Gut hormone release after intestinal resection

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SUMMARY   To investigate the possible role of gut and pancreatic hormones in the adaptive
responses to gut resection, plasma concentrations of the circulating hormones were measured, in
response to a test breakfast, in patients with either small or large intestinal resection and in
healthy control subjects. In 18 patients with partial ileal resection a significant threefold rise was
found in basal and postprandial levels of pancreatic polypeptide, a fourfold increase in motilin,
and more than a twofold increase in gastrin and enteroglucagon levels compared with healthy
controls. In contrast, nine patients with colonic resection had a threefold rise in levels of
pancreatic polypeptide only. One or more of these peptides may have a role in stimulating the
adaptive changes found after gut resection.

After small intestinal resection, there are two widely
reported alterations in morphology and physiology.
There is villous hyperplasia of the remaining small
intestine[1–3] with an equivalent functional
compensation. This presumably represents an
adaptive process to compensate for the diminished
absorptive surface area after resection.[4–6] These
adaptive responses are much more marked in the
ileum after proximal small intestinal resection, but
are also reported to occur in the jejunum after distal
small bowel resection, albeit to a lesser extent[7 8]
and also in the colon.[9 10] The mechanism of this
process may well be humorally mediated[11–14] and a
number of gastrointestinal hormones have trophic
actions.[15–17]

In addition, gastric hypersecretion has been
reported in these patients[18 19] which may be due
either to loss of an inhibitory factor present in the
ileum[20 21] to decreased degradation of gastrin or to
hypersecretion of gastrin.[22] The gastric hyper-
secretion in patients who have undergone ileal
resection for Crohn's disease relates to their surgery
and not to any remaining disease activity.[23] These
and other possible mechanisms are discussed in a
recent review.[22]

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In order to elucidate whether gut hormones might
be implicated in any of these alterations, we have
measured the circulating plasma concentrations of
several gut hormones before and after a standard
test breakfast in patients with resection of the small
and large intestine and in age- and sex-matched
healthy controls.

Methods

PATIENTS
Permission for these studies was obtained from the
Ethical Committees at each of the participating
centres and informed consent was given by all
subjects tested.

SMALL INTESTINAL RESECTION
Eighteen patients (10 men, eight women) had
previously undergone partial resection of the ileum.
Their mean age was 48 years (range 20–72 years)
and their mean weight was 54±3·3 (x ± SEM) kg,
which corresponded to 90±4% of ideal.

In 13 patients the underlying indication for
surgery was Crohn's disease. All of these had had
from 0·4 to 2 m of distal ileum resected. Two
patients had radiation-induced fibrosis necessitating
resection of all but 1 m of distal ileum. Another
patient needed resection of 1 m of terminal ileum for
ischaemic necrosis after volvulus. Another patient
had all his small intestine resected except for 5 cm of
distal ileum and 30 cm of jejunum after trauma.[24]

The median time of study from operation was three years with a range of one month to 24 years. The median number of bowel frequencies per day was four with a range of one to 20.

LARGE INTESTINAL RESECTION

Nine patients (four men, five women) had previously undergone total or partial colectomy. Their mean age was 34 years (range 21–62 years) with a mean weight of 53±4 kg (x ± SEM) which corresponded to 91±6% of ideal.

All but one of the patients underwent colectomy for inflammatory bowel disease (two with ulcerative colitis, six with Crohn's disease). The other case underwent resection of his sigmoid colon for carcinoma and diverticular disease. The extent of resection of the other cases varied between total proctocolectomy to right hemicolectomy. The median time from operation to study was 2½ years with a range of six months to eight years. The median number of bowel frequencies per day in five patients was five with a range of one to eight. The other four patients had ileostomies.

NORMAL SUBJECTS

Eleven healthy subjects (six men, five women) acted as normal controls. They had a mean age of 43 years (range 22–59 years). Their mean weight was 69±3 kg (x ± SEM) corresponding to 107±2% ideal. None had either present or past history of gastrointestinal or other significant illness. The median bowel frequency was one per day and ranged from every other day to twice a day.

TEST BREAKFAST

All subjects were fasted overnight and blood samples were taken before and for three hours after the standard breakfast. This consisted of two medium-sized boiled eggs, 60 g bread as toast, 10 g butter, 35 g marmalade, and 150 ml unsweetened orange juice. The breakfast contained 18 g protein, 22 g fat, and 66 g carbohydrate, equivalent to 530 Calories (2225 KJ).

Blood samples for hormone assays were taken into heparinised tubes and 400 Kallikrein-inhibitory units of aprotinin (Trasylol) per ml were added. Plasma was separated within 15 minutes of sampling and stored at −20°C until assay.

TECHNIQUES

Blood glucose estimation was carried out using standard glucose oxidase/peroxidase methodology as adapted for the autoanalyser.[25] Plasma hormone concentrations were measured by specific radioimmunoassays, which have previously been described in detail, and were carried out by conventional methods with antisera raised to pure natural gastrin,[26] pancreatic polypeptide,[27] and insulin[28] to pure porcine gastric inhibitory polypeptide (GIP)[29] and motilin,[30] and to natural bovine neurotensin.[31] Glucagon was measured using two separate systems, one using a C-terminal reacting antibody specific for pancreatic glucagon,[32] and a second reacting with the mid to N-terminal sequence of glucagon which also measured gut glucagon immunoreactivity and which showed complete cross-reactivity with porcine glicentin.[33] Enteroglucagon was derived by substraction of the specific pancreatic glucagon values from those obtained using the N-terminal glucagon assay. The assays were capable of detecting the following plasma changes with 95% confidence: gastrin 2 pmol/l, pancreatic polypeptide 4 pmol/l, GIP 3 pmol/l, enteroglucagon 10 pmol/l, and insulin 6 pmol/l. Statistical analysis was made

Table Results of patients in two resection groups and normal controls (mean ± SEM)

	Blood glucose (mmol/l)	Insulin (pmol/l)	GIP (pmol/l)	Gastrin (pmol/l)	HPP (pmol/l)	Pancreatic glucagon (pmol/l)	Motilin (pmol/l)	Entero-glucagon (pmol/l)	Neuro-tensin (pmol/l)
Normal subjects									
Basal	4·2±0·2	33±4	9±1	5±0·5	15±3	9±2	63±8	32±7	50±6
Peak rise	1·6±0·3	240±36	33±7	17±4	116±19	3±2	16±6	26±7	22±3
TIR	843±49	24·6±2·8	6·8±1·8	2·6±0·2	15·5±2·6	1·4±0·2	10·2±1·9	8·3±1·1	11·0±1·3
SI resection									
Basal	4·3±0·2	26±3	13±2·0	13±2†	60±21*	7±2	196±46*	64±11*	41±3
Peak rise	1·7±0·3	222±37	49±10	43±10*	271±32¶	4±1	117±29§	64±16*	23±3
TIR	898±73	24·3±3·3	8·1±1·2	6·1±1·3†	42·9±7·3§	1·2±0·2	43·7±11‡	19·1±3·1§	9·6±0·8
LI resection									
Basal	4·1±0·2	26±3	12±2·0	10±4	39±9†	7±1	56±14	16±5·5	38±9
Peak rise	1·8±0·3	197±36	43±8	29±8‡	284±53‡	3±1	57±26	27±5	26±6
TIR	928±63	22·3±4·2	7·6±1·2	5·0±1·8	39·5±8·9†	1·2±0·2	15·8±5·3	5·8±1·0	9·9±1·2

Statistical significance vs normal subjects: *p<0·05. †p<0·02. ‡p<0·01. §p<0·005. ¶p<0·001.
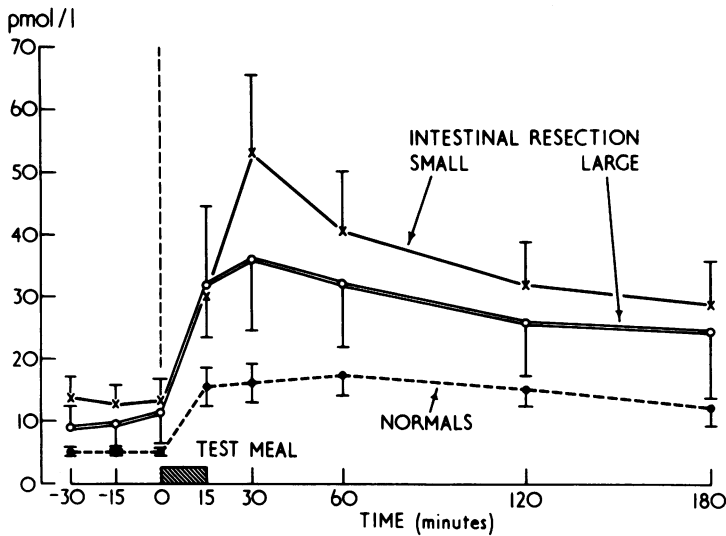TIR expressed as nmol.l⁻¹.180 min⁻¹ except for glucose – mmol.l⁻¹.180 min⁻¹.

Fig. 1   *Plasma gastrin responses (mean ± SEM) to a test meal in 11 normal subjects and in 18 patients with small and in nine patients with large intestinal resection.*

using Student's *t* test for unpaired data for parameters with normal distribution and using non-parametric (Whitney Mann U test) methodology for parameters with a known skewed distribution.

Results

Mean fasting levels, peak postprandial rises, and total integrated responses for blood glucose and gut hormones for both groups of intestinal resection patients and in healthy controls are shown in the Table.
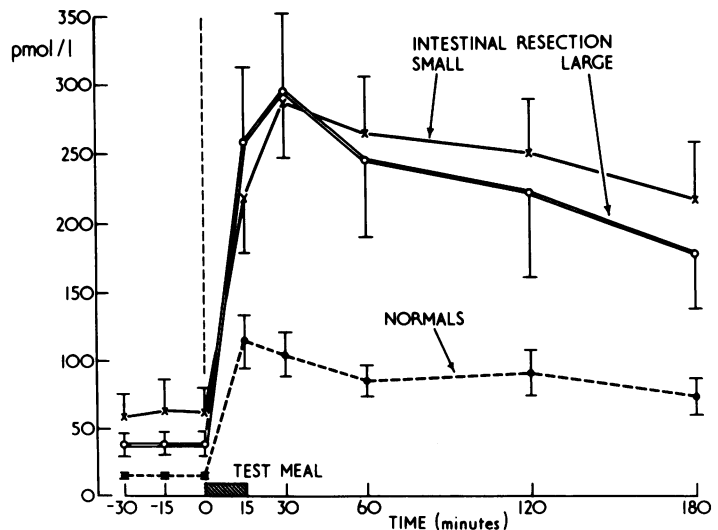
GASTRIN (Fig. 1)

Patients with partial ileal resection had significantly raised fasting levels, peak postprandial rises, and total integrated responses of plasma gastrin compared with healthy controls. Patients with large intestinal resection had plasma gastrin levels which, although slightly raised, were not significantly different from normal subjects. In addition, no correlation was found between gastrin levels and the extent of colonic resection.

PANCREATIC POLYPEPTIDE (Fig. 2)

Both groups of patients with gut resection had

Fig. 2   *Plasma human pancreatic polypeptide responses (mean ± SEM) to a test meal in 11 normal subjects and in 18 patients with small and in nine patients with large intestinal resection.*
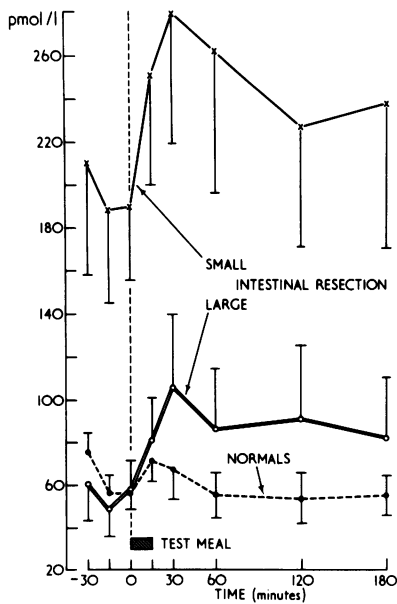
Fig. 3 *Plasma motilin responses (mean ± SEM) to a test meal in 11 normal subjects and in 18 patients with small and in nine patients with large intestinal resection.*

significantly raised fasting and postprandial plasma pancreatic polypeptide levels compared with control subjects.

MOTILIN (Fig. 3)
Patients with partial ileal resection had significantly raised basal levels, postprandial rises, and total integrated responses of plasma motilin. The group with colonic resection, however, had fasting plasma motilin levels which were similar to controls and an augmented postprandial response but this failed to reach statistical significance.

ENTEROGLUCAGON (Fig. 4)
Fasting plasma enteroglucagon levels, peak postprandial rises, and total integrated responses after the meal were all significantly greater than normal in the group with partial ileal resection. The group with colonic resection, however, had plasma enteroglucagon levels which were lower than control values but the difference did not reach statistical significance.

BLOOD GLUCOSE, INSULIN, GIP, PANCREATIC
GLUCAGON, AND NEUROTENSIN
There was no significant difference from normal in fasting or postprandial plasma levels or in total integrated responses of blood glucose, insulin, GIP,

pancreatic glucagon or in neurotensin in either group of patients with gut resection.

There was no correlation between any of the peptides measured and the length of time since resection, the length of gut resected, or the frequency of bowel habit with the exception of pancreatic polypeptide, where there was a significant positive correlation of bowel frequency with individual total integrated responses in patients with small intestinal resection ($r=0.59$, $p<0.01$).

Discussion

All the patients in this study had macroscopically normal proximal small intestines at operation apart from the two patients with massive resection of ileum and jejunum. In all but these two patients the plasma levels of glucose, insulin, pancreatic glucagon, and GIP were within normal limits after a standard meal. This confirms previous reports for glucose and insulin in man,[34] for GIP in Rhesus monkeys[35] and for insulin and pancreatic glucagon in dogs.[36] Impaired glucose tolerance but with normal insulin release after oral glucose has been reported to occur short-term (four to five weeks) after distal resection.[34] In another series, 13 patients were studied after massive small intestinal resection, seven of whom had jejunal resection as well as ileal.
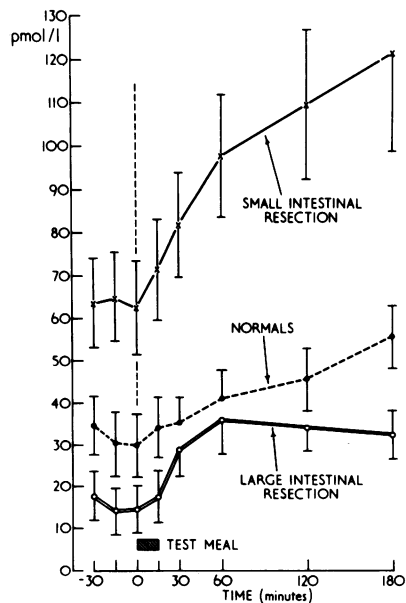

Fig. 4 *Plasma enteroglucagon responses (mean ± SEM) to a test meal in 11 normal subjects and in 18 patients with small and in nine patients with large intestinal resection.*

These patients had diminished insulin responses to oral glucose in both the short and long term.[37] They attributed the differences in findings to differences in the patients studied and the extent of small intestinal resection. These patients, however, like ours, had normal fasting levels of pancreatic glucagon with normal responses of both insulin and glucagon to intravenous arginine. These findings are consistent with the belief that the enteric site of the entero-insular axis resides in the duodenum and jejunum. In contrast patients with intact but diseased small bowel due to coeliac disease or tropical malabsorption have an impaired entero-insular response to the same stimulus.[38 39]

There is good evidence that a compensatory increase in cell number[40 41] and absorptive function occurs in the ileum after resection of the jejunum and also, to a lesser extent, in the upper small intestine after ileal resection. Small intestinal adaptation has also been reported to occur after colectomy.[42] It has further been demonstrated that the increase in ileal mucosal mass is related to loss of colon itself and is not secondary to any increase in ileal nutrition or loss of fluid and electrolytes.[43] These adaptive responses have been attributed to the alteration of intraluminal content but there is also persuasive evidence that adaptation is also mediated by humoral mechanisms. Thus, small bowel, either transplanted within an animal after resection,[44-46] or in animals parabiotically fed from resected animals,[11 47 48] undergoes adaptation in the absence of increased luminal nutrition. Enteroglucagon is a strong contestant for such a humoral factor. Thus circumstantial evidence, which includes data from the only reported secretory tumour of enteroglucagon[49] and other work,[50] suggests that this hormone is trophic to small intestinal mucosa including the jejunum. In rats, the intestinal response to starvation can be prevented by prior administration of glucagon-binding antibodies.[51] It is likely that this effect is mediated by interaction of these antibodies with enteroglucagon rather than pancreatic glucagon, as exogenous glucagon has been shown to reduce villous height and cell migration in rat enteric mucosa.[52] In an earlier, preliminary report in rats, raised enteroglucagon levels were found after both proximal and distal enteric resection. This was associated with hyperplasia of the enteroglucagon-containing cells and also with an increase in the enteroglucagon cell to enterocyte ratio.[53] It is interesting that ileal resection is followed by an increase in plasma levels of enteroglucagon as the ileum is the richest site of enteroglucagon cells in the gut.[33] No correlation, however, was found between the length of ileum resected and circulating plasma enteroglucagon

levels. Three patients could be classified as having massive small intestinal resection. One patient, with all but 70 cm of ileum resected for radiation-induced fibrosis had enteroglucagon levels which were slightly greater than the mean for the group. The second patient, who had had all his small intestine resected except for 4 cm of ileum and 10 cm of jejunum for traumatic infarction,[24] had very low levels of enteroglucagon. The third patient, who had his entire ileum and all but 60 cm of jejunum resected for leiomyosarcoma had fasting enteroglucagon levels which were only just below the mean for the entire group. From this small number of patients it would seem that only if virtually the entire small intestine is resected do basal and postprandial enteroglucagon levels fail to rise. The remaining jejunum or ileum, along with the colon, must still be able to hypersecrete enteroglucagon despite resection of a large proportion of enteroglucagon-containing small bowel. In dogs with extensive distal small bowel resection no difference from control animals was found in fasting or stimulated enteroglucagon.[54] There was no failure of release despite massive resection and the lack of rasied levels may be due to the extent of the resection, as in our second patient, or to species differences. Ileal mucosal hyperplasia has been described after colonic resection in the rat[42 43 55-57] and man.[58] The colectomy patients had reduced basal levels but normal postprandial responses of enteroglucagon, although the reason for this is not apparent. No correlation was found between the length of colon resected and either basal or postprandial enteroglucagon responses. Thus, in our patients with colonic resection, if mucosal hyperplasia occurred, it was not expressed in an increase in plasma enteroglucagon levels, at least not during a test meal.

The great majority of patients studied had inflammatory bowel disease as the indication for gut resection. We found in unoperated patients with both Crohn's disease and ulcerative colitis only a slight rise in fasting enteroglucagon levels with only a very small postprandial rise.[59] We feel, therefore, that the striking rise in plasma enteroglucagon levels seen in patients with small intestinal resection reflects the effect of their surgery rather than the underlying pathological state.

The modest increases in plasma gastrin seen in these patients is consistent with previous reports.[21 36] The levels found are well within the physiological range, however, and these concentrations are known to be without effect on small bowel mucosal growth and are well below the levels induced by pharmacological gastrin and pentagastrin administration which have been found to

induce hyperplasia in the duodenum but not in the remaining small bowel.[60] Furthermore, massive endogenous hypergastrinaemia, as in achlohydria, does not produce any significant alteration in small intestinal structure or function.[61] There is increasing evidence that gastrin is unlikely to be the mediator of intestinal adaption after intestinal resection.[62 63]

Motilin, a peptide localised in the upper small intestine has recently been shown to exert a powerful effect on both small and large intestine.[64] Plasma motilin has previously been found to be raised in several conditions accompanied by diarrhoea but, so far, it has not been clear whether this is a primary or secondary event.[65] It is interesting, therefore, that motilin was raised regardless of whether patients complained of diarrhoea or not. Thus, it seems to be a direct response to ileal resection rather than to alteration of bowel habit. The rise of pancreatic polypeptide in both groups of patients is unexplained. The main physiological effects of this enigmatic hormone are to reduce gallbladder contraction[66] and pancreatic enzyme secretion[67 68] and to stimulate water absorption in the distal small intestine.[69] In addition, low doses of pancreatic polypeptide reduced motility in both small and large intestine of the dog.[70] An increase in intestinal absorptive capacity and alteration in motility could be seen as adaptive mechanisms in patients with ileal or colonic resection.

After gut resection there follows a compensatory adaption of the remaining intestine. There is good evidence that these changes are humorally mediated. We have found that patients with ileal resection have significantly raised plasma levels of gastrin, motilin, pancreatic polypeptide, and enteroglucagon. These peptides may possibly represent the circulating mediators of such adaptive responses. It would, therefore, be of great interest to follow up these findings with further studies correlating intestinal histology, mucosal cell kinetics, absorptive function, and circulating gut hormones in patients with intestinal resection.

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