

Gastrointestinal hormones and apudomas

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Interest and developments in gastrointestinal hormones “exploded” since gastrin was isolated by Gregory et al¹ in 1964. Progress in radioimmunoassay and chromatography had been responsible for the “unleashing” of peptides whose nomenclature and properties are scarcely defined before newer peptides are identified and reported. It sometimes seems that there are more peptides than chemical effects attributed to them.

Coupled with advances in the chemistry of peptides has been their identification in several clinical syndromes. These syndromes are now more easily recognized than previously because of increasing awareness and the availability of specific therapy (e.g., cimetidine for Zollinger-Ellison syndrome).

Basic information about these hormones has been summarized in three recent reviews.²⁻⁴ In this paper, the three identified hormones (gastrin, secretin, and cholecystokinin-pancreozymin) are discussed, and also several of the candidate hormones (peptides that await further clarification before classification as hormones), their sites of origin, mechanism of action, and relation to clinical syndromes.

Cells of origin

Many peptides and hormones may share a common cell of origin. This concept was popularized by Pearse et al^{5,6} who noted the structural and chemical similarities of these cells. Anatomically, the cells are similar to ganglion cells of the neural crest. These cells also share chemical similarities (demonstrated by histochemical techniques). Five of these properties are high fluorogenic amine content, amine precursor uptake, amino acid decarboxylase, side-chain carboxyl groups, and specific immunochemical properties. These common characteristics have led to the acronym APUD cells for amine precursor uptake and decarboxylase cells. The current list of these cells includes at least 24 specific cells in the stomach, thyroid, islets of Langerhans (pancreas), duodenum and small intestine, large intestine and anterior pituitary.

Early investigations showed the origin of APUD cells to be from the neural crest. These cells have been shown to migrate to the foregut, midgut, and hindgut. If this hypothesis is correct, the origins date back 500 million years in lower vertebrates. Not all peptide secreting cells are APUD cells. Those from the parathyroid and most cells of the anterior pituitary are not included in this classification. These totipotent cells may become overactive and by hyperplasia, neoplasia, or dedifferentiation secrete one or more peptides and cause a variety of syndromes.

Mechanism of action

The mechanism of action for most hormones in man has not been defined. The most popular hypotheses

involve cyclic AMP, cyclic GMP, and adenylylase.^{7,8} The association between cyclic nucleotides and gastrointestinal hormones was suggested by Sutherland and Rall⁹ in 1958. A small heat-stable compound found in cellular membranes capable of stimulating glycogenolysis was isolated. This was 3',5'-cyclic AMP, and it is likely the cellular or "second" messenger (the circulating hormone is the first messenger). An important component in this system is adenylylase, an enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic AMP and pyrophosphate. Some hormones can penetrate the cell membrane directly (steroids, estrogens, androgens), but most peptides cannot. For these hormones a specific binding site is present on the cell. Little is known about the sites or numbers of receptors except they are numerous (600 to 1000 beta-adrenergic receptors may exist on each turkey erythrocyte).⁷ The binding site and affinity for receptors are specific. Little is understood about the coupling between hormone and receptor, although phospholipids may participate. Cations as Mg^{+} and Ca^{++} may influence adenylylase activity as well. Abnormalities in adenylylase are more than theoretical as diseases associated with defects in this system. These include cholera, pseudo-hypoparathyroidism, nephrogenic diabetes insipidus, and glycogen storage disease.

While enzymatic action of adenylylase can activate ATP to cyclic AMP, this is the first of the intracellular steps necessary before a cellular enzymatic function can be produced. Cyclic AMP activates a specific protein kinase which has two subunits, regulatory and catalytic. It is postu-

lated that a joined subunit is inactive but cyclic AMP dissociates these units, liberating a free catalytic component, the activated enzyme. There are many effects of cyclic AMP including contraction of the myocardium, relaxation of smooth muscle, aggregation of platelets, stimulation of exocrine pancreatic secretion, and perhaps increasing gastric acid secretion (through one or more mechanisms).

In vitro studies have shown that secretin, glucagon, vasopressin, steroids, and vasoactive intestinal polypeptide (VIP) increase 3',5'-cyclic AMP levels. Gastrin, CCK-PZ, pancreatic polypeptide, and prostaglandins do not increase cyclic AMP suggesting another mechanism of action.⁸

Gastrin

Most basic and clinical research has been with gastrin. In 1905 Edkins¹⁰ presented a paper "On the Chemical Mechanism of Gastric Secretion" in which he reported that antral mucosal extracts in anesthetized cats stimulated gastric acid secretion. He named the hormone gastrin (for gastric secretin). This work was reproduced and clarified by Komarov¹¹ in 1938. A significant advance was made by Gregory et al¹ in 1964 when they isolated a pure gastrin extract from hog antral mucosa. This extract was a polypeptide containing 17 amino acids in two peptide molecules (gastrin I and II). Many refinements and purifications have followed. There are at least five gastrin molecules. These include minigastrin (G13), little gastrin (G17), big gastrin (G34), consisting of at least six molecules, big big gastrin and a larger molecule (component I of Rehfeld).¹² The lat-

ter two molecules await chemical and biological definition.

Most circulating gastrin in man is produced in the antrum. Less is produced in the duodenum and upper jejunum (the antrum contains 5 to 10 times more gastrin than the duodenum). The pancreatic islets have little gastrin. Ninety percent of antral mucosal gastrin is G17 and this predominates in man. In pernicious anemia and the Zollinger-Ellison syndrome G34 is predominant. Walsh¹³ studied plasma clearance and gastric secretory activity of G17, G34, and G13. G34 was cleared more slowly than G17 or G13 and was as potent as G17 in stimulating gastric acid secretion; G13 was half as potent. Catabolism of the molecule is dependent on its size. The half life of infused G17 and G34 in dogs was 3" and 15", respectively. The larger forms are less readily metabolized. The kidneys play a major role in gastrin catabolism.^{14, 15} Several chemicals as well as mechanical stimuli release gastrin. Some of this work is based on animal experiments in which the stimulus and effect differ from man. In man the natural stimulus for gastrin release is food. High protein meals and the amino acid glycine are potent releasers of gastrin. Fat, carbohydrates, and intragastric alcohol are poor stimulants.

Mechanical distention of the stomach may release gastrin and cause acid hypersecretion; this work was in animals and not man. Recently, Olbe¹⁶ showed that mechanical distention of the antrum caused acid hypersecretion, but the mechanism was through a pyloro-oxynitic reflux not gastrin.

The vagal release of gastrin has been demonstrated by sham feeding

in animals and duodenal ulcer patients. When sham feeding was tested in normal man there was no gastrin release. It is likely that the mechanism of acid secretion is direct vagal stimulation. This variation in behavior may be due to a vagal inhibitor that is present in normal man but lacking in duodenal ulcer patients. Other hormones and chemicals may release gastrin (calcium, epinephrine, and calcitonin).^{17, 18}

Inhibition of gastrin release is primarily due to gastric acid. Conversely, any disease with decreased acid secretion, e.g., pernicious anemia, may be accompanied by increased levels of serum gastrin. Of increasing importance has been hormonal inhibition of gastrin secretion by other peptides—VIP, glucagon, and secretin.

Actions of gastrin

The effects of gastrin on the gastrointestinal tract in man are pharmacologic and physiologic. A pharmacologic effect is one that may not be present with ordinary concentrations of circulating hormone. There is disagreement about what is a pharmacologic effect of gastrin and what is a physiologic one. At least three actions of gastrin are physiologic: (1) stimulation of gastric acid secretion, (2) stimulation of pepsin secretion, and (3) a trophic effect on the stomach.

The major effect of gastrin is to increase gastric acid secretion. The mechanism of action which ultimately involves the parietal cell is complex, but probably involves an interaction between acetylcholine, histamine, and gastrin. Gastrin injections in rats are followed by a decrease in histamine content of the

stomach and the release of acetylcholine. Blockage of acetylcholine or histamine will diminish these effects of gastrin. The increased secretion of pepsin by gastrin is secondary to acid secretion.

The third effect of pepsin by gastrin on the stomach is trophic.¹⁹ This action is confined to the oxyntic area of the stomach, duodenum, and pancreas. Cellular integrity and mucosal blood flow in hypergastrinemic states are better maintained. Experimentally, when continuous infusions of gastrin were given, oxyntic mitosis, increased DNA and RNA synthesis was noted. In comparison no similar effect was seen after histamine infusion. Furthermore, rat stomachs perfused with pentagastrin showed a 100% to 200% increase in incorporation of amino acids.

Other pharmacologic actions of gastrin include stimulation of water and electrolyte secretion from stomach, pancreas, liver, small intestine; stimulation of the lower esophageal sphincter, decrease in gastric emptying, relaxation of the pyloric sphincter and ileocecal valve. Gastrin also potentiates the release of gastrin inhibitory polypeptide (GIP), VIP, insulin, and calcitonin.

Clinical application

The major impact of serum gastrin determinations done by radioimmunoassay has been to diagnose the Zollinger-Ellison syndrome. Although gastrin levels are elevated in many diseases, there are few in which levels four to five times normal are found. These include the Zollinger-Ellison syndrome, retained antrum, pernicious anemia, and hypergastrinemic hyperchlorhydric duodenal ulcer.²⁰

Normal values of serum gastrin

will vary at each laboratory, but as specificity of the assay and experience increase, the values decrease. Normal values in our laboratory are 100 ± 50 pg/ml. Values depend on the laboratory, age of the subject, and obviously the amount of acid in the stomach.

While absolute values of gastrin in the Zollinger-Ellison syndrome vary, levels four times normal should be suspected.²¹ The importance is obvious. When the Zollinger-Ellison syndrome is untreated or unrecognized, the mortality is still high (78%). Most effects of this syndrome are due to gastrin overproduction. These include increased pancreatic output, increased lower esophageal sphincter pressure, and massive gastric hypersecretion.

Sixty percent of patients with the Zollinger-Ellison syndrome have malignant pancreatic tumors and nearly half have metastasized at the time of surgery. Fewer patients have benign tumors, hyperplasia, or tumors of ectopic gastrin production.²¹ When the diagnosis is clear, total gastrectomy is mandatory, except in the rare instance when isolated duodenal wall or ectopic tumors are present. When the diagnosis is in doubt stimulatory tests with secretin and calcium are done.^{18, 22} These tests stimulate gastrin release in Zollinger-Ellison syndrome, but not in duodenal ulcer or "G" cell hyperplasia. The other diseases that are marked by high levels of serum gastrin should be differentiated by careful history, biopsy, and stimulatory tests.

Antral or "G" cell hyperplasia is a controversial syndrome that is marked by high levels of serum gastrin but no rise in serum gastrin with antral stimulation. Immunofluores-

cent study of the "G" cells is positive.²³

The role of gastrin in duodenal ulcer disease is unclear; high, low, and normal values have been reported.²⁴ When increased absolute values may be difficult to demonstrate in duodenal ulcer patients a defect in inhibition may be present. Lastly, disease which impairs gastrin catabolism (e.g., renal disease), may also be associated with increased levels of serum gastrin.

Secretin

Secretin was the first hormone identified by Bayliss and Starling²⁵ in 1902. A denervated loop of jejunum in an anesthetized dog was isolated and a small amount of hydrochloric acid was placed in the lumen. This was followed by an increased flow of pancreatic juice. Despite this early work nearly 60 years elapsed before this hormone was synthesized by Bodanszky et al²⁶ in 1966. A reliable, reproducible radioimmunoassay for secretin is still difficult. Many early assays may have been contaminated by other members of the secretin family (VIP, glucagon). Much work on this assay has been done by Bloom²⁷ who, in addition to establishing normal values in man, has defined some of the physiologic effects of secretin.

The site of production of secretin is the S cell in the duodenal mucosa. The molecule has 27 amino acids and it is strongly basic because of arginine and histidine units.

Although a variety of properties and effects have been attributed to secretin, it is difficult to know what is a pharmacologic effect and what is physiologic. The presumed major effects of secretin are thought to be an

increased volume of pancreatic bicarbonate, increase in pancreatic blood flow, decrease in gastric acid output to food and gastrin, and insulin releasing effect inhibition of glucagon release, increase in pepsin output, and perhaps lowering of the esophageal sphincter pressure.

Because of difficulties in secretin assay it is difficult to know what stimulates its release and what are its physiologic actions. The strongest stimulus for secretin release is acid in the duodenum, particularly a pH of 4.5 or less. Lowering the pH below 3.0 does not increase pancreatic bicarbonate output (assuming titratable acid is constant).²⁸ Vagal stimulation does not increase secretin output, but vagotomy, atropine, or local anesthetics applied to the duodenal mucosa do diminish the release of secretin. Sugar in the duodenum, oral feeding, and products of fat and protein and amino acids are not, as was previously thought, effective stimuli for secretin release in man.²⁹

The probable physiologic actions of secretin include an increase in pancreatic output of water, electrolytes, trypsin and insulin, an increased volume and electrolyte output of bile by the liver, decreased gastric emptying in the stomach, reduced resting and gastrin stimulated pressure of the lower esophagus and decreased motility of the duodenum. These effects are subject to modification as techniques to measure secretin improve.

The clinical applications of secretin assay are presently limited. In duodenal ulcer disease impaired secretin release to duodenal acidification has been shown. Elevated tumor levels have been reported by Schmitt et al³⁰ in a patient with the watery diarrhea

syndrome. As the radioimmunoassay becomes available and more specific, its applications will increase and precise data will be available.

Cholecystokinin-pancreozymin

Ivy and Oldberg³¹ noted the fat in the intestine stimulated gallbladder contraction. Fifteen years later, in 1943, Harper and Raper³² noted increased pancreatic secretion in similar experiments. It is now recognized that both actions are hormonal, and because of its first activity it is called cholecystokinin or CCK-PZ.

The amino acid sequence has been determined, but the hormone has not yet been synthesized. CCK has two molecules, one of 33, the other 39 amino acids. The potency of CCK lies in its eight terminal amino acids.³³

Immunofluorescent studies have localized the cell of production to the mucosa of the jejunum and duodenum. Measurement of CCK has been difficult due to limited methods and a limited amount of pure CCK-PZ available to develop a radioimmunoassay.^{33, 34} Go and Reilly³³ have cautioned against over-interpretation or over-reliance on the present CCK assays.

Stimuli to CCK release include duodenal, amino acids, food, fatty acids, and hydrochloric acid. Duodenal perfusions of amino acids have been followed by CCK release, particularly phenylalanine and tryptophan.³⁵

Fatty acids longer than eight chains are effective releasers of CCK-PZ. In contrast hydrogen ions are weak releasers of CCK-PZ. The mechanism of action of CCK may be through cyclic guanosine 3',5' monophosphate.

Clinical applications of CCK-PZ

are limited because of the problems in its measurement and availability. Elevated levels have been found in the Zollinger-Ellison syndrome and in one patient with watery diarrhea.³⁰ There may be practical applications of CCK because of its latter properties. As a powerful stimulant to small bowel contractility it may have a role in ileus. In contrast to the above three hormones, the remaining peptides await promotion to hormonal status. Many are newly described or discovered and will be of value in the years ahead.

Gut glucagon (enteroglucagon)

Enteroglucagon is a hormone different and separate from pancreatic glucagon. The term gut glucagon is descriptive and includes at least three peptides that arise from the mucosa of the small intestine.^{4, 36} Two of these molecules have a molecular weight of 3500 (enteroglucagon) and the third has a molecular weight of 2900 (glucagon-like immunoreactivity GII). The existence of enteroglucagon was suggested by Unger et al³⁷ in 1961 and eluted by chromatography in 1968.

The biochemical structure of gut glucagon is similar to secretin and VIP. Fourteen amino acids are identical and in similar positions to the secretin molecule. Two molecular forms of enteroglucagon exist in avians. The cells of glucagon production in many species (rat, baboon, man, dog, and cat) are the gastric fundus; GII arises from cells of the intestine (many of which are in the ileum).

Radioimmunoassay techniques have been developed that differentiate pancreatic glucagon, gut glucagon, and enteroglucagonoid hor-

mone. With this assay it will be possible to better define the actions of each.³⁸

Both forms of gut glucagon are glycogenolytic and stimulate mobilization of carbohydrate stores. Enteroglucagonoid increases rapidly after the ingestion of food. This response is enhanced by gastric resection or bypass of the pylorus. The release of enteroglucagonoid is accompanied by a rise in serum insulin. These actions may be responsible for lowering blood glucose and lessening symptoms of the dumping syndrome (elevated levels have been found in dumping). Increased levels have also been present in the watery diarrhea syndrome. Even more unusual has been the syndrome of necrolytic migratory erythema, hyperglycemia, dilated bowel, and benign or malignant pancreatic tumors that secrete glucagon.³⁹ Cure may follow resection of a solitary pancreatic tumor.

VIP

VIP is a 28-amino acid peptide residue with broad biological activities on the cardiovascular, respiratory, and gastrointestinal systems.

This peptide was first isolated by Said and Mutt.⁴⁰ It is distributed throughout the intestinal tract with highest concentrations in the ileum, jejunum, and colon. Most studies of the biological actions of VIP have been in animals. Its peripheral vasodilatory actions resulted in its name. In the guinea pig it dilates the trachea and pulmonary vessels. In the gastrointestinal tract it inhibits histamine and pentagastrin stimulated acid secretion; it inhibits pepsin secretion and relaxes smooth muscle. Its effects on the pancreas include electrolyte and water secretion and

an increase in bile flow. In the small intestine it stimulates secretion, increases mucosal levels of cyclic AMP and stimulates glycogenolysis, lipolysis and increases insulin release.⁴¹⁻⁴³

The clinical importance and relevance of VIP have been in its isolation in serum and tissue of patients with the watery diarrhea syndrome and more recently in a patient with carcinoid syndrome.⁴⁴ The watery diarrhea syndrome is caused by benign or malignant pancreatic tumors, islet cell hyperplasia, adrenal medullary, or retroperitoneal tumors. The syndrome is characterized by severe watery diarrhea, hypokalemia and hypochlorhydria or achlorhydria. At least 75 cases have been reported, many in the past few years. The diagnosis should be suspected from the history, particularly when other more common causes of diarrhea are excluded. Stool potassium levels are elevated, hypokalemia is present, and gastric acid may be absent or the levels low. When benign tumors are present cure may follow resection. For malignant tumors that have metastasized, steroids, streptozotocin, 5-fluorouracil, or radiation therapy may relieve symptoms.

GIP

GIP was isolated from the CCK-PZ molecule by Brown et al⁴⁵ in 1969 and was named because it inhibited stomach motility and secretion. This peptide has 43 amino acids and a molecular weight of 5100. In humans GIP has been localized to the duodenum and jejunal mucosa.

Glucose may release GIP and there may be a lesser peak with fat stimulation. GIP may now be measured by radioimmunoassay. The levels in normal man are 250 pq/ml. The clinical

applications of GIP are limited. Earlier reports of elevated GIP levels in watery diarrhea were probably inaccurate.⁴⁶

Bombesin and other candidate hormones

A peptide isolated from the skin of frogs that stimulated gastrin release from the antrum stimulates pancreatic secretion and contraction of the gallbladder (all in dogs).^{47, 48} Its activities in man are unknown. Motilin is an 11-amino acid polypeptide with a molecular weight of 2700. Its cell of origin is the enterochromaffin cells of the intestine. This peptide enhances motility of transplanted and denervated fundic pouches. Radioimmunoassay is available but clinical effects and activities are unknown.

Chymodenin is a basic polypeptide with a molecular weight of 5000 isolated from impure secretin and cholecystokinin.⁴⁹ Studies in rabbits have shown a rise in pancreatic secretion rich in chymotrypsinogen. This suggests that specific pancreatic enzymes may be controlled by a specific regulator. The implications of this concept are both intriguing and unconventional.

Avian pancreatic polypeptide (APP) was isolated by Kimmel et al⁵⁰ during the purification of insulin. The biological actions may vary with species. In dogs it stimulated basal secretion of acid and inhibited pentagastrin stimulated secretion. Also in dogs low doses of APP relaxed the gallbladder without affecting gastric acid or bile flow. A radioimmunoassay species specific is available. APP has been isolated by immunofluorescence studies in apudomas.

Coherin is a polypeptide isolated

from posterior pituitary glands; it is chemically distinct from oxytocin and vasopressin.⁵¹ When injected into dogs it inhibited jejunal contractions followed by propagated contractions lasting 2 to 5 hours.

Urogastrone is an inhibitory substance found in the urine of man and animals capable of inhibiting gastric acid secretion.⁵² Pepsin response or cholinergic stimulation is also reduced. This hormone may be active in man. It may be measured by radioimmunoassay but the site of production is unknown.

Bulbogastrone is released from the duodenal bulb by acidification.⁵³ It has not been chemically identified but its mechanism of action is believed to be inhibition of acid secretion. Experimentally the duodenal bulb is the specific site of acid inhibition as postbulbar duodenal segments do not have these inhibitory properties. Inhibition of gastrin stimulated acid secretion by all stimuli follows bulbogastrone injection. Further studies are needed to define its structure and physiological properties.

Enteroxyntin, a humoral mechanism caused by the introduction of food into the small intestine resulting in gastric acid secretion was observed by Gregory and Ivy in 1941.⁵⁴ The nature of this substance has not been identified positively. Much work has been done by Orloff et al.⁵⁵ The substance does not appear to be histamine or gastrin, extra antral gastrin or CCK-PZ. Because this substance arises from the small intestine and stimulates the oxyntic cells, Grossman⁵⁶ suggested the name entero-oxyntin. It may arise from the mucosa of the small intestine. It may be the humoral mediator of acid hyperse-

cretion following portosystemic shunts or small bowel resection. There is indirect evidence for this.

The variety of peptides and hormones that arise from the intestinal tract has rapidly increased in the past 10 years. I suspect radioimmunoassay will be developed for all of these peptides and clinical applications or physiologic functions then identified. Perhaps the next step will be synthesis of these substances so that clinical use may stimulate deficient biochemical actions or treat clinical syndromes caused by excess production of circulating peptides.

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