Gut hormones in gastrointestinal disease

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Considerable advances have been made in the understanding of the physiology of gut hormones. Thus, knowledge of the mechanisms of release and of the actions of many of the hormones is rapidly expanding. The known clinical importance of gut hormones is at present confined only to the excess production of gastrin, VIP, and pancreatic glucagon by endocrine tumours. The role of these three and the other gut hormones in disease states affecting the pancreas and gut has been studied little. Investigation of the patterns of gut hormone release in alimentary disease may provide new insight into the pathophysiology of these disorders. Not only may gut hormones be implicated as primary agents in the pathological processes, but also secondary changes in gut hormone release may be related to compensatory and adaptive mechanisms. Further insight may also be gained into the normal physiological roles of the hormones themselves through the effects of diminished or augmented release found in gut diseases. We have, therefore, studied the gut hormone profile after a normal meal in several well defined gastrointestinal diseases, with features summarised in Table 1.

The distribution of the known gut hormones has been elucidated by the combined techniques of quantitative immunocytochemistry and radioimmunoassay of extracted tissues (Bloom *et al.*, 1975; Bryant and Bloom, 1979). The hormones have characteristic locations which are summarised in Table 2.

Diseases affect the alimentary tract in many different ways, some of them affecting only certain portions of the gut.

It is to be expected that the release of gut hormones from areas damaged by the disease would be abnormal. The release of other hormones from areas of bowel uninvolved in disease, however, might also show secondary changes.

The plasma levels of most gut hormones rise substantially after food. Thus the stimulus to hormone release used in studying the various disease states was a 'physiological' test breakfast. This consisted of two medium-sized boiled eggs, 10 g butter, 60 g bread as toast, 35 g marmalade, and

Disease or pathological state	Area maximally affected	Clinical and pathological features
Coeliac disease	Duodenum, jejunum	Flat mucosa, proximal malabsorption, increased enterocyte turnover, increased ileal absorption
Acute tropical sprue	Entire small intestine	Flat mucosa, malabsorption, delayed transit time
Pancreatic insufficiency	Exocrine pancreas	Reduced enzyme secretion, malabsorption
Morbid obesity	—	CHO intolerance, increased insulin release
Morbid obesity and jejunoileal bypass	Most of small intestine out of continuity	Weight loss, improved CHO tolerance, villous hypertrophy
Crohn's disease	Terminal ileum	Inflammation of whole gut wall, diarrhoea
Ulcerative colitis	Colon	Mucosal inflammation, diarrhoea
Infective diarrhoea	Ileum, colon	Transient severe diarrhoea
Gut resection	Ileum, colon	Shortened bowel, villous hypertrophy

Table 1 Characteristics of diseases studied

Hormone	Principal location
Gastrin	Antrum
GIP (Glucose-dependent insulin-releasing polypeptide)	Duodenum, jejunum
Motilin	Duodenum, jejunum
Secretin	Duodenum
Pancreatic polypeptide	Pancreas
Neurotensin	Ileum
Enteroglucagon	Ileum, colon

Table 2 Principal distribution of gut hormones measured

150 ml of unsweetened orange juice (containing a total of 18 g protein, 22 g fat, 66 g carbohydrate, and 530 kilocalories).

Coeliac disease

This disease of unknown aetiology is characterised by a flat mucosa involving predominantly the duodenum and jejunum. Although rarely it may extend to affect a short segment of proximal ileum, the distal

small intestine and colon are not involved (Rubin *et al.*, 1960; Booth *et al.*, 1962). Similarly, the stomach and pancreas escape direct involvement by the pathological process. Although there is loss of villi in the proximal small intestine resulting in a flat mucosa, there is in fact hyperplasia of the enteroblasts (Booth, 1970) and a greatly increased rate of enterocyte production from the base of the crypts (Wright *et al.*, 1973). Since there is a great reduction in the effective mucosal absorptive surface area in the upper small intestine, reduced absorption of ingested food occurs, so that the intestinal contents descend further down the gut than normal. There is also a compensatory increased absorption of several substances in the ileum beyond the diseased part (Schedl *et al.*, 1968; MacKinnon *et al.*, 1975; Silk *et al.*, 1975). These adaptive mechanisms might well be mediated via gut hormones. Despite the absence of direct involvement of the pancreas, there is associated impairment of pancreatic exocrine and endocrine function in that a considerable reduction occurs in the secretion of pancreatic bicarbonate and enzymes after perfusion of the duodenum with acid or amino-acids (Worning *et al.*, 1967; Wormsley, 1970; Colombato *et al.*, 1977). Administration of exogenous secretin and cholecystokinin, however, is followed by a normal pancreatic secretory response. This suggests that there is a failure of release of the relevant gut hormones from the upper small intestine. In addition an increased incidence of diabetes mellitus is reported to occur in coeliac disease (Walsh *et al.*, 1978).

GUT HORMONE PROFILE (FIG. 1)

Patients with untreated coeliac disease have a relative failure of release of both GIP and secretin, two hormones localised to the area of maximal mucosal damage in coeliac disease (Besterman *et al.*, 1978d). A failure of cholecystokinin release has also been reported (DiMagno *et al.*, 1972; Low-Beer *et al.*, 1975), which would fit with the observed diminished pancreatic endocrine and exocrine response to intraduodenal stimuli.

In our studies, the release of gastrin and pancreatic polypeptide, whose tissues of origin are unaffected, was entirely normal. Plasma motilin levels were slightly increased above normal, following a tendency for this peptide to be raised in steatorrhoeal conditions. Plasma enteroglucagon levels, in contrast, were greatly raised. Not only were basal levels significantly increased, but a massive rise was seen after the test breakfast. These abnormalities were reversed on successful treatment with a gluten-free diet. Enteroglucagon has been suggested to have a trophic action on mucosal growth (Jacobs *et al.*, 1976) and an action slowing intestinal transit (Bloom,

Fig. 1 Postprandial gut hormone profile in coeliac disease (integrated 3 hour response expressed as % of normal).

1972). Both of these actions would be appropriate to coeliac disease, and may contribute to the increased rate of enterocyte turnover, the increased ileal absorption, and also to the clinical impression that many of these patients have slow transit times. Neurotensin is another predominantly ileal hormone. In contrast to enteroglucagon, the release of this hormone was only mildly increased compared to normal.

Tropical malabsorption (acute tropical sprue)

Tropical malabsorption (TM) is characterised clinically by the sudden onset of diarrhoea in a previously healthy subject while travelling in a tropical country. The diarrhoea progresses to overt malabsorption with steatorrhoea, weight loss, folate deficiency, and anaemia. The pathophysiology of the condition is poorly understood. These patients have a flat mucosa, usually to a milder degree than that found in coeliac disease, but involving the entire small intestine rather than just the duodenum and jejunum (Morson and Dawson, 1972; Mathan, 1973). It is of interest that they have a significantly delayed small intestinal transit (Cook, 1978). As in coeliac disease, they are also reported to have a relative

failure of pancreatic exocrine function after a Lundh test meal¹ (Balagopal *et al.*, 1975).

GUT HORMONE PROFILE (FIG. 2)

Eight patients with severe TM were studied (Besterman *et al.*, 1979a). There was a significant diminution of both GIP and insulin release associated with a delayed and impaired rise in blood glucose. In contrast, however, plasma motilin levels were greatly raised. Basal plasma enteroglucagon concentrations were also much higher than in normals, with only a small further rise after the test breakfast. This pattern differs from that seen in coeliac disease, possibly reflecting the different pathophysiological processes and the greater area of gut involved in tropical malabsorption. Gastrin, neurotensin, and pancreatic polypeptide responses were all similar to normal.

Fig. 2 Postprandial gut hormone profile in acute tropical sprue (integrated 3 hour response expressed as % of normal).

Crohn's disease

This disease is characterised by inflammation of the gut wall often affecting segments of bowel with apparently normal areas in between. The distal ileum is the area most often affected, but the rectum, colon, and jejunum may also be involved.

¹A mixture of casein hydrolysate and vegetable oil.

GUT HORMONE PROFILE (FIG. 3)

Fourteen patients with Crohn's disease were studied (Besterman *et al.*, 1978c). After the test breakfast the release of the upper small intestinal hormone GIP was increased, in contrast to the poor rise found in coeliac disease and acute tropical sprue. Motilin, however, showed the greatest response, though there was also an augmented pancreatic polypeptide response. Fasting plasma enteroglucagon levels in these patients and the postprandial response were both greater than normal, but of a lower order of magnitude than in coeliac disease.

Fig. 3 Postprandial gut hormone profile in Crohn's disease (integrated 3 hour response expressed as % of normal).

Ulcerative colitis

This inflammatory bowel disease affects the mucosa and submucosa of the colon. Thus, the principal hormone-containing areas are all normal.

GUT HORMONE PROFILE (FIG. 4)

In 24 patients with ulcerative colitis the response of GIP after the test breakfast was entirely normal (Besterman *et al.*, 1978c). Basal plasma motilin levels were significantly raised. There was an augmented gastrin response which might be secondary to hypochlorhydria (acid studies were not performed) or possibly due to loss of some colonic gastric inhibitory substance secondary to the pathological damage. Both enteroglucagon and pancreatic polypeptide, as in Crohn's disease, showed a moderately raised response.

Fig. 4 Postprandial gut hormone profile in ulcerative colitis (integrated 3 hour response expressed as % of normal).

Infective diarrhoea

Twelve patients, previously in good health, required urgent admission to an isolation hospital for severe diarrhoea which required intravenous fluid and electrolyte treatment. Pathogens were isolated in only four patients, the rest presumably had either bacterial or viral pathogens which were not identifiable in the routine laboratory. They all subsequently made uneventful recoveries.

GUT HORMONE PROFILE (FIG. 5)

The test breakfast was eaten at an early time during recovery. The responses of pancreatic polypeptide

and GIP were normal (Besterman *et al.*, 1979b). In contrast, augmented responses of gastrin, motilin, and enteroglucagon were found. These may relate to compensatory mechanisms occurring in the gut to the diarrhoea. As the diarrhoea abated basal motilin levels fell in parallel.

Fig. 5 Postprandial gut hormone profile in infective diarrhoea (integrated 3 hour response expressed as % of normal).

Pancreatic insufficiency

Gross steatorrhoea and malabsorption may occur as a result of chronic pancreatitis causing extensive gland destruction and thus considerable reduction in pancreatic enzyme output. The intestinal mucosa in these cases is normal. Gut hormone release in sixteen patients with chronic pancreatitis and proved pancreatic exocrine insufficiency were studied (Besterman *et al.*, 1978a). The commonest aetiological factor was excess alcohol intake but some patients had biliary disease and in a few no predisposing cause could be identified. The patients had either grossly impaired or absent responses to injected secretagogues or to a Lundh test meal. All had subsequently improved on being treated with

pancreatic enzyme supplements. All patients had either pancreatic calcification or other abnormality discovered at laparotomy, or endoscopic retrograde cannulation of the pancreatic duct (ERCP), and many were diabetic.

GUT HORMONE PROFILE (FIG. 6)

In these patients the GIP response was entirely normal in contrast to the diminished release in coeliac disease and acute tropical sprue, in both of which the malabsorption is secondary to mucosal damage. The gastrin response was diminished but both the motilin and enteroglucagon responses were increased. The increased enteroglucagon release was, however, much less than that found in association with atrophic small intestinal mucosa. This could suggest that the grossly raised levels in coeliac disease and acute tropical sprue are not merely secondary to the steatorrhoea (fat is a potent stimulant of enteroglucagon release) as this is much greater in the patients with pancreatic insufficiency.

The most striking finding in patients with pancreatic insufficiency was the gross failure of pancreatic polypeptide release following the test breakfast (Adrian *et al.*, 1979). This probably reflects the extensive damage to pancreatic tissue as the pancreatic polypeptide cells are scattered throughout the pancreatic parenchyma.

Fig. 6 Postprandial gut hormone profile in pancreatic insufficiency (integrated 3 hour response expressed as % of normal).

Intestinal resection

The subsequent effects of surgical removal of a length of intestine depend on the site and on the length of gut resected. The loss of absorptive area may give rise to severe malabsorption, even when only a short length of distal ileum has been resected (for example failure of vitamin B₁₂ and bile salt absorption). After small intestinal resection there is villous hypertrophy of the mucosa of the remainder (Porus, 1965; Dowling and Gleeson, 1973). This compensatory mechanism is probably stimulated by a humoral agent, enteroglucagon being a possibility.

We have studied patients who have undergone varying degrees of gut resection for a number of different pathological states (Besterman *et al.*, 1978b). The commonest indication for surgery was Crohn's disease when most patients had between one and two metres of terminal ileum resected. Partial resection of the ascending or transverse colon or both was carried out for Crohn's disease or ulcerative colitis. Neoplasia, trauma, and post-radiation fibrosis were less common reasons.

GUT HORMONE PROFILE (FIG. 7)

There was no significant difference between the effects of partial ileal and partial colonic resection in the responses of gastrin, pancreatic polypeptide, GIP, and neurotensin. The post-breakfast release of both gastrin and pancreatic polypeptide was greater than normal in both groups of patients. Raised gastrin levels after intestinal resection have been reported by others (Straus *et al.*, 1974) and this may be relevant to the gastric acid hypersecretion which occurs in these patients (Frederick *et al.*, 1965; Osborne *et al.*, 1966). The GIP and neurotensin responses, in contrast, were similar to normal. There was, however, a striking difference in the responses of motilin and enteroglucagon between the two groups of patients. The patients with partial resection of the colon had only mildly raised motilin responses and even a somewhat decreased enteroglucagon release. Those with partial resection of the ileum had a greatly augmented motilin response and also a substantially increased release of enteroglucagon.

Despite the pathological heterogeneity of these groups and variations in the time between operation and the study, clear patterns of gut hormone response are found. These changes, varying with the different types of intestinal resection, may well reflect important compensatory mechanisms.

Morbid obesity and the effect of jejunioileal bypass

The control of appetite and the regulation of body weight are very poorly understood. An interaction

Fig. 7 Postprandial gut hormone profile after gut resection (integrated 3 hour response expressed as % of normal).

between the gut and the hypothalamus is likely, with the sensation of satiety possibly being mediated by a gut hormone. Gross obesity is accompanied by metabolic disturbances, sometimes profound, which give rise to increased morbidity and mortality. Glucose intolerance and raised insulin levels may give rise later to frank diabetes mellitus. Morbid obesity may be literally life-threatening and one form of treatment which has been widely used is the operation of jejunioileal bypass. Seven inches of proximal jejunum are anastomosed to seven inches of distal ileum, with the remaining small intestine left out of contact with food as a blind loop. Patients invariably lose weight after this procedure, but rarely do they return to ideal body weight. The weight loss is thought not to be the result of malabsorption secondary to the vast reduction in mucosal surface area, but to a self-imposed decrease in the amount of ingested food. Eating any great amount of food is usually associated with diarrhoea and abdominal pain from distension.

The operation of jejunioileal bypass of itself may give rise to metabolic complications. One adaptive feature which is observed in these patients is villous

hypertrophy of the remaining small intestine (Fenyö *et al.*, 1976; Iversen *et al.*, 1976; Dudrick *et al.*, 1977). The role of gut hormones in the control of satiety and their involvement in these metabolic complications is not known.

GUT HORMONE PROFILE (FIG. 8)

In 19 patients with morbid obesity ($225 \pm 7\%$ ideal weight) no abnormality of gut hormone release was found to match the exaggerated blood glucose and insulin responses to the test breakfast (Besterman *et al.*, 1978e). Thus, deficiency of none of the gut hormones measured in the present 'profile' seems responsible for the failure of satiety mechanisms. There is a relatively drastic alteration of functional gut anatomy after jejunioileal bypass. This is reflected by several alterations in the pattern of gut hormone release in 21 patients studied between two and twelve months after bypass ($181 \pm 8\%$ ideal weight). The

Fig. 8 Gut hormone profile after jejunioileal bypass for morbid obesity (integrated 3 hour response expressed as % of normal).

gastrin response was moderately increased, fitting with the known gastric hypersecretion occurring in these patients. The GIP response was greatly reduced, and insulin release was also much less than normal, being greatly reduced compared with the increased release in obesity. HPP and motilin responses were normal. There was an eightfold increase in neurotensin and a massive sixteenfold increase in enteroglucagon after the test meal compared to normal. The augmented neurotensin response may be relevant to the altered carbohydrate metabolism. The exaggerated enteroglucagon levels may well be a factor in the villous hypertrophy. Both of these hormones may also have an effect on gut motility.

Irritable bowel syndrome (IBS)

This common diagnosis is made by exclusion of demonstrable organic disease and is usually regarded as a 'functional' disorder. Abnormalities of intestinal motility have been described (Misiewicz, 1974) and abnormal gut hormone release has been postulated as an aetiological factor (Harvey, 1977).

GUT HORMONE PROFILE

A total of 42 patients with IBS were studied. Nineteen had abdominal pain and frequency of bowel action, 11 had pain and constipation, and 12 had pain but normal bowel function. All had been thoroughly investigated and no organic disease found. In contrast to all other disease groups studied, these patients had entirely normal responses of all the gut hormones measured.

Conclusions

The study of differential gut hormone release in various diseases affecting different segments of the gut has shown many abnormalities. In general a failure of hormone release has been found when the hormone under study is located in the area of maximal disease activity. Thus a diminished GIP response is found in coeliac disease and a greatly reduced release of human pancreatic polypeptide is seen in pancreatic insufficiency. Increased hormonal release may be secondary to the altered function of the gut. Thus ingested food will reach the ileum and constitute an increased stimulus when there is malabsorption in the jejunum, or if the anatomy has been altered to eliminate much of the proximal small gut. These phenomena might be thought to explain the very great release of enteroglucagon found in coeliac disease, in acute tropical sprue, after ileal resection, and after jejunoileal bypass operation. However, in considering malabsorption alone as an explanation of the findings in coeliac disease and

tropical sprue, the absence of such augmented responses in pancreatic insufficiency, when the degree of steatorrhoea was much greater, must be remembered. In the gut resection group, highly significant rises of enteroglucagon occurred in many patients who had undergone removal of only a small length of ileum. In addition, in all the groups of patients with very large enteroglucagon responses, significantly raised basal levels were found. These properties, shared by very different diseases, have a number of factors in common. Each disease group has a reduction in the effective mucosal absorptive surface area in the small intestine. A number of compensatory mechanisms are observed. For instance, in coeliac disease increased absorption in the ileum beyond the diseased portion and an increased enterocyte turnover occurs; in tropical sprue there is delayed transit; in both gut resection and jejunoileal bypass villous hypertrophy is seen. Observations on a patient with excessive secretion of enteroglucagon by an endocrine tumour (Bloom, 1972) suggest that delayed intestinal transit and villous hypertrophy might well be actions of this hormone.

The study of gut hormones in disease states thus identifies many situations where there is an abnormality of hormone release. Abnormal gut hormone release may help in the further understanding of the pathophysiology of several gut diseases which have remained enigmas for many years. Hypo- and hypersecretion of the individual gut hormone and correlation with the altered gut function may also provide important new insight into the normal physiology of the hormone. Lastly, it is not inconceivable that a simplified gut hormone profile, based perhaps on just three blood samples taken by a clinic nurse, may in the future provide an additional investigational tool towards the diagnosis of gastrointestinal disease.

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