stimulating insulin release when taken orally (Marks & Samols, 1969), suggesting that its insulin-stimulating effect is mediated through one or more of the intestinal insulin-stimulating hormones. The degree of hyperglycaemia after ingestion of fructose or galactose is similar and small; however, ingestion of galactose elevates circulating concentrations of gastric inhibitory polypeptide, whereas fructose does not (Sykes et al., 1979). The stimulation of insulin secretion by galactose, but not fructose, is consistent with a gastric-inhibitory-polypeptide-mediated effect; when fructose is given, a similar degree of hyperglycaemia in the absence of elevated gastric-inhibitory-polypeptide concentrations is incapable of stimulating insulin secretion.

Release of gastric inhibitory polypeptide is dependent on absorption of nutrient. Addition of chloridzin to an oral glucose load will inhibit both absorption of glucose and release of the polypeptide (Ebert & Creutzfeldt, 1978; Sykes et al., 1980), providing another mechanism to prevent inappropriate insulin secretion. Insulin can suppress release of gastric inhibitory polypeptide, providing a feedback-control mechanism, although the evidence as to whether insulin has the ability to inhibit both fat and glucose-induced polypeptide, or fat-induced polypeptide alone, is conflicting (Sirinek et al., 1978; Andersen et al., 1978).

It is possible that an overactive entero-insular axis is involved in the pathogenesis of hyperinsulinaemia of obesity. Obese subjects have exaggerated gastric-inhibitory-polypeptide response to fat and a mixed meal and the feedback control of the fat-induced polypeptide is also defective (Creutzfeldt et al., 1978).

Conclusions

Is gastric inhibitory polypeptide the only incretin? Infusion of antisera to the polypeptide in rats decreased the incretin effect of intraduodenal glucose, but did not abolish it (Ebert et al., 1979). There are several gastrointestinal peptides that stimulate insulin secretion, but that, as yet, have only been partially purified (Turner & Marks, 1972). Many gastrointestinal peptides are also present in the central nervous system, and there is evidence for a neural as well as an endocrine component of the entero-insular axis, with some gut peptides functioning as neurotransmitters. After pancreatectomy and orthotopic transplantation of a denervated pancreatic graft, Jakob et al. (1970) found that oral-glucose tolerance and insulin response deteriorate, whereas intravenous-glucose tolerance remains unchanged. The finding does, however, need confirmation, as other authors (Lindkaer Jensen et al., 1976) have been unable to demonstrate any significant decrease in the incretin effect in denervated pancreases. Further study is likely to show that the entero-insular axis is a complex system of which gastric inhibitory polypeptide forms only one part.

Brown, J. C., Dryburgh, J. R., Mocchia, P. & Pederson, R. A. (1975) in Gastrointestinal Hormones (a Symposium held in Galveston, TX, U.S.A., on 19 October 1974) (Thompson, J. C., ed.), pp. 537–547, University of Texas Press, Austin, TX

The diffuse neuroendocrine system in gastroenterology

JULIA M. POLAK* and STEPHEN R. BLOOM†
*Department of Histology and Histology, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 OHS, U.K.
†Department of Histochemistry and ‡Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 OHS, U.K.

In 1938 Feyrter postulated the existence of a ‘diffuse endocrine gland’. Using conventional histology he noted the presence of many poorly stained (‘clear’) cells, diffusely distributed in various regions of the gastrointestinal tract, but for many years this concept remained a mere speculation.

The discovery of numerous peptide hormones from the gastrointestinal tract and the observation that these are produced by specialized endocrine ‘clear’ cells scattered among the other epithelial non-endocrine cells reinforced Feyrter’s early concept.

The existence of a ‘diffuse endocrine system’ distinct from the classical ‘glandular endocrine system’ is now well recognized.

Glandular endocrine systems consist of a compact mass of cells which makes extirpation possible. Also the hormone concentration in efferent blood can be measured after a specific stimulus. In contrast the diffuse endocrine systems consist of scattered single cells and nerve fibres throughout the body. This makes extirpation impossible. Although there is a synchronized response to stimuli, the local response cannot yet be measured.

Brain and gut peptides

In 1931 von Euler & Gaddum extracted a similar peptide from both the brain and the gut. But the full realization that there are many peptides common to both sites did not come for more than 40 years after the discovery that somatostatin, originally thought to be a hypothalamic peptide, was present also in the gut (Arimura et al., 1975). The list of ‘neuropeptides’ has increased rapidly and now includes: vasomotor...
Peptides in the autonomic nervous system

These 'neuropeptides' are found, in the periphery, not only in classical endocrine cells, but also in cell bodies and fibres of the peripheral autonomic innervation. It has therefore been necessary to expand the original concept of a 'diffuse neuroendocrine system' into that of a 'diffuse neuroendocrine system' incorporating this recently discovered 'peptidergic' component of the autonomic innervation (Polak & Bloom, 1979a).

The diffuse neuroendocrine system of the gut

This system is extremely well represented in the gut. At least 13 peptides have been successfully extracted from it. Some of them are mostly found in cell bodies and nerve fibres of the autonomic innervation (Fig. 1c), whereas others are principally localized in epithelial endocrine cells, distributed along the entire length of the gut, intermingled with non-endocrine cells. They are frequently connected to the gut lumen by microvilli. In addition they are provided with numerous cytoplasmic secretory granules which, by their differing size, shape and electron density, characterize the various cell types (Fig. 1b).

Technology

The most favoured methods for the study of the distribution and tissue localization of the gut peptides are immunological. Immunocytochemistry produces information regarding the localization of these peptides in cells or nerves, whereas radioimmunoassay indicates their various molecular forms as well as the precise quantity present in blood and tissue.

Individual peptides

Peptide hormones acting via the circulation. Eight peptide hormones extracted from the gut are known to act via the circulation. Their distribution, cellular origin and biochemical characteristics are listed in Table 1. Further details are given in the accompanying paper (Bloom & Polak, 1980).

Neuropeptides. The majority of the 'neuropeptides' are extensively distributed, being found not only within the gut, but also in many other organs, e.g. lung, genito-urinary tract, skin and salivary glands (Polak & Bloom, 1979a).

The spectrum of actions of these peptides is wide, and a specific action is probably dependent on their anatomical distribution. The effect of a neuropeptide seems to be only local or 'paracrine'; that is, it is confined to the site of release. Thus the presence of some of the neuropeptides in the circulation may merely reflect an overflow phenomenon.

Vasoactive intestinal polypeptide. Vasoactive intestinal polypeptide is a 28-amino acid peptide originally extracted in large quantities from the gut and later found to be present, also in large quantities, in the brain. It has a wide spectrum of actions including muscle relaxation, vasodilation and intestinal secretion (Said, 1978). In the gut it is found from the oesophagus to the rectum and is localized by immunocytochemistry mainly in the innervation of the gut wall. Fine varicose nerve fibres are seen in both plexi as well as in the two muscle layers the mucosa and the submucosa. These nerve fibres originate from intrinsic cell bodies, which can occasionally be immunostained. However, full proof of their intrinsic origin has been given by the use of separate cultures of the two main plexi, which give rise to numerous peptide-containing nerve fibres (Jessen et al., 1979).

An intense vasoactive intestinal polypeptide innervation is also found in the salivary glands, pancreas, genito-urinary tract and neurohypophysis.

(a) Pathology. (i) Tumour pathology. Vasoactive intestinal polypeptide has been shown to be the agent responsible for the Verner Morrison (WDHA) syndrome (watery diarrhoea hypokalaemia achlorhydria). Large quantities of vasoactive intestinal polypeptide, enkephalin(s), somatostatin, neotensin, substance P, gastrin/CCK and bombesin.

Fig. 1. Fine varicose vasoactive intestinal polypeptide fibres in the human gut wall (a) and typical endocrine cell at the ultrastructural level with numerous electron-dense secretory granules (sg) and microvilli (mu) in the apical pole (b). Magnification: (a), x 500; (b), x 7500.
polypeptide are found in the circulation and the tumour (pancreatic or neural) (Bloom & Polak, 1975).

(ii) Non-tumour pathology. A significant decrease in vasoactive intestinal polypeptide from 236 ± 43 pmol/g (controls) to 75 ± 22 pmol/g wet wt. (means ± s.d.; P < 0.005) has recently been found in the gut in Chagas' disease (Polak et al., 1979).

Vasoactive intestinal polypeptide nerves are markedly decreased in the areas of severe ganglionitis and aganglionosis which are characteristic of this disease. Similar findings have also been noted in Hirschprung's disease, another bowel disease consisting of severe segmental colonic aganglionosis (Polak et al., 1979).

Conversely, in the inflammatory bowel condition of Crohn's disease, a significant decrease in vasoactive intestinal polypeptide content (252 ± 49 pmol/g wet wt.; controls 121 ± 9 pmol/g) and immunostained nerves is frequently found (Polak et al., 1978a).

Substance P. Substance P is an 11-amino acid peptide found not only in the gut and brain, but also in many areas of sensory transmission such as skin, genito-urinary tract and lung (Skrabanek & Powell, 1977). It is principally present in the autonomic innervation. In the gut its distribution and its system of intrinsic cell bodies parallels closely that of vasoactive intestinal polypeptide.

(a) Pathology. A significant decrease in substance P fibres has also been noted in both Chagas' and Hirschsprung's disease (Polak et al., 1979).

Somatostatin. Somatostatin is a 14-amino acid peptide found principally in the brain and the D-cells of the gut and pancreas. It is a powerful inhibitor not only of all the gut hormones, but also of many gastrointestinal functions (Bloom, 1978).

(a) Pathology. Tumours of the pancreas often produce somatostatin, either alone or combined with other hormones (Bloom et al., 1978). It has recently been suggested that somatostatin deficiency may be a pathogenic factor in two separate diseases: duodenal ulceration (Chayvialle et al., 1978) and neonatal hypoglycaemia with hyperinsulinism (Polak & Bloom, 1979b).

Enkephalins. [Methionine]- and [leucine]-enkephalins are pentapeptides which differ by only one amino acid residue at the C-terminal. [Methionine]enkephalin forms part of a larger group of peptides known as endorphins (ENDOgenous MORPHINE) (Guillemin, 1978). The enkephalins, in an approximate methionine/leucine ratio of 4, are found in the gut, mainly in the innervation, in the brain and in some sympathetic tissue, including the carotid body (Polak & Bloom, 1979a).

Bombesin. This is a 14-amino acid peptide originally extracted from the discoglossid frog Bombina bombina (Erspamer & Melchiorri, 1973). Bombesin is present mostly in brain, gut and lung. In the gut, immunocytochemistry localizes it to nerves (man and other mammals) and cells (birds), but exclusively to endocrine cells in the lung (human and other mammals) (Polak et al., 1978b).

Conclusions

Nervous versus hormonal control of the gut. Pavlov's original concept of neural control of the gut was swept away by the revolutionary idea of 'chemical (hormonal) messengers' put forward by Bayliss & Starling (1902). These two apparently opposing views are now reconciled by the findings of identical regulatory peptides in both the endocrine and neural components of the gut.

The autonomic nervous system of the gut. In 1899 Dogiel challenged Langley's (1898) bipartite division of the autonomic nervous system, by describing a third type of neuron in the myenteric plexus of the gut. Seventy one years later, Baumgarten et al. (1970) convincingly showed at the electron-microscopical level a third type of neuron containing large electron-dense secretory granules (P-type) quite distinct from the small adrenergic or cholinergic granules. The complexity and variety of the autonomic nerve fibres was later emphasized by Cooke & Burnstock (1976). The finding of at least four neuropeptides vasoactive intestinal polypeptide, substance P, enkephalins and bombesin) in the autonomic innervation further underlines the existence of an important non-cholinergic non-adrenergic, possibly peptidergic, component of the system.

In addition, the discovery of this peptidergic component suggests an explanation for the number of atropin-resistant neurally mediated gut responses such as the intestinal vasodilation which can now be mimicked by small amounts of some of these neuropeptides, injected into the local circulation (Fahrenkrug et al., 1978). High concentrations of peptides (e.g. vasoactive intestinal polypeptide) are also found in the local nervous drainage after nerve stimulation.

Common embryological origin. Pearse's prophecy (1969) that the diffuse endocrine system would be found to be merely an embryonic outpouch of the brain has been largely fulfilled by the finding of identical peptides in both the brain and gut. Gastrointestinal physiology and pathology. Gastrointestinal functions are controlled by numerous factors including the gastrointestinal hormones and the neuropeptides. We now know the distribution and site of origin of these peptides in the gut. We also know of their powerful influence on a number of gut functions (e.g. motility, secretion) in health and disease. Further investigation of their actions and interactions will lead to a better understanding of gut physiology and pathology.

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Pharmacology of gastrointestinal hormones: an overview

U. T. STRUNZ and L. DEMLING
Friedrich-Alexander Universität zu Erlangen-Nürnberg,
8520 Erlangen, Schlossplatz 4, Federal Republic of Germany

Clinical disorders of gastrointestinal hormones

VINCENT MARKS
Department of Biochemistry, Division of Clinical Biochemistry,
University of Surrey, Guildford, Surrey GU2 5XH, U.K.

The gastrointestinal (GI) hormones have provided a fruitful field for investigation by chemists, physiologists and pharmacologists, but for clinicians who had hoped to find in them the answer to many of the world’s ills they have so far proved a disappointment. None of the gastrointestinal hormones that have been characterized to date has emerged as a major cause of illness and many have still to be demonstrated to be associated, let alone causally involved, with any disease process at all.

Functional diseases of the traditional compact ductless glands are generally associated with either over- or under-secretion of their hormonal products. These, in turn, are responsible for producing well-defined clinical syndromes amenable to correction either by extirpation of the gland or replacement by exogenous hormones.

Elucidation of the clinical consequences of conventional endocrine disease has been facilitated by the relative ease with which discrete organs, such as thyroid, suprarenal, pituitary and parathyroid glands, can be removed surgically, their secretory hormone. Moreover, since spontaneously occurring products isolated and characterized, and made available for replacement therapy. Since, therefore, is the ability to produce selective, and necessarily short-term, hormone deficiency by passive immunization; (2) the fortuitous discovery of selective endocrine cell poisons analogous to alloxan for the B-cells of the pancreas; (3) ‘experiments of nature’, i.e. spontaneously occurring diseases, in which one type of endocrine cell only is affected.

The diseases in man that can be attributed to abnormalities of GI hormone secretion are: (1) diabetes, due to insulin deficiency and/or defective B-cell function; (2) hyperinsulinism, perhaps more aptly termed dysinsulinism, due to insulinomas; and (3) Zollinger–Ellison, (4) glucagonoma, (5) Verner–Morrison, (6) carcinoid and, possibly, (7) somatostatinoma syndromes, though, apart from the Zollinger-Ellison syndrome, whose presence is indicated usually, if not invariably, by anatomically recognizable abnormalities of the gastrointestinal endocrine cells, usually in the pancreas but also, very occasionally, in the alimentary tract itself. Most of these lesions behave as malignant tumours, though a minority, mainly insulinomas, are benign or rarely non-neoplastic.

Other diseases have been postulated, on the basis of their known pharmacological actions, to be due to functional abnormalities of GI hormone secretion, without associated anatomical abnormalities, but evidence of this is almost entirely lacking.

At the present time there is little reason to believe, beyond conjecture, that deficiency of any single GI hormone, except insulin, is responsible for disease in man or experimental animals.

Production of hormonal deficiency by ablation of its cells of origin is impossible in the case of GI hormones without producing such gross interference with other hormones, let alone nutrition, as to make interpretation impossible. The greatest hope for elucidation of the consequences of hormone depletion rests therefore on: (1) the ability to produce selective, and necessarily short-term, hormone deficiency by passive immunization; (2) the fortuitous discovery of selective endocrine cell poisons analogous to alloxan for the B-cells of the pancreas; (3) ‘experiments of nature’, i.e. spontaneously occurring diseases, in which one type of endocrine cell only is affected.

The diseases in man that can be attributed to abnormalities of GI hormone secretion are: (1) diabetes, due to insulin deficiency and/or defective B-cell function; (2) hyperinsulinism, perhaps more aptly termed dysinsulinism, due to insulinomas; and (3) Zollinger–Ellison, (4) glucagonoma, (5) Verner–Morrison, (6) carcinoid and, possibly, (7) somatostatinoma syndromes, though, apart from the Zollinger–Ellison syndrome, which is due to excessive and inappropriate gastrin secretion, the aetiological agents responsible for the other syndromes are not known for certainty. They may not be the same in every case of