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Leonard R. Johnson

胃肠道生理学

Gastrointestinal Physiology

SIXTH EDITION

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Gastrointestinal Physiology

Sixth Edition

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Gastrointestinal Physiology

The Mosby Physiology Monograph Series

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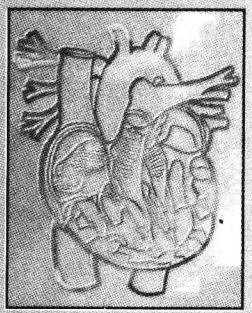

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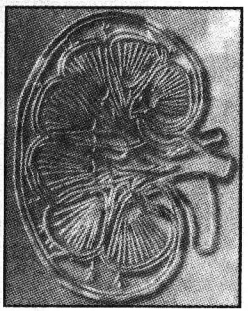

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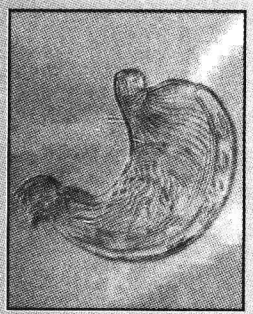

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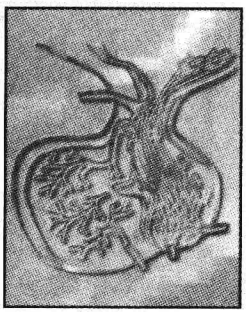

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Preface

The first edition of *Gastrointestinal Physiology* appeared in 1977. It developed as a result of the authors' teaching experiences and the need for a book on gastrointestinal physiology written and designed for medical students and beginning graduate students. This sixth edition is written by the same authors and directed to the same audience. As with any new edition, those involved usually believe that it is significantly better than the previous one. The contributors and I feel strongly that this edition is such an improvement. All chapters contain significant amounts of new material and have been brought up-to-date with current information, without introducing undue amounts of controversy to confuse students.

The sixth edition has two added features that we feel will assist students in understanding the material. First, key words now appear in bold type the first time they are defined. Second, a summary of the major concepts is included at the end of each chapter. This is meant to aid the student in organizing his or her thoughts about the material presented.

The entire book is still written by the original authors. I am again indebted to them for their ability to transmit their expertise in a lucid and concise manner. Their contributions arrived on schedule, and anyone who has had the experience of editing a volume realizes how rare that is.

We are all grateful to our own students for pointing out ways to improve the book. Numerous colleagues in other medical schools and professional institutions have added their suggestions and criticisms as well. We are thankful for their interest and help, and we hope that anyone having criticisms of this edition or suggestions for improving future editions will transmit them to us.

Finally, I thank Ms. Easter Jenkins for typing my own chapters and helping with the communications and organizational work that are a necessary part of such a project.

Leonard R. Johnson

Contents

CHAPTER 1

Regulation

Peptides of the Gastrointestinal Tract

LEONARD R. JOHNSON

THE FUNCTIONS OF THE GASTROINTESTINAL (GI) tract are regulated by peptides, derivatives of amino acids, and a variety of mediators released from nerves. All GI hormones are peptides, but it is important to realize that not all peptides found in digestive tract mucosa are hormones. The GI tract peptides can be divided into endocrines, paracrines, and neurocrines, depending on the method by which the peptide is delivered to its target site.

Endocrines, or **hormones,** are released into the general circulation and reach all tissues (unless excluded from the brain by the blood-brain barrier). Specificity is a property of the target tissue itself. Specific receptors, which recognize and bind the hormone, are present on its target tissues and absent from others. There are five established GI hormones; in addition, some GI peptides are released from endocrine cells into the blood but have no known physiologic function. Conversely, several peptides have been isolated from mucosal tissue and have potent GI effects, but no mechanism for their physiologic release has been found. Members of these latter two groups are classified as candidate hormones.

Paracrines are released from endocrine cells and diffuse through the extracellular space to their target tissues. Their effects are limited by the short distances necessary for diffusion. Nevertheless, these agents can affect large areas of the digestive tract by virtue of the scattered and abundant distributions of the cells containing them. A paracrine agent can also act on endocrine cells. Thus a paracrine may release or inhibit the release of an endocrine substance, thereby ultimately regulating a process remote from its origin. Histamine, a derivative of the amino acid histidine, is an important regulatory agent that acts as a paracrine.

Some GI peptides are located in nerves and may act as **neurocrines** or neurotransmitters. A

neurocrine is released near its target tissue and needs only to diffuse across a short synaptic gap. Neurocrines conceivably may stimulate or inhibit the release of endocrines or paracrines. **Acetylcholine** (ACh), though not a peptide, is an important neuroregulator in the GI tract. One of its actions is to stimulate acid secretion from the gastric parietal cells.

■ GENERAL CHARACTERISTICS

The GI tract is the largest endocrine organ in the body, and its hormones were the first to be discovered. The word *hormone* was coined by W. B. Hardy and used by Starling in 1905 to describe secretin and gastrin and to convey the concept of bloodborne chemical messengers. The GI hormones are released from the mucosa of the stomach and small intestine by nervous activity, distention, and chemical stimulation coincident with the intake of food. Released into the portal circulation, the GI hormones pass through the liver to the heart and back to the digestive system to regulate its movements and secretions. These hormones also regulate the growth of the stomach, small and large intestines, and pancreas.

The GI peptides have many different types of actions. Their effects on water, electrolyte, and enzyme secretion are well known, but they also influence the motility, growth, and release of other hormones, as well as intestinal absorption. Many of these actions overlap; two or more GI peptides may affect the same process in the same direction, or they may inhibit each other. Many of the demonstrated actions of these peptides are pharmacologic and do not occur under normal circumstances. This chapter is concerned primarily with the physiologic effects of the GI peptides.

The actions of the GI peptides also may vary in both degree and direction among species. The actions discussed in the remainder of this chapter are those occurring in humans.

■ DISCOVERY

Four steps are required to establish the existence of a GI hormone. First, a physiologic event such as a meal must be demonstrated to provide the stimulus to one part of the digestive tract that subsequently alters the activity in another part. Second, the effect must persist after all nervous connections between the two parts of the tract have been severed. Third, from the site of application of the stimulus a substance must be isolated that, when injected into the blood, mimics the effect of the stimulus. Fourth, the substance must be identified chemically, and its structure must be confirmed by synthesis.

Five GI peptides have achieved full status as hormones. They are secretin, gastrin, cholecystokinin (CCK), gastric inhibitory peptide (GIP), and motilin. There is also an extensive list of "candidate" hormones whose significance has not been established. This list includes several chemically defined peptides that have significant actions in physiology or pathology but whose hormonal status has not been proved. These are pancreatic polypeptide, neurotensin, and substance P. In addition, two known hormones, glucagon and somatostatin, have been identified in GI tract mucosa; their possible function as GI hormones is currently being investigated. Some of these peptides function physiologically as paracrines or neurocrines.

Secretin, the first hormone, was discovered in 1902 by Bayliss and Starling and was described as a substance, released from the duodenal mucosa by hydrochloric acid, that stimulated pancreatic bicarbonate and fluid secretion. Jorpes and Mutt isolated it and identified its amino acid sequence in 1966. It was synthesized by Bodanszky and coworkers later the same year.

Edkins discovered **gastrin** in 1905, stating to the Royal Society that "in the process of the absorption of digested food in the stomach a substance may be separated from the cells of the mucous membrane which, passing into the

blood or lymph, later stimulates the secretory cells of the stomach to functional activity." For 43 years investigators were preoccupied by the controversy over the existence of gastrin. The debate intensified when Popielski demonstrated that histamine, a ubiquitous substance present in large quantities throughout the body (including the gastric mucosa), was a powerful gastric secretagogue. In 1938 Komarov demonstrated that gastrin was a polypeptide and was different from histamine. By 1964 Gregory and his colleagues had extracted and isolated hog gastrin; Kenner and his group synthesized it the same year. After 60 years all of the criteria for establishing the existence of a GI hormone had been satisfied.

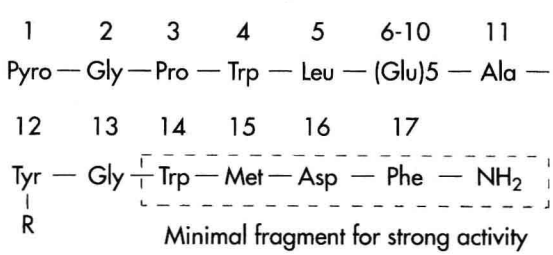
In 1928 Ivy and Oldberg described a humoral mechanism for the stimulation of gallbladder contraction initiated by the presence of fat in the intestine. The hormone was named **cholecystokinin** after its primary action. The only controversy involving CCK was a mild one over nomenclature. In 1943 Harper and Raper described a hormone released from the small intestine that stimulated pancreatic enzyme secretion and accordingly named it *pancreozymin.* As Jorpes and Mutt carried out the purification of these two substances in 1968, it became obvious that both properties resided in the same peptide. For the sake of convenience and because it was the first action described, this hormone was called CCK.

In 1969 Brown and his coworkers described the purification of a powerful enterogastrone from intestinal mucosa. **Enterogastrone** literally means a substance from the intestine *(entero-)* that inhibits *(-one)* the stomach *(gastr-).* By 1971 this peptide had been purified, isolated, sequenced, and named **gastric inhibitory peptide** after its ability to inhibit gastric secretion. Released from the intestinal mucosa by fat and glucose, GIP also stimulates insulin release. Following proof that the release of insulin was a physiologic action of the peptide, GIP became the fourth GI hormone. The insulinotropic effect of GIP requires elevated amounts of serum glucose. For this reason, and because it is doubtful whether the inhibitory effects of the peptide on the stomach are physiologic, it has been suggested that its name be changed to glucose-dependent insulinotropic peptide. In either case it is still referred to as GIP.

Brown and his coworkers also described the purification of **motilin** in the early 1970s. Motilin is a linear 22-amino acid peptide purified from the upper small intestine. During fasting it is released cyclically and stimulates upper GI motility. Its release is under neural control and accounts for the interdigestive migrating myoelectric complex.

■ CHEMISTRY

The GI hormones and some related peptides can be divided into two structurally homologous families. The first consists of gastrin (Figure 1-1) and CCK (Figure 1-2). The 5 C-terminal amino acids are identical in these two hormones. All the biologic activity of gastrin can be reproduced by the 4 C-terminal amino acids. This tetrapeptide, then, is the minimum fragment of gastrin needed for strong activity and is about



Gastrin I, R = H Pyro = pyroglutamyl
Gastrin II, R = SO_3H

Figure 1-1 ■ Structure of human little gastrin (G 17).

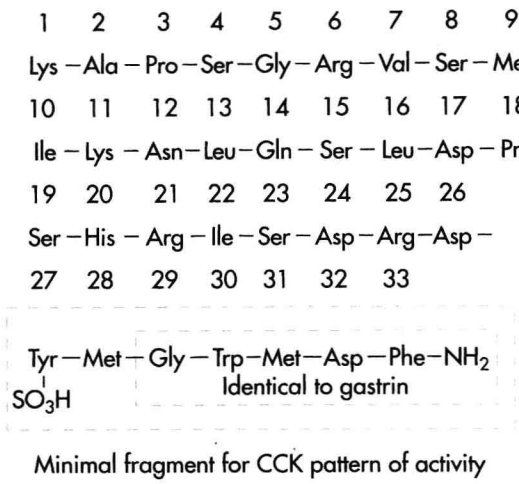


Figure 1-2 ■ Porcine CCK.

one sixth as active as the whole 17-amino acid molecule. The sixth amino acid from the C-terminus of gastrin is tyrosine, which may or may not be sulfated. When sulfated, the hormone is called **gastrin II.** Both forms occur with equal frequency in nature. The N-terminus of gastrin is pyroglutamyl, and the C-terminus is phenylalamide (see Figure 1-1). Note that the NH_2 group following Phe does not signify that this is the N-terminus but that this C-terminal amino acid is amidated. These alterations in structure protect the molecules from aminopeptidases and carboxypeptidases and allow most of them to pass through the liver without being inactivated.

CCK, which has 33 amino acids, contains a sulfated tyrosyl residue in position 7 from the C-terminus (see Figure 1-2). CCK can activate gastrin receptors (e.g., those for acid secretion, also called CCK-B receptors); gastrin can activate CCK receptors (e.g., those for gallbladder contraction, also called CCK-A receptors). Each hormone, however, is much more potent at its own receptors than at those of its homologue. CCK is always sulfated in nature, and desulfation produces a peptide with the gastrin pattern of activity. The minimally active fragment for the CCK pattern of activity is therefore the C-terminal heptapeptide. In summary, peptides belonging to the gastrin-CCK family having a tyrosyl residue in position 6 from the C-terminus or an unsulfated one in position 7 possess the gastrin pattern of activity—strong stimulation of gastric acid secretion and weak contraction of the gallbladder. Peptides with a sulfated tyrosyl residue in position 7 have cholecystokinetic potency and are weak stimulators of gastric acid secretion. Obviously the tetrapeptide itself and all fragments less than 7 amino acids long possess gastrin-like activity.

The second group of peptides is homologous to secretin and includes **vasoactive intestinal peptide** (VIP), GIP, and **glucagon,** in addition to secretin (Figure 1-3). Secretin has 27 amino acids, all of which are required for substantial activity. Pancreatic glucagon has 29 amino acids, 14 of which are identical to those of secretin. Glucagon-like immunoreactivity has been isolated from the small intestine, but the physiologic significance of this **enteroglucagon** has not been established. Glucagon has no active fragment, and like secretin the whole molecule is required before any activity is observed. There is evidence that secretin exists as a helix; thus the entire amino acid sequence may be necessary to form a tertiary structure with biologic activity.

GIP and VIP each have 9 amino acids that are identical to those of secretin. Each has many of the same actions as secretin and glucagon. This group of peptides is discussed in greater detail later in the chapter.

Most peptide hormones are heterogeneous and occur in two or more molecular forms. Gastrin, secretin, and CCK have all been shown to exist in more than one form. Gastrin was originally isolated from hog antral mucosa as a heptadecapeptide (see Figure 1-1), which is now re-

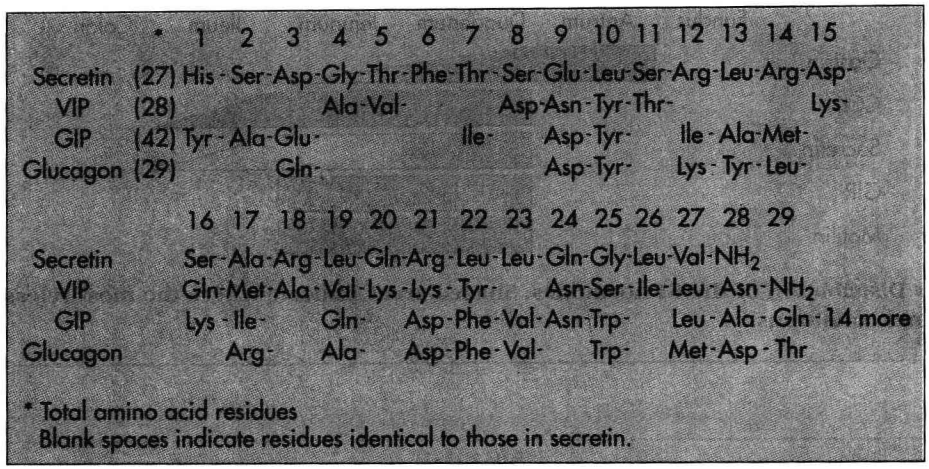


Figure 1-3 ■ Structures of the secretin family of peptides.

ferred to as **little gastrin** or **G 17.** It accounts for 90% of antral gastrin. Yalow and Berson demonstrated heterogeneity by showing that the major component of gastrin immunoactivity in the serum was a larger molecule that they called **big gastrin.** On isolation big gastrin was found to contain 34 amino acids; hence it is called **G 34.** Trypsin splits G 34 to yield G 17 plus a heptadecapeptide different from G 17. Therefore G 34 is not simply a dimer of G 17. An additional gastrin molecule (G 14) has been isolated from tissue and contains the C-terminal tetradecapeptide of gastrin. Current evidence indicates that most G 17 is produced from pro G 17 and most G 34 from pro G 34. Thus G 34 is not a necessary intermediate in the production of G 17.

During the interdigestive (basal) state, most human serum gastrin is G 34. Unlike those of other species, the duodenal mucosa of humans contains significant amounts of gastrin. This is primarily G 34 and is released in small amounts during the basal state. After a meal a large quantity of antral gastrin, primarily G 17, is released and provides most of the stimulus for gastric acid secretion. Smaller amounts of G 34 are released from both the antral and the duodenal mucosa. G 17 and G 34 are equipotent, although the half-life of G 34 is 38 minutes and that of G 17 is about 7 minutes.

■ DISTRIBUTION AND RELEASE

The GI hormones are located in endocrine cells scattered throughout the GI mucosa from the stomach through the colon. The cells containing individual hormones are not clumped together but are dispersed among the epithelial cells. The nature of this distribution makes it virtually impossible to surgically remove the source of one of the GI hormones and examine the effect of its absence without compromising the digestive function of the animal.

The endocrine cells of the gut are members of a widely distributed system termed **amine precursor uptake decarboxylation** (APUD) cells. These cells are all derived from neuroendocrine-programmed cells originating in the embryonic ectoblast.

The distributions of the individual GI hormones are shown in Figure 1-4. Gastrin is most abundant in antral and duodenal mucosa. Most

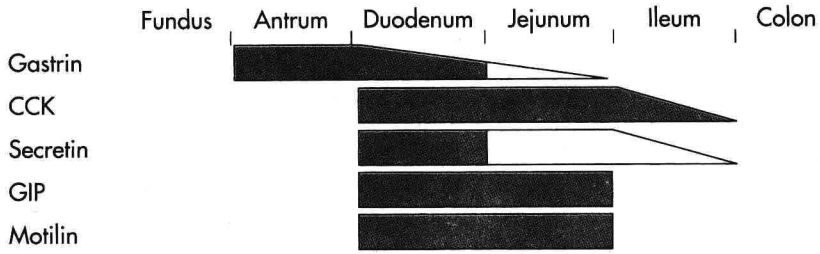


Figure 1-4 ■ Distribution of the GI hormones. Shaded areas indicate where the most release occurs under normal conditions.

TABLE 1-1

Releasers of gastrointestinal hormones

	Hormones				
	Gastrin	**CCK**	**Secretin**	**GIP**	**Motilin**
Protein	S	S	O	S	O
Fat	O	S	S−	S	S−
Carbohydrate	O	O	O	S	O
Acid	I	S−	S	O	S−
Distention	S	O	O	O	O
Nerve	S	O	O	O	S

S, Physiologic stimulus for release; S−, of secondary importance; O, no effect; I, inhibits release physiologically.

of its release under physiologic conditions is from the antrum. Secretin, CCK, GIP, and motilin are found in the duodenum and jejunum.

Ultrastructurally, GI endocrine cells have hormone-containing granules concentrated at their bases, close to the capillaries. The granules discharge, releasing their hormones in response to a number of events that are either the direct or the indirect result of neural, physical, and chemical stimuli associated with eating a meal and the presence of that meal within the digestive tract. These endocrine cells have microvilli on their apical borders that presumably contain receptors for sampling the luminal contents.

Table 1-1 lists the stimuli that are physiologically important releasers of the GI hormones. Gastrin and motilin are the only hormones demonstrated as being released directly by neural stimulation. Protein in the form of peptides and single amino acids releases both gastrin and CCK. Fatty acids containing eight or more carbon atoms or their monoglycerides are the most potent stimuli for CCK release. Fat must be broken down into an absorbable form before releasing CCK, evidence that the receptors for release are triggered during the process of absorption. Carbohydrate, the remaining major foodstuff, does not alter the release of gastrin, secretin, or

CCK but does stimulate GIP release. GIP is also released by fat and protein. The strongest stimulus for secretin release is H^+. Secretin is released when the pH in the duodenum falls below 4.5. Secretin also is released by fatty acids. This may be a significant mechanism for secretin release because the concentration of fatty acids in the lumen is often high. CCK can also be released by acid, but except during hypersecretion of acid, the physiologic significance of this mechanism of release has not been established. The purely physical stimulus of distention activates antral receptors, causing gastrin release; for example, inflating a balloon in the antrum releases gastrin. During a meal the pressure of ingested food initiates this response. The magnitude of the response is not as great as originally believed, however, and the contribution that distention makes to the total amount of gastrin released in humans is probably minor. Gastrin can also be released by calcium, decaffeinated coffee, and wine. Pure alcohol in the same concentration as the alcohol in wine does not release gastrin but does stimulate acid secretion. Motilin is released cyclically (approximately every 90 minutes) during fasting. This release is prevented by atropine and ingestion of a mixed meal. Acid and fat in the duodenum, however, increase motilin release.

In addition to releasing secretin, acid exerts an important negative feedback control of gastrin release. Acidification of the antral mucosa below a pH of 3.5 inhibits gastrin release. Patients with atrophic gastritis, pernicious anemia, or other conditions characterized by the chronic decrease of acid-secreting cells and hyposecretion of acid may have extremely high serum concentrations of gastrin because of the absence of this inhibitory mechanism.

There are several instances in which hormones alter the release of GI peptides. Secretin and glucagon, for example, both inhibit gastrin release. CCK has been shown to stimulate glucagon release, and four GI hormones (secretin, gastrin, CCK, and GIP) increase insulin secretion. Elevated serum calcium stimulates both gastrin and CCK release. It is doubtful whether any of these mechanisms, with the exception of release of insulin by GIP, play a role in normal GI physiology. Some, however, may become important when circulating levels of hormones or calcium are altered by disease.

■ ACTIONS AND INTERACTIONS

The effects of pure GI hormones have been tested on almost every secretory, motor, and absorptive function of the GI tract. Each peptide has some action on almost every target tested. Even though large doses of hormone are sometimes necessary to produce an effect, either stimulatory or inhibitory, the fact that receptors for each hormone are present on most target tissues is demonstrated. To indicate the myriad activities possessed by these peptides, many of their actions are summarized in Table 1-2.

The important physiologic actions of the GI hormones are depicted in Table 1-3. Numerous guidelines have been proposed for determining whether an action is physiologic. The action should occur in response to endogenous hormone released by normal stimuli (i.e., those present during a meal). In other words, an exogenous dose of hormone should produce the effect in question without elevating serum hormone levels above those produced by a meal. An acceptable guideline for exogenous infusion is a dose that produces 50% of the maximal response (D_{50}) of the primary action of the hormone. The hormone should be administered as a continuous intravenous infusion rather than as a single bolus because the latter produces transient, unphysiologically high serum levels.

The primary action of gastrin is the stimulation of gastric acid secretion. On a molar basis it is 1500 times more potent than histamine. In humans the D_{50} is 1 nanogram (ng) kilogram (kg)·minute. There is considerable debate about