PROCEEDINGS OF THE NUTRITION SOCIETY

The Three Hundred and Ninety-sixth Meeting was held jointly with the British Society of Gastroenterology at the University of Salford on 24 April 1984. The British Society of Gastroenterology/Nutrition Society/Glaxo International Teaching Day followed on 25 April 1984 and papers from this Meeting are also presented

SYMPOSIUM ON 'NUTRITIONAL ASPECTS OF NORMAL AND PATHOLOGICAL GUT FUNCTION'

The gut hormone response to food

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The functioning of the gastrointestinal tract is controlled (1) by a complex system of extrinsic and intrinsic nerves that secrete both peptide and non-peptide neurotransmitters, (2) by paracrine cells that secrete their products into the immediate surroundings, and (3) by mucosal endocrine cells that secrete peptides into the circulation. Together, these components form the 'diffuse neuroendocrine system' (Polak & Bloom, 1980) which exerts a finely-modulated control over every element of gut function. The many peptides secreted by this system are often loosely called 'gut hormones', but only for one of these, gastrin, is there sufficient evidence that it acts as a hormone under physiological conditions. Neuropeptides such as vasoactive intestinal polypeptide may overspill into the circulation, as may peptides such as somatostatin which fulfils both a paracrine and a neurocrine role. This does not mean that such peptides function as true hormones. This account will be confined to the peptide products of the mucosal endocrine cells that release them into the blood in response to luminal stimuli. Table 1 summarizes the peptides of this type, with their principal locations and proposed actions. It will be seen that many of them occur in multiple molecular forms, both with respect to chain-length and, in the case of the gastrins, with respect to sulphation of the tyrosyl residue at the active site of the molecule.

Changes in plasma concentrations of these peptides are readily studied in human volunteers by specific radioimmunoassay of samples taken before, during and after a mixed test meal. The response can then be further dissected by giving

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Table 1. *Principal types of peptide secreted by mucosal endocrine cells of the gut*

Peptide	Main location	Principal molecular forms (no. of amino acid residues)	Proposed main actions
Gastrin	Gastric antrum	17*, 34*	Stimulates gastric acid secretion Trophic to gastric mucosa
Cholecystokinin	Upper small intestine	8†, 33†‡, 39†‡	Stimulates pancreatic enzyme secretion Trophic to pancreas
Secretin	Upper small intestine	27‡	Stimulates pancreatic fluid and bicarbonate secretion
Motilin	Upper small intestine	22‡ and larger unsequenced form	Stimulates gastrointestinal motility
GIP	Upper small intestine	42‡ and larger unsequenced form	Enhancement of insulin secretion
Enteroglucagon	Ileum and colon	37‡, 69‡	Trophic to small intestinal mucosa?
Neurotensin	Ileum	13	Paracrine role?

GIP, gastric inhibitory polypeptide.
*Tyrosyl residue either sulphated or unsulphated.
†Tyrosyl (position 7 from carboxy-terminus) sulphated.
‡Value from pig.

isoenergetic amounts of protein, fat or carbohydrate, fluid loads, acids or alkalis, or by applying distension with intraluminal balloons. Such techniques can also be applied to patients with various gastrointestinal disorders, or after surgical procedures.

The gastrin response

Fasting plasma gastrin concentrations show a distribution markedly skewed towards the lower values, the modal concentration being below 5 pmol/l (Bryant & Adrian, 1982). The predominant molecular form in the fasting state is gastrin-34, but the antrum secretes a preponderance of gastrin-17 which has a much shorter half-life but also a greater potency than gastrin-34. Radioimmunoassays that react with both these forms will typically show a rise of about 15 pmol/l within 15 min of the start of a small (2225 kJ) mixed test meal, tailing off very slowly, so that an elevation is still detectable after 5 or 6 h. With respect to gastrin, as with many of the other gut peptides, Western man spends most of his waking life either eating or in the endocrinologically-postprandial state. Vagotomy drastically reduces the gastrin response, and antrectomy or gastrectomy abolishes it almost totally.

Antral distension, whether by balloon (Grossman *et al.* 1948) or by a fluid load (Soares *et al.* 1977), provides a partial stimulus, but the most effective chemical stimulus from food substances is that of small peptides and amino acids (Richardson *et al.* 1976), the initial products of protein digestion.

Gastrin-17 is the gut peptide for which a physiological hormonal function is best attested. Its immediate role is to act on the parietal cells to stimulate gastric acid

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secretion. Rates of acid secretion in response to gastrin-17 elevations induced by giving varying doses of peptone are closely correlated with the rates obtained at equivalent elevations produced by gastrin-17 infusions (Lam *et al.* 1980). However, gastrin by itself is only a weak stimulant of acid secretion when tested on isolated parietal cells, but it strongly potentiates the action of histamine on these cells (Soll, 1978). It enhances the production of histamine, and may perhaps be regarded as both a promoter and finely-adjustable amplifier of the paracrine histamine stimulus to gastric acid secretion. Its action summates with that of cholinergic (vagal) stimulation, which in turn releases gastrin from the antral G cells. The mutually-interdependent control mechanisms for the regulation of gastrin and gastric acid secretion are exceedingly complex. One of the major limbs of the system is a long-term feedback control from the hydrogen ion concentration. Any deficiency of the parietal cell response leads to a resetting of gastrin synthesis and release, resulting in the raised basal and stimulated levels seen in hypochlorhydria, and the gross elevation in achlorhydria. A short-term control mechanism may be seen in the reciprocal response of gastrin and somatostatin to cholinergic agonists (Saffouri *et al.* 1980), gastrin being released and somatostatin secretion being suppressed, so that cholinergic stimulation can override the paracrine inhibitory effect of somatostatin.

The immediate effects of gastrin are clearly appropriate to the digestive activity of the stomach. However, in addition to its immediate effects, gastrin, like some other gut peptides, has long-term effects that may be no less important. These are trophic effects that play a part in adaptation of the gut to longer-term changes in food intake, or to compensate for pathological damage. Gastrin thus stimulates the growth of the oxyntic mucosa (Crean *et al.* 1969), or reverses the atrophy induced by removing most of the endogenous gastrin by antrectomy (Johnson *et al.* 1975). The marked trophic effect of gastrin is seen in the Zollinger–Ellison syndrome, where the excessive secretion of gastrin from a tumour produces giant gastric mucosal folds.

The cholecystokinin response

The cholecystokinin response to foods has proved exceptionally difficult to assess, because of problems encountered in developing satisfactory radio-immunoassays for this group of peptides. Most cholecystokinin antibodies cross-react with the gastrins, and gastrin immunoreactivity measured by a gastrin-specific assay then has to be subtracted from the total. Even so, reliable estimation has required chromatographic procedures, unsuitable for handling large numbers of samples (Lamers *et al.* 1979). Many published results express gross overestimates of cholecystokinin concentrations and provide little confidence that estimates actually relate to true concentrations of one or more of the many molecular forms of the peptide. One attempt to overcome such difficulties is to develop an antiserum to the amino-terminal region of the cholecystokinin octapeptide which does not cross-react with gastrins (Adrian *et al.* 1983). This provides the possibility of direct estimation of cholecystokinin octapeptide without subtracting gastrin immunoreactivity.

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The results of the more careful studies would indicate that fasting plasma concentrations of cholecystokinin octapeptide are low (less than 1 pmol/l) and that after a standard mixed meal a rise of 5–10 pmol/l occurs, with a very similar time-course to that of gastrin. The original work of Ivy & Oldberg (1928) showed that the cholecystokinin response, as estimated by gall-bladder contraction, was elicited by the products of protein and fat digestion but not by undigested protein or fat. In addition, trypsin inhibitors also stimulate cholecystokinin release (e.g. Kanno *et al.* 1979).

Although it is widely accepted that cholecystokinin has a physiological hormonal role in stimulating gall-bladder contraction and pancreatic enzyme secretion, some doubt has remained, chiefly because of unreliable earlier estimates of circulating cholecystokinin concentrations. However, exogenous cholecystokinin octapeptide, given at rates resulting in the low rises of plasma concentration now known to be physiological, does cause an increase in gall-bladder pressure in the pig (Adrian *et al.* 1980), and infusions of cholecystokinin-33 and cholecystokinin octapetide on a background of secretin stimulates pancreatic enzyme secretion in man, with a half-maximal response at plasma concentrations of 5–10 pmol/l (Valenzuela *et al.* 1979).

The control of pancreatic secretion is at least as complicated as that of gastric secretion. How important is the cholecystokinin response in influencing pancreatic secretion? Certainly the pancreatic innervation is responsible for a large measure of the enzyme secretory response. Autotransplantation of the denervated pancreas in dogs leads to a dramatic fall in the pancreatic enzyme response to intestinal stimulants, whereas the response to caerulein, a cholecystokinin analogue, remains intact (Solomon & Grossman, 1979). Furthermore, pancreatic enzyme secretion is initiated much more quickly than can be accounted for by the appearance of cholecystokinin in the portal circulation (Singer *et al.* 1980). It looks as if cholecystokinin is playing a supplementary, maintaining role, rather than the primary role, in the pancreatic enzyme response.

Like gastrin, cholecystokinin has an important trophic effect, in this case on the pancreas (Petersen *et al.* 1978), and it may be this that provides the hormone with its *raison d'être*. The periodical release of cholecystokinin in response to its food stimulants produces pancreatic growth to match the regular requirements for secretion.

Secretin and motilin responses

Secretin and motilin are exceptional in that their secretory responses are short-lived, and secretin release is almost certainly not directly stimulated by food. The stimulus for its release is duodenal acidification, with a threshold at about pH 4. In the thorough study by Schaffalitzky de Muckadell & Fahrenkrug (1978), intraduodenal pH and plasma secretin concentrations were continuously monitored before, during and after a mixed test meal, with and without cimetidine pretreatment to reduce gastric acid secretion. Short-lived secretin responses correlated well with drops in the intraduodenal pH, and secretin release was much

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reduced by cimetidine administration. The release of secretin after a meal will depend on the buffering capacity of the food, the rate of gastric emptying and the acid response to the meal: these contribute to the intersubject variation seen in most studies. As pancreatic fluid and bicarbonate secretion are stimulated by physiological concentrations of secretin (Greenberg *et al.* 1979; Schaffalitzky de Muckadell *et al.* 1979) there is little doubt that secretin participates in the regulation of duodenal pH via its effects on the pancreas, supplementing the control exerted by the vagus nerve. Secretin and cholecystokinin potentiate the effects of each other on the pancreas (Grossman, 1974), secretin also potentiating the trophic effect of cholecystokinin or its caerulein analogue (Solomon *et al.* 1979).

The typical motilin response to a mixed meal is a short-lived and variable increase in plasma concentrations, followed by a prolonged quiescent or inhibitory phase (Christofides *et al.* 1979). Motilin is released by duodenal acidification or alkalinization and by fat, but its release is inhibited by glucose. It is also released by distension of the stomach by balloon or water load. In the interdigestive period, plasma motilin concentrations rise with the onset of an activity front (phase III) of the interdigestive myoelectric complex (Vantrappen *et al.* 1979), and infusions of motilin can initiate the phase III migrating contraction. However, phase III contractions are not necessarily caused by motilin, as motilin release can be suppressed by pancreatic polypeptide infusions without preventing phase III contractions (Christofides & Bloom, 1981). It seems more probable that motilin release is consequential on the contraction. There thus seems to be a complex interaction between the nervous and endocrine systems whereby motilin may be acting as an amplifier of nervous action. Gastric emptying is significantly accelerated by infusion of physiological levels of motilin (Christofides *et al.* 1981).

The GIP response

GIP, whose biological actions are given by its alternative full names of gastric inhibitory or glucose-dependent insulinotropic polypeptide, has a prolonged release response to a mixed meal, but reaches its peak plasma concentration of about 35 pmol/l rather later than gastrin, at 60 min (Sarson, 1982). The specific stimuli for its release are glucose and fat. It is now apparent that inhibition of gastric acid secretion and motility by GIP (Maxwell *et al.* 1980) only occurs at supraphysiological concentrations. Thus, although GIP fulfils many of the criteria of the 'enterogastrone' proposed by Kosaka & Lim (1930), it does not do so under physiological conditions. Its other major proposed effect, that of augmenting the insulin response to raised plasma glucose concentrations (Dupre *et al.* 1973), is also in question. Infusion of glucose and purified porcine GIP into human volunteers to simulate the plasma levels of each seen after an oral glucose load fails to produce an adequate increase in insulin release to account for the 'incretin' effect (Sarson *et al.* 1984). However, there is now evidence that human GIP is not identical to porcine GIP, so that this peptide may yet prove to be a contributor to the incretin effect.

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The enteroglucagon response

The predominant form of enteroglucagon in man has a molecular size similar to that of glicentin, the predominant form in the pig (Ghatei *et al.* 1983). Its release in response to a standard mixed meal is similar in time-course to that of GIP. The stimuli for this are glucose and digested fats impinging on the enteroglucagon cells of the intestine, whose distribution with a gradient of increasing cell numbers per unit length towards the terminal ileum would seem to make them ideal monitors of upper small intestinal absorptive function. The more glucose and long-chain fatty acids that reach the lower small intestine, the more enteroglucagon is released. The postulate that enteroglucagon might be responsible for a feedback control mechanism to stimulate growth of the small intestinal mucosa originated from a patient with a renal tumour that secreted enteroglucagon (Bloom, 1972). This patient had constipation and gross villous hypertrophy with slow intestinal transit on barium meal examination, features that were reversed on resection of the tumour. Subsequently, in a variety of experimental situations, mucosal growth of the small intestine, as measured by the crypt cell production rate, has correlated closely with plasma enteroglucagon concentrations (Al-Mukhtar *et al.* 1982). An enteroglucagon-enriched chromatographic fraction of rat intestinal extract brought about a dose-dependent increase in the incorporation of tritiated thymidine into jejunal mucosa cultures (Uttenthal *et al.* 1982*a*), but insufficient quantities of pure enteroglucagon have been available to perform conclusive experiments to establish the trophic effect.

The neurotensin response

Neurotensin has a rather similar distribution to that of enteroglucagon within the gastrointestinal tract, and responds to the same food stimuli, particularly to fat. Its endocrine function, however, remains uncertain because possibly its only known action at physiological plasma concentrations in man is to stimulate the release of another peptide of uncertain role, pancreatic polypeptide (e.g. Lee *et al.* 1984). It may be that its pharmacological effects of vasodilatation and inhibition of intestinal motility indicate a paracrine role in the ileum, as these possible local effects might tend to aid fat absorption (Hammer & Leeman, 1981). The pharmacology of neurotensin release has been studied in the isolated, arterially perfused rat ileum (Gill *et al.* 1984) with results that suggest that its release is modulated by a complex interaction of cholinergic, bombesin and somatostatin influences.

Influence of pathology on gut hormone responses

Many gastrointestinal pathologies modify the gut hormone response to food. Reduction of the intragastric acid concentration, whether by atrophic gastritis, H_2-receptor antagonists or alkalis, will tend to augment gastrin secretion. Dumping syndrome leads to a rapid loading of the small intestine with gastric contents, and hence to rapid and sometimes dramatically-augmented

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enteroglucagon and neurotensin responses (Bloom *et al.* 1972; Blackburn *et al.* 1980). Coeliac disease, damaging primarily the upper small intestinal mucosa, leads to a reduction of GIP and secretin responses, but overloads the lower small intestine and produces exaggerated enteroglucagon and neurotensin release (Besterman *et al.* 1978). Diarrhoeal diseases of whatever origin seem to increase motilin release (Christofides, 1982).

Influence of food constituents on gut hormone responses

Considerable attention has been focused on the effects of various food constituents or additives in recent years. An increased viscous fibre content of the Western human diet has been widely advocated, and has been extensively tested in diabetics, with beneficial effects on post-prandial glycaemia. Fibres such as pectin and guar gum are thought to slow glucose absorption through their viscosity effect at the mucosal surface and on intestinal transit time. In slowing delivery of glucose to the intestinal mucosa throughout its length, these agents reduce the GIP and enteroglucagon responses to carbohydrates or mixed meals (Jenkins *et al.* 1980; Uttenthal *et al.* 1982*b*). Conversely, an α-glucosidase (*EC* 3.2.1.20) inhibitor such as acarbose, which has also been tested in diabetics, reduces glucose formation in the upper small intestine and hence reduces GIP responses, but increases the carbohydrate load to the lower intestine and augments the enteroglucagon response (Uttenthal *et al.* 1983). Other in vivo inhibitors of starch and oligosaccharide digestion may be expected to have similar effects. Trypsin inhibitors augment cholecystokinin secretion; rats fed on uncooked soya-bean meal had considerably elevated plasma concentrations of cholecystokinin and showed a significant increase in pancreatic weight compared with rats fed on soya-bean meal in which the trypsin inhibitor had been inactivated by heat treatment (Adrian *et al.* 1982). The influence of such agents, whether occurring naturally or as food additives, on gut peptides with a trophic effect on the gastrointestinal tract should be borne in mind when developments in food technology bring about significant changes in human or animal diets.

Conclusion

It is apparent that the secretion of individual gut peptides is controlled by an exceedingly complex interaction of luminal stimuli with neurocrine, paracrine and endocrine influences. Their regulatory functions are, in turn, expressed through such interactions, so that the response of the gut is the resultant of these influences. Thus the assignation of simple, primary hormonal functions to the gut peptides has in most cases not been possible. Probably their immediate role is in fine-tuning of gut function, or as long-stop regulatory mechanisms that can take over when other control systems fail. The long-term trophic effects of some of the peptides in regulating adaptive responses to diet and pathological states may prove to be as significant to the organism as their short-term regulatory effects.

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