this study describes the circulating concentrations of GLP-2 during fasting and following nutrient ingestion in seven short bowel patients with intestinal failure and seven age and sex matched controls.

Material and methods

PATIENTS

Seven short bowel patients (less than 150 cm remnant small bowel and a colectomy) depending on parenteral support, and seven healthy, age and sex matched controls were recruited for the study. Table 1 compares the patients and controls. Five women and two men were studied in each group. No differences in age could be shown between groups according to the pair selection of the control subjects, and no differences regarding weight,

Abbreviations used in this paper: BEE, basal energy expenditure; GLP-2, glucagon-like peptide 2; PGDP, proglucagon derived peptides.

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Table 1 A comparison of patients with intestinal failure and sex and age matched healthy control subjects

	Intestinal failure (n=7)	Control subjects (n=7)	*p Value
Sex (F/M)	5/2	5/2	—
Age (y)	47.1 (43.6–56.4; 42.3–62.4)	49.8 (43.8–52.7; 39.9–66.4)	1.00
Weight (kg)	54.4 (48.4–68.6; 46.0–71.7)	61.0 (56.6–64.3; 53.7–80.0)	0.26
Height (m)	166 (163–173; 159–179)	167 (167–172; 158–182)	0.62
Body mass index (kg/m ²)	19.9 (18.1–23.6; 17.1–26.2)	21.5 (20.6–23.0; 19.9–24.2)	0.26
Basic energy expenditure (MJ/day)	5.4 (5.2–5.9; 5.1–7.5)	5.7 (5.5–5.8; 5.4–7.6)	0.17

Results are expressed as median (25–75% percentiles; range).

*Mann-Whitney rank sum test.

Table 2 Patient characteristics

	Wet weight (kg/day)	Energy (MJ/day)
Diet intake	4.30 (2.62 to 4.74; 1.86 to 6.32)	10.40 (7.43 to 10.67; 6.4 to 10.7)
Parenteral supply	3.00 (1.95 to 3.82; 1.50 to 4.50)	4.52 (2.75 to 5.50; 1.62 to 5.52)
Faecal excretion	4.44 (3.01 to 4.80; 2.12 to 5.66)	5.11 (4.88 to 7.16; 4.57 to 7.69)
Absolute absorption	0.44 (–1.89 to 1.70; –3.02 to 1.78)	4.72 (2.22 to 5.24; 1.44 to 5.80)
Urine excretion	1.92 (1.40 to 2.80; 1.33 to 4.76)	Not measured
Overall balance	1.03 (–0.79 to 1.59; –1.42 to 1.88)	8.34 (7.03 to 8.49; 5.97 to 11.42)

Results are expressed as median (25–75% percentiles; range).

height, body mass index, and basic energy expenditure, calculated by the Harris-Benedict equations,¹⁰ were seen.

In the patients, short bowel syndrome was a result of Crohn's disease in five and mesenteric infarction in two. None of the patients with Crohn's disease had any clinical or biochemical signs of active disease, and none of the patients or controls had had stomach or duodenal surgery. The length of the remnant small intestine from the ligament of Treitz had been measured peroperatively in all patients. In patients the remnant small bowel length averaged 111 cm (range 30–150 cm), and all patients had a jejunostomy. All patients were in a stable phase: the last small bowel resection had been performed 7.2 years before the study (range 1.4–21.4 years), and the patients had been dependent on home parenteral nutrition (HPN) for 8.2 years (range 1.4–20.5 years).

All patients were closely monitored and had continuity of care in the programme for patients with intestinal failure on HPN at Rigshospitalet, Copenhagen. As part of the programme, the intestinal absorption was measured in all patients with intestinal failure within a year prior to entering this study. During a 48 hour balance period the spontaneous energy and wet weight intake, and faecal energy and weight loss were measured.¹¹ Analysis was performed on homogenised and freeze dried aliquots of dietary and faecal samples. Dietary and faecal energy was determined by bomb calorimetry in an IKA adiabatic calorimeter, model C 4000 A (IKA-Analysentechnik, Heitersheim, Germany). Table 2 presents the results of the balance studies. The absolute wet weight absorption was barely positive due to net secretion in three patients, and on average the intestinal energy absorption only provided approximately 70% of the basal energy expenditure (BEE) as calculated by the Harris-Benedict equations. All patients had a wet weight absorption below 1.78 kg/day and an energy absorption below 109% of BEE, justifying the need for parenteral fluid and energy support.

STUDY PROTOCOL

The patients and controls were admitted twice for two test meals. They were requested to fast overnight prior to admission; the height and fasting body weight of the patients and controls were measured. At the first admission, the patients and controls were given meal A: 300 ml of a standardised liquid orange Nutridrink (Nutricia A/S, Allerød, Denmark) with an energy content of 1.88 MJ (450 kcal) and a protein:carbohydrate:fat energy ratio of 13%:48%:39%. It contained no fibre. During the second admission the patients and controls were given meal B: a large but ordinary breakfast consisting of rye bread, toast, butter, cheese, jam, yoghurt, banana, and orange juice (755 g), with an energy content of 3.92 MJ (936 kcal) and a protein:carbohydrate:fat energy ratio of 10%:52%:37%, evaluated from food tables.¹² The content of dietary fibres was approximately 8 g.

Peripheral venous blood was collected at 15 minutes before and 10, 20, 30, 45, 60, 120, and 180 minutes after the start of the meals, which were completed in 15 minutes.

None of the control subjects received any medications on a regular basis prior to the study. The weight and energy content of the parenteral supplements were calculated from information given by the manufacturers. The patients received their usual parenteral supplements and medication prior to admission.

HORMONE ANALYSIS

Blood samples were collected in ice chilled 10 ml tubes containing EDTA and a specific dipeptidyl peptidase IV inhibitor, valine pyrrolidide (a generous gift from Dr TE Hughes, Novartis Institute for Biomedical Research, Summit, New Jersey, USA), in final concentrations of 3.7 and 1 mmol/l, respectively. The tubes were immediately shaken, subsequently kept on ice and centrifuged at 4°C for 10 minutes within 45 minutes from collection. The plasma was separated and stored at –20°C until analysed. GLP-2 immunoreactivity was measured with a specific NH₂ terminal radioimmunoassay as recently described.² The selected antiserum (code 92160) could be used in a final dilution of 1/35 000 and had a binding affinity for proglucagon of 126–159 of approximately 10¹⁰ l/mol. It showed no cross reaction with GLP-1 1–36 NH₂, GLP-1 7–36 NH₂, glicentin, oxyntomodulin, glucagon, pituitary adenyl cyclase activating polypeptide, vasoactive intestinal peptide, growth hormone releasing factor, gastric polypeptide, secretin, and peptide histidine isoleucine amide in concentrations up to 5 nmol/l. The experimental detection limit was 5 pmol/l, and the intra-assay coefficient of variation was 2.3% at a concentration of 40 pmol/l. The plasma samples from experiments A and B were analysed in two separate batches.

ETHICS

Procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. The protocol was approved by the Ethics Committee for

Table 3 Glucagon-like peptide 2 response following meals A and B (pmol/l)

	Time								
	-15 min	10 min	20 min	30 min	45 min	60 min	90 min	120 min	180 min
<i>Meal A</i>									
Patients	32 (19–52)	37 (25–51)	34 (33–46)	38 (32–49)	42 (27–45)	36 (24–39)	30 (24–36)	38 (20–41)	25 (16–50)
Controls	39 (32–44)	51 (28–75)†	67 (38–83)†	72 (39–85)†	65 (39–79)†	68 (41–69)†	54 (44–66)†	51 (40–65)†	44 (37–49)†
*p Value	0.54	0.38	0.10	0.10	0.17	0.07	0.07	0.05	0.32
<i>Meal B</i>									
Patients	5 (4–7)	8 (7–10)	10 (5–14)	6 (6–12)	8 (5–16)	8 (6–15)	9 (2–10)	7 (6–8)	6 (5–9)
Controls	9 (6–11)	48 (28–62)†	48 (31–64)†	50 (32–61)†	51 (35–64)†	59 (39–68)†	48 (32–50)†	41 (23–52)†	29 (16–38)†
*p Value	0.07	0.002	0.007	0.002	0.004	0.004	<0.001	0.002	<0.001

Results are expressed as median (25–75% percentiles).

†Friedman repeated measures analysis of variance on ranks, pairwise multiple procedure (Dunnett's method) versus control (-15 minutes), $p < 0.05$.

*p value, Mann-Whitney rank sum test, patients *v* controls.

Medical Research in Copenhagen, Denmark. Patients gave their informed consent.

STATISTICAL ANALYSIS

Results of the study participants are expressed as medians with 25% and 75% percentiles shown in brackets. The GLP-2 response, increment, and area under the curve in the short bowel patients was compared with the response, increment, and area under the curve in the control subjects by a non-parametric Mann-Whitney rank sum test at all sample times measured. A Friedman repeated measures analysis of variance on ranks was used to detect differences in the GLP-2 response within the two groups at the different sample times, and a multiple pairwise procedure was used as the post hoc test to compare the GLP-2 responses at the times measured to the baseline value (-15 minutes). The SigmaStat for Windows Version 2.0 (Copyright 1992–1995, Jandel Corporation, Erkrath, Germany) was used for statistical calculations. A value of $p < 0.05$ was considered significant.

Results

Table 3 gives the plasma GLP-2 response to meal A (the smaller liquid meal) and meal B (the larger breakfast). The GLP-2 response following meal A was modest in both the short bowel patients and the control subjects. The median GLP-2 concentration increased in the control subjects from a baseline value of 39 pmol/l to a peak concentration of 72 pmol/l at 30 minutes. In these subjects, a significant increase in the plasma GLP-2 concentration was shown at all times measured compared with the baseline values ($p < 0.05$). In the short bowel patients, the median GLP-2 concentration was 32 pmol/l at baseline, and the peak value was 42 pmol/l at 45 minutes. A significant increase in the GLP-2 response could not, however, be detected within the group of short bowel patients ($p = 0.88$). When comparing plasma GLP-2 concentrations in the short bowel patients and their controls, no significant differences could be shown at any of the times measured. The calculated area under the curve was, however, significantly larger after meal A in the control subjects compared with the short bowel patients (7053 (5224–9143) versus 3830 (1220–14059) min.pmol/l, $p = 0.04$).

The GLP-2 response following meal B was also modest in the short bowel patients. The median GLP-2 concentration was 5 pmol/l at

baseline, and the peak value was only 10 pmol/l at 20 minutes. Thus, a significant increase in the GLP-2 response could not be shown within the group of short bowel patients ($p = 0.24$). In the control subjects, the median GLP-2 concentration increased from a baseline value of 9 pmol/l to a peak concentration of 59 pmol/l at 60 minutes. A significant increase in the plasma GLP-2 concentration was shown at all times measured compared with the baseline values ($p < 0.05$). Comparing the plasma GLP-2 concentrations in the short bowel patients and their controls, significant differences could be shown at all times measured, except at baseline (-15 minutes). The GLP-2 concentration remained at 50% of the peak value 180 minutes after meal B. Subsequently, the calculated area under the curve was significantly larger after meal B in the control subjects compared with the short bowel patients (1565 (1224–2662) versus 9272 (6218–10929) min.pmol/l, $p = 0.002$).

As the baseline values of the GLP-2 concentrations differed between the two test meals, both in the short bowel patients and in the control subjects, the increment was defined as the actual GLP-2 values minus the baseline value (fig 1). Again the GLP-2 increment following meal A was modest in both the short bowel patients and their controls. A significant difference in the GLP-2 increments between short bowel patients and their controls was observed at 60 minutes (0 versus 24 pmol/l, respectively, $p = 0.03$), while differences were borderline significant only ($p < 0.10$) at 20, 30, 90, and 120 minutes. The area under the curve was larger in the control subjects compared with the short bowel patients (148 (-1321 to 1149) versus 3830 (1169 to 4632) min.pmol/l, $p = 0.04$).

Doubling of the dietary energy and wet weight load in meal B not only led to a significant larger GLP-2 increment in the control subjects compared with the short bowel patients at all times, but the increment was also larger than the increment observed in the control subjects after meal A at 10, 60, and 90 minutes, and borderline increased ($p = 0.05$) at 120 and 180 minutes. In general the increment in the GLP-2 response in the short bowel patients was negligible at all times, and none of the short bowel patients had an increment exceeding 21 pmol/l. Again, the area under the curve was larger in the control subjects compared with the short bowel patients (525

Figure 1 Plasma glucagon-like peptide (GLP) 2 increment after meals A (300 ml Nutridrink) and (solid breakfast) in short bowel patients with a jejunostomy and sex and age matched controls. * $p < 0.05$, ** $p < 0.01$, Mann-Whitney rank sum test.

(194–1436) versus 8048 (4874–8623) min.pmol/l, $p = 0.004$).

Discussion

This is the first study describing the impaired meal stimulated GLP-2 response in short bowel patients with less than 150 cm of small bowel ending in a jejunostomy. GLP-2 is mainly produced in the ileum and is believed to influence jejunal growth, gastric emptying, and intestinal transit. Two test meals were used in this study describing an effect of increasing dietary load on the GLP-2 response. Meal A consisted of 300 ml of a liquid Nutridrink (1.88 MJ). Meal B provided approximately double the amount of energy and wet weight and consisted of a large ordinary breakfast with macronutrient ratios resembling the composition of the Nutridrink. Meal A led to a moderate GLP-2 response in the control subjects, while meal B caused a more notable initial response; a prolonged response was maintained for at least 180 minutes (table 3). The GLP-2 response was much smaller in the short bowel patients regardless of the dietary load.

The baseline values of the GLP-2 concentration varied between the two test meals, both in the controls and the short bowel patients. Thus, the baseline value of the GLP-2 concentration was 30–40 pmol/l prior to meal A, which was much higher than the concentration of 5–10 pmol/l prior to meal B. In order to compare the GLP-2 responses after meals A and B, the increment was defined as the actual value minus the baseline value at a given time. By this comparison (fig 1) it could be shown that the magnitude and duration of the GLP-2 responses were dependent on the meal size.

The blood samples taken at baseline were subsequently reanalysed in one batch in order to find an explanation for the differences in the baseline GLP-2 values. By this analysis no significant differences were found between the patients or the controls prior to the two meals (median GLP-2 values ranging from 16 to 40 pmol/l); the most likely explanation of the initial differences is that the blood tests were

analysed in two batches and a drift in the baseline may have occurred.

In normal humans, digestion and absorption of most nutrients occur in the duodenum and jejunum.^{13 14} Intubation experiments have shown that most carbohydrates and proteins are absorbed in the upper 200 cm of the jejunum.¹³ Fat is absorbed over a longer length of the intestine, a distance which increases as oral intake rises.¹⁴ This study indicates that the GLP-2 response and duration depends on meal size. One may hypothesise that a sufficient absorption in the upper jejunum only allows a minimal delivery of nutrients to the ileum, unless the dietary load is increased. This may explain the modest GLP-2 response in the control subjects after meal A. If the dietary load, on the other hand, is increased beyond the absorptive capacity of the jejunum, nutrients and fluid may pass into the ileum. This may stimulate the L cells and increase the circulating concentrations of GLP-2 (as well as GLP-1). Little is known regarding the nature of the L cell stimulating agent. One may speculate on the specific stimulation from unabsorbed macronutrients (carbohydrates, fibres, protein, or fatty acids)¹⁵ or simply a stimulation from a mechanical distension, due to the increased volume entering the ileum. An increased production of the proglucagon derived peptides has been shown in rat models of intestinal adaptation, where a segment of the distal ileum was transposed into the mid-duodenum.¹⁶ Intriguingly, it has been suggested that such transposition leads not only to an increase in the epithelial weight of the transposed ileal segment, but also in the jejunum. It may be hypothesised that the L cells serve as sensors in the distal intestine, providing feedback information to the upper intestine in order to optimise nutrient and fluid absorption. Increasing loads of nutrients or fluid into the ileum may stimulate the secretion of GLP-2 (and GLP-1), which subsequently may decrease gastric emptying, increase intestinal transit time, and increase the jejunal absorption through an upregulation of jejunal growth.

It has previously been shown that the ileal adaptive response to jejunectomy is notable with increases in the various indexes of mucosal structure and function in the region of 70–100% compared with controls. In contrast, the changes in the jejunal remnant after ileectomy are modest with, at most, 20–30% increases in the markers of the adaptive response.¹⁷ The lack of jejunal adaptation in patients with an ileectomy may be due to the removal of GLP-2 producing tissue. Thus, the patients with a jejunostomy of less than 100 cm rarely adapt to live without parenteral supplements. Besides the problems with nutrient absorption these patients have additional problems in maintaining fluid balance, as they lose large volumes of fluid and sodium from their stoma.¹⁸

Rapid early liquid gastric emptying is described in the patients with jejunostomy which contrasts to the findings in patients with a retained colon, in whom gastric emptying was normal. Thus, in the absence of much of the small intestine, the colon has been described to act as a brake to gastric emptying. The mechanism could be neural or humoral, and so far peptide YY, produced by the terminal ileum and colon,¹⁹ has been suggested to be responsible for the colonic braking mechanism.²⁰ However, other hormones, GLP-2 and GLP-1 included, are likely to be involved in regulation of the intestinal transit. Morgan *et al* investigated GLP-1 secretion in response to a 625 kcal mixed test meal (84 g carbohydrate, 27 g fat, 18 g protein) in 12 short bowel patients and 12 healthy controls.²¹ Six of the patients had undergone end jejunostomy operations (residual jejunal length 50–160 cm) and six had undergone jejunocolic anastomoses (residual length 25–75 cm). In contrast to the present study of the GLP-2 response in patients with a jejunostomy, a persistence of a GLP-1 response to nutrients, albeit a somewhat attenuated one compared with control subjects, was found in both groups of patients. In patients with a preserved colon, GLP-1 could be secreted from cells in the colon, but in the patients with a jejunostomy circulating GLP-1 must have originated from cells situated in the upper small intestine. The function of the residual jejunum and the need for parenteral support was not described in the study of Morgan *et al*. These patients may have had a better adaptation to surgery compared with the patients in our study, explaining the persistence of the GLP-1 response.

The actions of GLP-2 offer new perspectives in the treatment of short bowel patients with no ileal function and these patients actually constitute the majority of the increasing number of patients with intestinal failure receiving home parenteral nutrition.^{22–25} Hence, this new and apparently specific

intestinotrophic and transit modulating agent, which has now been synthesised for application in clinical trials, may promise well as a treatment for ileal resected patients with a jejunostomy and threatening or overt intestinal failure.

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