REVIEW ARTICLE

The gastrointestinal endocrine system

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Gastrointestinal endocrinology is the study of the hormonal regulation of digestion. A number of characterized polypeptide hormones have been localized in specific gastroenteropancreatic endocrine cells. The fact that some of these hormones are also found in nerve and brain cells has given rise to the concept of a gut–brain axis. The functional capacities of these endocrine cells are determined by their anatomic location; the luminal exposure of gastroenteric endocrine cells represents an additional avenue for stimulation and release that is not open to pancreatic endocrine cells. Gastroenteropancreatic hormones regulate carbohydrate metabolism, gastric acid secretion, pancreatic exocrine and gallbladder function, gastrointestinal motility and blood flow. These important regulatory hormones may in turn be controlled by a series of gastroduodenal releasing hormones.

Diabetes mellitus is the most important metabolic disorder related to a gastroenteropancreatic hormone imbalance. Most tumours producing these hormones are of pancreatic origin and produce a number of hormones; insulinomas and gastrinomas are detected readily because of the serious metabolic disturbances they cause. Other instances of altered circulating concentrations of these hormones result from rather than cause the disease.

The challenge of future study is to determine if postprandial changes in the plasma concentrations of these hormones are sufficient or necessary, or both, for the control of digestion.

L'endocrinologie gastrointestinale est l'étude de la régulation hormonale de la digestion. Un certain nombre d'hormones polypeptidiques caractérisées ont été localisées dans des cellules endocrines gastroentéropancréatiques spécifiques. Le fait que certaines de ces hormones soient aussi retrouvées dans les cellules nerveuses et cérébrales a donné naissance au concept d'un axe intestinal–cérébral. La capacité fonctionnelle de ces cellules endocrines est déterminée par leur localisation anatomique; l'exposition des cellules endocrines gastroentériques dans la lumière des voies digestives constitue un mode de stimulation et de libération hormonale que ne possèdent pas les cellules endocrines pancréatiques. Les hormones gastroentéropancréatiques régissent le métabolisme glucidique, la sécrétion d'acide gastrique, la fonction exocrine du pancréas et de la vésicule biliaire, la motilité gastrointestinale et le débit sanguin. À leur tour ces importantes hormones de régulation peuvent être sous la dépendance d'une série d'hormones gastroduodénales de libération.

Le diabète sucré constitue le plus important trouble métabolique relié à un déséquilibre des hormones gastroentéropancréatiques. La plupart des tumeurs sécrétrices de ces hormones sont d'origine pancréatique et produisent plusieurs hormones; les insulinomes et les gastrinomes sont facilement décelés à cause des importants déséquilibres métaboliques qu'ils occasionnent. Les autres cas de modifications des concentrations circulantes de ces hormones sont plutôt le résultat que la cause de cette maladie.

À l'avenir le défi de la recherche consistera à déterminer si les changements postprandiaux des concentrations plasmatiques de ces hormones sont suffisants ou nécessaires, ou les deux, pour contrôler la digestion.

Gastroenteropancreatic endocrine cells are scattered throughout the digestive tract. Advances in protein chemistry have provided the techniques necessary for the isolation, purification and characterization of a large number of polypeptide hormones from the digestive tract. These hormones regulate carbohydrate metabolism, gastric acid secretion, pancreatic exocrine and gallbladder function, gastrointestinal motility and blood flow. By means of immunohistochemical and radioimmunochemical techniques these hormones have been localized in gastroenteropancreatic endocrine and nerve cells and in brain cells. In addition, gastrointestinal endocrinology has focused upon the measurement of circulating hormone concentrations in physiologic and pathophysiologic conditions. Both avenues of research have produced exciting results that gave rise to the concept of the gut–brain axis and the concept of different modes of hormone release (endocrine, luminal and paracrine) from gastroenteropancreatic endocrine cells. It is frustrating that, despite the enormous effort invested to generate a vast amount of information, the gastrointestinal endocrine system remains poorly understood.

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Hormone isolation and structure

Gastroenteropancreatic hormones are small protein molecules; each hormone has a unique sequence of amino acids that determines its structure and chemical characteristics.[1] The hormones found in mammalian gastroenteropancreatic endocrine cells are listed in Table I. Most of these hormones were characterized by the ability of their structure to influence a specific physiologic activity. Analysis of their amino acid sequences has revealed two main families of hormones:[2] the gastrin family, with gastrin, cholecystokinin and motilin, and the secretin family, with secretin, pancreatic glucagon, gastric inhibitory polypeptide and vasoactive intestinal polypeptide. The structural similarities result in some comparable activities for the members of each hormone family. Characteristics for recognition of target cell receptors are coordinated such that intra- and interfamily structural differences are sufficient to produce activities that antagonize certain physiologic processes. This interplay between hormone activities must be considered when one is assessing the meaningfulness of single plasma hormone concentrations. Two identified hormones have opposing effects upon gastric acid secretion (gastrin stimulates and gastric inhibitory polypeptide inhibits); to assess the hormonal control of gastric acid secretion both should be considered.

Hormone localization and assay

The structure of gastroenteropancreatic hormones is usually sufficiently distinctive that specific antisera can be raised. These antisera have permitted the development of immunohistochemical techniques to localize hormone-containing cells and radioimmunoassay techniques to measure circulating and tissue hormone concentrations. The hormone recognition characteristics of the antiserum determine the sensitivity and specificity of the assay. These characteristics vary from one antiserum to another. Recognition problems can arise when hormones exist in different molecular sizes, as with insulin (proinsulin and insulin), glucagon (pancreatic glucagon and enteroglucagon), gastrin (component I, G-34, G-17 and G-14) and cholecystokinin (cholecystokinin variant, cholecystokinin and octapeptide).[3,4] Some antisera have recognition properties common to a number of species, while others are species-specific.

Radioimmunoassays have been developed for most of these hormones. The many problems and pitfalls of the assays have been discussed.[5] When interpreting radioimmunoassay data in the light of physiological studies or clinical diagnosis one must remember that a radioimmunoassay is a structural assay and not a direct measure of the biologic activity of the hormone.

Immunohistochemical and radioimmunoassay techniques have been used to chart the distribution of these hormones. Some of the hormones are present in a number of locations, not just in the digestive tract. For example, gastrin is present in antral and duodenal endocrine cells,[6] vagal nerve cells[7] and brain cells.[8] Cholecystokinin, which was initially found in the upper small intestine,[9] has the highest concentration of any hormone detected in the brain.[10] A number of hormones isolated initially outside the gastrointestinal tract have been found in gastroenteropancreatic tissues: somatostatin, thyrotropin releasing hormone, substance P, neurotensin and adrenocorticotropin.[11-13] The detection of hormones common to gastroenteropancreatic and brain endocrine cells created the concept of a gut–brain axis. Most of these endocrine cells have the ability for *A*mine *P*recursor *U*ptake and *D*ecarboxylation. Pearse[14] claimed that APUD cells originate from the neuroectoderm; however, substantial evidence exists for an endodermal origin for gastroenteropancreatic endocrine cells.[15,16]

Table I—Polypeptide hormones found in mammalian gastroenteropancreatic endocrine cells

Endocrine cells	Polypeptide hormones*
Gastro	Gastrin, somatostatin, gastric glucagon, substance P, enkephalin
Entero	Gastrin, somatostatin, secretin, cholecystokinin, enteroglucagon, motilin, gastric inhibitory polypeptide, vasoactive intestinal polypeptide, substance P, enkephalin, neurotensin
Pancreatic	Insulin, pancreatic glucagon, somatostatin, human pancreatic polypeptide, thyrotropin releasing hormone

*The hormonal status of some of these polypeptides is in question, as is outlined in the text.

Gastroenteropancreatic endocrine cells

These cells are classified as either open or closed.[17] Those situated in the luminal mucosa are open. They can be affected by circulatory, luminal or intercellular factors and have the potential for a secretory response via circulatory (endocrine), luminal (exocrine) or intercellular (paracrine) routes. Pancreatic endocrine cells clustered within the islets of Langerhans are closed. They cannot be affected by luminal factors, nor can they secrete into the lumen. The anatomic locations of cells govern their functional capabilities.

Endocrine secretion can readily be detected in the circulation, while luminal and paracrine secretion cannot. Evidence has been presented for luminal secretion of gastrin, somatostatin, secretin, vasoactive intestinal polypeptide and substance P.[18-20] Paracrine secretion is the release of a hormone from one cell that affects neighbouring cells, probably without being detectable in the circulation; therefore, only by indirect evidence, the presence of a metabolic effect in the absence of a detectable circulating or luminal hormone response, can paracrine secretion be assumed.

Physiology

Gastroenteropancreatic hormones are one of the factors regulating the digestive process. The stomach is an important control centre for digestion, and the ingestion of nutrients is a stimulus for the release of these hormones. For a number of them active digestion and absorption of nutrients in the stomach and upper small intestine are necessary for their release. The stomach and upper small intestine generate signals (hormones) that activate a properly coordinated sequence of digestive events. The introduction of nutrients into the stomach and subsequently the upper small intestine causes rapid release of some of these hormones. Carbohydrate ingestion rapidly causes the release of gastric inhibitory polypeptide,[21] neurotensin[22] and enteroglucagon,[23] which suggests that carbohydrate absorption alone cannot stimulate the release of these jejunal and ileal hormones. Fat ingestion causes the release of motilin within 15 minutes, while the intraduodenal instillation of fat has no effect upon plasma motilin concentrations (S.M. Collins and colleagues: unpublished data). These findings suggest that gastric and duodenal hormones may act as control signals for hormone release from jejunal and ileal endocrine cells.

Support for this conjecture comes from a recent report of the isolation of a gastrin-releasing protein from the fundus of the stomach.[24] Despite the luminal exposure of the antral gastrin-producing G-cells there is still a gastric hormone involved in the regulation of gastrin release. Chymodenin, a releasing protein isolated from the upper small intestine, causes the release of chymotrypsinogen specifically from pancreatic acinar cells.[25] These two isolated releasing proteins could be the first of a series of gastroenteric regulatory hormones that control nutrient-induced hormone release from gastroenteropancreatic endocrine cells. It is possible that such regulatory hormones are involved in the capacity of the stomach to send satiety signals to the brain.

Carbohydrate metabolism is the most important metabolic process controlled by gastroenteropancreatic hormones. Pancreatic hormones are fundamental to the regulation of carbohydrate metabolism. Insulin lowers the blood sugar level, while glucagon increases it. The fine tuning of insulin and glucagon release could be controlled by pancreatic islet somatostatin and thyrotropin releasing hormone. The former inhibits the release of both insulin and glucagon;[26] the latter enhances arginine-induced glucagon release.[27] Augmented insulin responses to ingested as compared with intravenously administered glucose have revealed a significant contribution of extrapancreatic hormones (incretins) to the control of carbohydrate homeostasis.[28] Gastric inhibitory polypeptide (GIP), or glucose-induced insulin-releasing polypeptide, is the best characterized incretin. In normoglycemia this hormone is without effect, but it enhances insulin release when the blood sugar level rises.[29] The released insulin then inhibits further release of gastric inhibitory polypeptide. Thus, circulating glucose concentrations result partly from a complex interaction of gastroenteropancreatic hormone activities.

Gastric acid secretion is another metabolic process regulated by these hormones. Gastrin released from antral endocrine cells stimulates gastric acid secretion.[30] Until recently it was believed that this process occurred via an endocrine pathway. The detection of gastrin in gastric juice raised the possibility that luminal gastrin might directly induce the parietal cells to release acid. Recent studies have shown that luminal gastrin can be detected subsequently in the circulation.[18] Luminal gastrin may have a physiologic role in the regulation of gastric acid secretion. Furthermore, luminal hormone release may have to be generally considered as a significant physiologic phenomenon for all hormones produced in open endocrine cells.

Gastric inhibitory polypeptide released by acid from the upper small intestine is a potent inhibitor of gastric acid secretion.[31] For proper assessment of the hormonal contribution to the control of gastric acid secretion it would be necessary to consider the circulating concentrations of gastrin and gastric inhibitory polypeptide concomitantly. With this approach one could assess the possibility that an elevated level of the latter might cancel out the stimulatory effect of an elevated level of the former.

Pancreatic exocrine function is controlled by gastroenteropancreatic hormones. Secretin stimulates pancreatic bicarbonate and juice flow,[32] while cholecystokinin stimulates enzyme secretion.[33] Chymodenin specifically stimulates chymotrypsinogen release.[34] Pancreatic polypeptide, a new pancreatic hormone, inhibits pancreatic exocrine function.[35] The cells containing pancreatic polypeptide are in the islet periphery and exocrine parenchyma. These locations may have functional significance since human pancreatic polypeptide has been detected in pancreatic juice[36] and may play a role in the inhibition of pancreatic exocrine function.

Gastroenteropancreatic hormones are involved in the control of gallbladder function, gastrointestinal motility and blood flow. Cholecystokinin causes gallbladder emptying[33] and pancreatic polypeptide inhibits it.[35] Motilin affects gastrointestinal motility; its effects are seen on the lower esophageal sphincter, gastric emptying and migrating myoelectric complex activities.[37] These activities occur with what seem to be physiologic doses of motilin; however, the physiologic significance of motilin as a controlling factor remains to be established.

Vasoactive intestinal polypeptide (VIP) is a potent vasodilator found in endocrine and nerve cells.[38] Its presence in nerves and the absence of a meal-induced change in its plasma concentrations raise the question of the significance of the circulating hormone. If vasoactive intestinal polypeptide functions as a neurotransmitter or a neural mediator, then plasma measurements may be without meaning. The predicament with this hormone has focused attention on the prospect that gastroenteropancreatic hormones may play dual roles as circulating hormones and neurotrans-

mitters. With some of them the neurotransmitter function may be prominent.

Pathophysiology

The only important metabolic abnormality related to a gastroenteropancreatic hormone imbalance is diabetes mellitus. Juvenile-onset diabetes is usually associated with complete lack of insulin and is controlled by replacement therapy with daily insulin injections. Maturity-onset diabetes is usually associated with sluggish release of insulin and is controlled commonly by diet or by sulfonylurea or biguanide therapy, or both. A recent study has shown a clear correlation between the insulin secretory reserve and the frequency of diabetic complications (retinopathy and sensory neuropathy).[39] Persons with diabetes whose peak insulin response was less than 60 μU/ml were free of complications. This finding suggests that maintenance of an adequate insulin secretory reserve may help prevent diabetic complications. One approach to minimizing the glycemic stress upon the pancreas would be greater use of dietary fibre by persons with diabetes.[40]

Metabolic abnormalities are also caused by the autonomous release of pancreatic hormones from tumours. The released hormones must cause a serious metabolic insult for the tumour to be detected. Most such tumours produce a number of hormones and are of pancreatic origin. There is evidence to suggest that the tumour cells develop from pluripotent pancreatic duct cells that have the potential to produce all gastroenteropancreatic hormones;[41] they do not develop from pancreatic islet endocrine cells. Such tumours have been detected in the duodenum[42] and the lung.[43] Since most of these tumours produce a number of hormones some may go undetected because while one hormone stimulates a metabolic process another inhibits it, so that the net result is no observed metabolic disturbance. Tumours containing insulin, glucagon, somatostatin, gastrin, human pancreatic polypeptide, gastric inhibitory polypeptide and vasoactive intestinal polypeptide have been described.[44] Those producing insulin and gastrin are the most commonly detected since their effects upon carbohydrate metabolism and gastric acid secretion are readily recognized.

Study of insulinomas[45] and gastrinomas[42] has produced a number of interesting observations. Each tumour has unique biochemical and morphologic characteristics. Hormone concentration, hormone component distribution, presence and type of cellular granules and immunohistochemical staining with different hormone antisera vary from one tumour to another. Because of this tumour heterogeneity each case must be treated as unique, with previous clinical experience used as a guideline.

The watery diarrhea (Vernor–Morrison) syndrome is a good example of a heterogeneous tumour and disease whose hormonal factors are poorly understood.[46] A number of disease mechanisms culminate in watery diarrhea, which is not always associated with hypokalemia and achlorhydria. Laxative abuse can result in some of the symptoms of the Vernor–Morrison syndrome.[47] The number of causes of watery diarrhea is almost equalled by the number of hormones suggested as active mediators; these include gastrin and glucagon,[48] secretin,[49] gastric inhibitory polypeptide,[50] vasoactive intestinal polypeptide[43] and human pancreatic polypeptide.[51] Vasoactive intestinal polypeptide is the most popular candidate at the moment; however, since it has not been detected in all the tumours it cannot be the sole agent. It seems that watery diarrhea is produced by the combination of a number of hormones and that each patient has an unique hormonal spectrum.

Plasma concentrations of gastroenteropancreatic hormones are altered as the result of a number of diseases. These alterations occur when physiologic feedback mechanisms are absent (e.g., in achlorhydria, which results in elevated gastrin levels,[52] and in diabetes, which results in elevated levels of gastric inhibitory polypeptide[29]) and when hormone catabolism is diminished (e.g., in renal disease, which results in elevated levels of gastrin,[53] glucagon,[54] gastric inhibitory polypeptide,[55] human pancreatic polypeptide[56] and motilin[57]). The concept of gastroenteropancreatic hormone profiles may be valuable in assessing a number of hormonal activities in one disease.

Perspectives

An important outstanding question in gastrointestinal endocrinology is what functions gastroenteropancreatic hormones really have in digestion. Each hormone has specific effects upon digestive functions. Postprandial changes in plasma hormone concentrations occurring concomitantly with changes in digestive function suggest a causal relationship. However, it is not clear if the postprandial hormone responses are sufficient to induce the observed changes in digestive function. To clarify this situation it is necessary to relate changes in endogenous hormone concentrations to digestive function. It would be valuable to assess digestive function in groups with altered circulating concentrations of gastroenteropancreatic hormones. Perhaps the elevated plasma concentrations of these hormones in patients with renal disease cause poor digestive function, which results in poor nutritional status.[58]

Lack of a postprandial circulatory response cannot be taken as evidence against a hormone's having a physiologic role since a number of these hormones also reside in nerve cells. Measurement of their circulating concentrations may be inappropriate. Further study will reveal if the main function of these hormones is that of a neurotransmitter or a neural mediator. Lack of a circulatory response can also be interpreted as meaning that an open endocrine cell is releasing its hormone into the lumen; this would not be detectable in the periphery. Because of these possible activities of gastroenteropancreatic hormones, circulating concentrations and responses cannot be important criteria in the assessment of the physiologic status of a hormone.

Gastrointestinal endocrinology is beginning to reveal the intricacies

of hormonal involvement in digestion. Further extensive study is necessary to approach many of the outstanding questions.

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