

# Gastrointestinal Hormones: Introduction and Index

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Digesting, absorbing and assimilating a meal requires precise coordination of a huge number of physiologic processes. [Control over gastrointestinal function](#) is, as one would expect, provided by nervous and endocrine systems.

The hormones most important in controlling digestive function are synthesized within the gastrointestinal tract by cells scattered in the epithelium of the stomach and small intestine. These endocrine cells and the hormones they secrete are referred to as the [enteric endocrine system](#). Interestingly, most if not all "GI hormones" are also synthesized in the brain.

The following discussions assume some familiarity with the [anatomy and physiology of the digestive system](#).

Core information on gastrointestinal endocrinology is presented in the following topics:

- [Overview of Gastrointestinal Hormones](#)
- [Gastrin](#)
- [Cholecystokinin](#)
- [Secretin](#)
- [Ghrelin](#)
- [Motilin](#)

Advanced and supplemental topics related to gastrointestinal hormones:

- [Enteroglucagon and Glucagon-Like Peptides](#)
- [Gastric Inhibitory Peptide](#)
- [Vasoactive Intestinal Peptide](#)

## Overview of Gastrointestinal Hormones

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If you are like most people, you eat several meals and occasional snacks each day, but rarely think about the immense number of tasks that must be performed by your digestive system to break down, absorb and assimilate those nutrients. **Robust control**

systems are required to coordinate digestive processes in man and animals, and are provided by both the nervous and endocrine systems. Endocrine control over digestive functions is provided by the so-called enteric endocrine system, which is [summarized elsewhere](#).

There are *a bunch* of hormones, neuropeptides and neurotransmitters that affect gastrointestinal function. Interestingly, a number of the classical GI hormones are also synthesized in the brain, and sometimes referred to as "brain-gut peptides". The significance of this pattern of expression is not clear.

The following table summarizes the effects and stimuli for release of the major gastrointestinal hormones, each of which is discussed in more detail on subsequent pages:

| Hormone                                               | Major Activities                                                                                                                                                                             | Stimuli for Release                                                                 |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <a href="#"><u>Gastrin</u></a>                        | Stimulates <a href="#"><u>gastric acid secretion</u></a> and proliferation of gastric epithelium                                                                                             | Presence of peptides and amino acids in gastric lumen                               |
| <a href="#"><u>Cholecystokinin</u></a>                | Stimulates secretion of <a href="#"><u>pancreatic enzymes</u></a> , and <a href="#"><u>contraction and emptying of the gall bladder</u></a>                                                  | Presence of fatty acids and amino acids in the small intestine                      |
| <a href="#"><u>Secretin</u></a>                       | Stimulates <a href="#"><u>secretion of water and bicarbonate from the pancreas</u></a> and <a href="#"><u>bile ducts</u></a>                                                                 | Acidic pH in the lumen of the small intestine                                       |
| <a href="#"><u>Ghrelin</u></a>                        | Appears to be a strong stimulant for appetite and feeding; also a potent stimulator of <a href="#"><u>growth hormone</u></a> secretion.                                                      | Not clear, but secretion peaks prior to feeding and diminishes with gastric filling |
| <a href="#"><u>Motilin</u></a>                        | Apparently involved in stimulating <a href="#"><u>housekeeping patterns of motility</u></a> in the stomach and small intestine                                                               | Not clear, but secretion is associated with fasting                                 |
| <a href="#"><u>Gastric inhibitory polypeptide</u></a> | Inhibits <a href="#"><u>gastric secretion</u></a> and <a href="#"><u>motility</u></a> and potentiates release of insulin from beta cells in response to elevated blood glucose concentration | Presence of fat and glucose in the small intestine                                  |

## Gastrin

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**Gastrin is a major physiological regulator of gastric acid secretion. It also has an important trophic or growth-promoting influence on the gastric mucosa.** Gastrin is

synthesized in G cells, which are located in gastric pits, primarily in the antrum region of the [stomach](#) and binds receptors found predominantly on [parietal](#) and [enterochromaffin-like cells](#).

## Structure of Gastrin and the Gastrin Receptor

**Gastrin is a linear peptide that is synthesized as a preprohormone and is post-translationally cleaved to form a family of peptides with identical carboxytermini.** The predominant circulating form is gastrin-34 ("big gastrin"), but full biologic activity is present in the smallest peptide (gastrin-14 or minigastrin). Further, full bioactivity is preserved in the five C-terminal amino acids of gastrin, which is known as **pentagastrin**. Importantly, the five C-terminal amino acids of gastrin and [cholecystinin](#) are identical, which explains their overlapping biological effects.



**The gastrin receptor is also one of the receptors that binds cholecystinin**, and is known as the CCK-B receptor. It is a member of the G protein-coupled receptor family. Binding of gastrin stimulates an increase in intracellular  $Ca^{++}$ , activation of protein kinase C, and production of inositol phosphate.

## Control and Physiologic Effects of Gastrin

**The primary stimulus for secretion of gastrin is the presence of certain foodstuffs, especially peptides, certain amino acids and calcium, in the gastric lumen.** Also, as yet unidentified compounds in coffee, wine and beer are potent stimulants for gastrin secretion. Secretion of this hormone is inhibited when the luminal pH of the stomach becomes very low (less than about 3).

**Gastrin appears to have at least two major effects on gastrointestinal function:**

- **Stimulation of gastric acid secretion:** Gastrin receptors are found on [parietal cells](#), and binding of gastrin, along with histamine and acetylcholine, leads to fully-stimulated acid secretion by those cells. Canine parietal cells have roughly 44,000 gastrin receptors each, and in that species, it has been demonstrated that immunoneutralization of gastrin blocks secretion of acid in response to intragastric administration of peptides. [Enterochromaffin-like \(ECL\) cells](#) also bear gastrin receptors, and recent evidence indicates that this cell may be the most important target of gastrin with regard to regulating acid secretion. Stimulation of ECL cells by gastrin leads to histamine release, and histamine

binding to H2 receptors on parietal cells is necessary for full-blown [acid secretion](#).

- **Promotion of gastric mucosal growth:** Gastrin clearly has the ability to stimulate many aspects of mucosal development and growth in the stomach. Treatment with gastrin stimulates DNA, RNA and protein synthesis in gastric mucosa and increases the number of parietal cells. Another observation supporting this function is that humans with hypergastrinemia (abnormally high blood levels of gastrin) consistently show gastric mucosal hypertrophy.

In addition to parietal and ECL cell targets, gastrin also stimulates pancreatic acinar cells via binding to cholecystinin receptors, and gastrin receptors have been demonstrated on certain populations of gastric smooth muscle cells, supporting pharmacologic studies that demonstrate a role for gastrin in regulating gastric motility.

## Disease States

**Excessive secretion of gastrin, or hypergastrinemia, is a well-recognized cause of a severe disease known as Zollinger-Ellison syndrome**, which is seen at low frequency in man and dogs. The hallmark of this disease is gastric and duodenal ulceration due to excessive and unregulated secretion of gastric acid. Most commonly, hypergastrinemia is the result of gastrin-secreting tumors (gastrinomas), which develop in the pancreas or duodenum.

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# Cholecystinin

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**Cholecystinin plays a key role in facilitating digestion within the small intestine.** It is secreted from mucosal epithelial cells in the first segment of the small intestine (duodenum), and stimulates delivery into the small intestine of [digestive enzymes from the pancreas](#) and [bile from the gallbladder](#). Cholecystinin is also produced by neurons in the [enteric nervous system](#), and is widely and abundantly distributed in the brain.

## Structure of Cholecystinin and Its Receptors

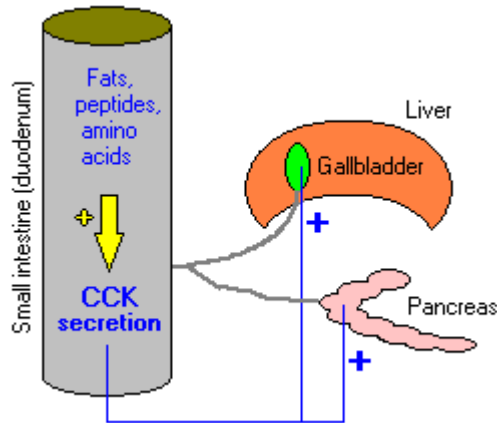
As mentioned previously, cholecystinin and [gastrin](#) are highly similar peptides. Like gastrin, **cholecystinin is a linear peptide that is synthesized as a preprohormone, then proteolytically cleaved to generate a family of peptides having the same carboxy ends.** Full biologic activity is retained in CCK-8 (8 amino acids), but peptides of 33, 38 and 59 amino acids are also produced. In all of these CCK peptides, the tyrosine seven residues from the end is sulfated, which is necessary for activity.



**Two receptors that bind cholecystokinin have been identified.** The  $CCK_A$  receptor is found abundantly on pancreatic acinar cells. The  $CCK_B$  receptor, which also functions as the gastrin receptor, is the predominant form in brain and stomach. Both receptors have seven transmembrane domains typical of G protein-coupled receptors.

## Control and Physiologic Effects of Cholecystokinin

Foodstuffs flowing into the small intestine consist mostly of large macromolecules (proteins, polysaccharides and triglyceride) that must be digested into small molecules (amino acids, monosaccharides, fatty acids) in order to be absorbed. Digestive enzymes from the pancreas and bile salts from the liver (which are stored in the gallbladder) are critical for such digestion. **Cholecystokinin is the principle stimulus for delivery of pancreatic enzymes and bile into the small intestine.**



The most potent stimuli for secretion of cholecystokinin are the presence of partially-digested fats and proteins in the lumen of the duodenum (a particularly potent stimulus is pictured above). **An elevation in blood concentration of cholecystokinin has two major effects that facilitate digestion:**

- **Release of digestive enzymes from the pancreas** into the duodenum. Older literature refers to cholecystokinin as *pancreozymin*, a term coined to describe this effect.
- **Contraction of the gallbladder to deliver bile** into the duodenum. The name cholecystokinin (to "move the gallbladder") was given to describe this effect. Cholecystokinin is also known to stimulate secretion of bile salts into the biliary system.

Pancreatic enzymes and bile flow through ducts into the duodenum, leading to digestion and absorption of the very molecules that stimulate cholecystokinin secretion. Thus, when absorption is completed, cholecystokinin secretion ceases.

Injection of cholecystokinin into the ventricles of the brain induces satiety (lack of hunger) in laboratory animals. In view of its pattern of secretion relative to feeding, it would make physiologic sense that this hormone might participate in [control of food intake](#). However, recent experiments suggest that cholecystokinin is at best a minor player in regulation of food intake.

**In addition to its synthesis in small intestinal epithelial cells, cholecystokinin has been clearly demonstrated in neurons within the wall of the intestine and in many**

**areas of the brain.** It seems, in fact, to be the most abundant neuropeptide in the central nervous system. Secretion of cholecystokinin from neurons appears to modulate the activity of other hormones and neuropeptides, but it seems safe to say the understanding its role in function of the brain is rudimentary at best.

## Disease States

Diseases resulting from excessive or deficient secretion of cholecystokinin are rare. Cholecystokinin deficiency has been described in humans as part of autoimmune polyglandular syndrome, and was manifest as a malabsorption syndrome clinically similar to pancreatic exocrine insufficiency. Additionally, there is mounting evidence that aberrations in expression of cholecystokinin or its receptor within the human brain may play a part in the pathogenesis of certain types of anxiety and schizophrenia. Clearly, a much better understanding of the role of cholecystokinin in brain function is required.

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# Secretin



The small intestine is periodically assaulted by a flood of acid from the stomach, and it is important to put out that fire in a hurry to avoid acid burns. **Secretin functions as a type of fireman: it is released in response to acid in the small intestine, and stimulates the pancreas to release a flood of bicarbonate base, which neutralizes the acid.** Secretin is also of some historical interest, as it was the first hormone to be discovered.

## Structure of Secretin and Its Receptors

Secretin is synthesized as a prohormone, then proteolytically processed to yield a single 27-amino acid peptide by removal of the signal peptide plus amino and carboxy-terminal extensions. The sequence of the mature peptide is related to that of glucagon, [vasoactive intestinal peptide](#) and [gastric inhibitory peptide](#).

The secretin receptor has seven membrane-spanning domains and characteristics typical of a G protein-coupled receptor.

## Control and Physiologic Effects of Secretin

Secretin is secreted in response to one known stimulus: acidification of the duodenum, which occurs most commonly when liquified ingesta from the stomach are released into the small intestine.

The principal target for secretin is the [pancreas](#), which responds by secreting a bicarbonate-rich fluid, which flows into the first part of the intestine through the pancreatic duct. Bicarbonate ion is a base and serves to neutralize the acid, thus preventing acid burns and establishing a pH conducive to the action of other digestive enzymes. A similar, but quantitatively less important response to secretin is elicited by [bile duct cells](#), resulting in additional bicarbonate being dumped into the small gut.

As acid is neutralized by bicarbonate, the intestinal pH rises toward neutrality, and secretion of secretin is turned off.

## Disease States

Diseases associated with excessive or deficient secretion of secretin are not recognized.

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# Ghrelin

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**Ghrelin was discovered as the peptide hormone that potently stimulates release of growth hormone from the anterior pituitary. It was subsequently determined that ghrelin, along with several other hormones, has significant effects on appetite and energy balance. The predominant source of ghrelin is epithelial cells in the stomach.**

## Structure of Ghrelin and Its Receptor

**Ghrelin is synthesized as a preprohormone, then proteolytically processed to yield a 28-amino acid peptide.** An interesting and unique modification is imposed on the hormone during synthesis in the form of an n-octanoic acid bound to one of its amino acids; this modification is necessary for biologic activity.

Synthesis of ghrelin occurs predominantly in epithelial cells lining the fundus of the stomach, with smaller amounts produced in the placenta, kidney, pituitary and hypothalamus.

The ghrelin receptor was known well before ghrelin was discovered. Cells within the [anterior pituitary](#) bear a receptor that, when activated, potently stimulates secretion of [growth hormone](#) - that receptor was named the **growth hormone secretagogue receptor** (GHS-R). The natural ligand for the GHS-R was announced in 1999 as ghrelin, and ghrelin was named for its ability to provoke growth hormone secretion (the suffix ghre means "grow").

Ghrelin receptors are present on the cells in the pituitary that secrete growth hormone,

and also have been identified in the hypothalamus, heart and adipose tissue.

## Control and Physiologic Effects of Ghrelin

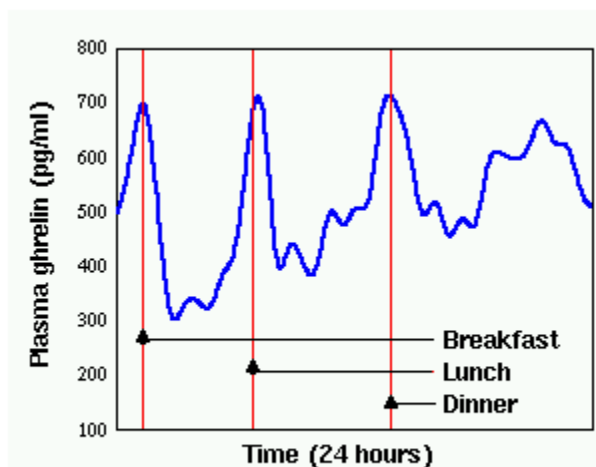
**At least two major biologic activities have been ascribed to ghrelin:**

**Stimulation of growth hormone secretion:** Ghrelin, as the ligand for the growth hormone secretagogue receptor, potently stimulates secretion of growth hormone. The ghrelin signal is integrated with that of growth hormone releasing hormone and somatostatin to [control the timing and magnitude of growth hormone secretion](#).

**Regulation of energy balance:** In both rodents and humans, **ghrelin functions to increase hunger** through its action on hypothalamic feeding centers. This makes sense relative to increasing plasma ghrelin concentrations observed during fasting (see below). Additionally, humans injected with ghrelin reported sensations of intense hunger. Ghrelin also appears to **suppress fat utilization in adipose tissue**, which is somewhat paradoxical considering that growth hormone has the opposite effect. Overall, ghrelin seems to be one of several hormonal signals that communicates the state of energy balance in the body to the brain.

Other effects of ghrelin include stimulating gastric emptying and having a variety of positive effects on cardiovascular function (e.g. increased cardiac output). It is not totally clear whether the cardiovascular effects are a direct effect of ghrelin or represent an indirect effect of ghrelin's ability to stimulate growth hormone secretion.

**Blood concentrations of ghrelin are lowest shortly after consumption of a meal, then rise during the fast just prior to the next meal.** The figure to the right shows this pattern based on assays of plasma ghrelin in 10 humans during the course of a day.



Adapted from Cummings et al. *Diabetes* 50:1714, 2001.

## Disease States

Ghrelin concentrations in blood are reduced in obese humans compared to lean control subjects, but whether this is cause or effect is not defined. Patients with anorexia nervosa have higher than normal plasma ghrelin levels, which decrease if weight gain occurs.

Prader-Willi syndrome is another disorder relevant to ghrelin science. Affected patients develop extreme obesity associated with uncontrollable and voracious appetite. The plasma ghrelin levels are exceptionally high in comparison to patients similarly obese due to other causes. Prader-Willi syndrome is clearly a complex disease with many defects; it may be that excessive ghrelin production contributes to the appetite and obesity components.

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## Motilin

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Motilin is a 22 amino acid peptide secreted by endocrinocytes in the mucosa of the proximal small intestine. Based on amino acid sequence, motilin is unrelated to other hormones.

**Motilin participates in controlling the pattern of smooth muscle contractions in the upper gastrointestinal tract.** There are two basic states of [motility of the stomach and small intestine](#): the fed state, when foodstuffs are present, and the interdigestive state between meals. Motilin is secreted into the circulation during the fasted state at intervals of roughly 100 minutes. **These bursts of motilin secretion are temporarily related to the onset of "housekeeping contractions", which sweep the stomach and small intestine clear of undigested material** (also called the [migrating motor complex](#)).

Control of motilin secretion is largely unknown, although some studies suggest that an alkaline pH in the duodenum stimulates its release.

**An interesting aspect of the motilin story is that erythromycin and related antibiotics act as nonpeptide motilin agonists**, and are sometimes used for their ability to stimulate gastrointestinal motility. Administration of a low dose of erythromycin will induce a migrating motor complex, which provides additional support for the conclusion that motilin secretion triggers this pattern of GI motility, rather than results from it.

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## Enteroglucagon and Glucagon-Like

# Peptides

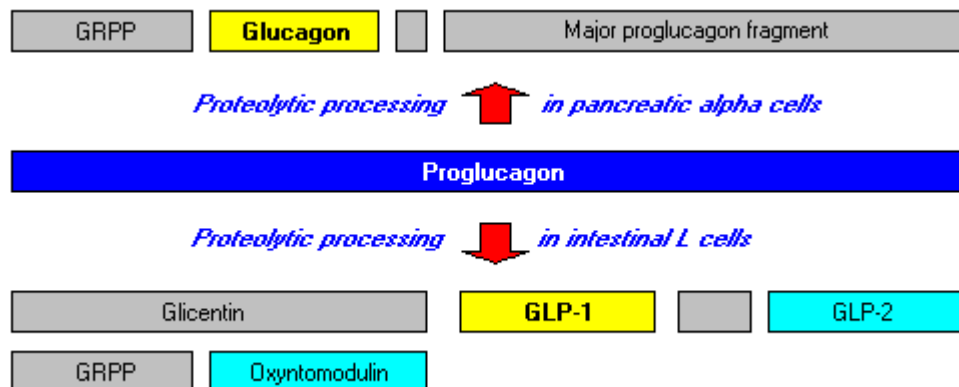
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[Glucagon](#) is best known as a peptide hormone secreted from [pancreatic islets](#) that participates in control of glucose metabolism. Glucagon is synthesized initially as the protein proglucagon, which, in mammals, is encoded by a single gene. Within alpha cells of the pancreas, proglucagon is processed by proteolytic cleavage into glucagon itself, and several biologically inactive peptides.

**Interestingly, the proglucagon gene is also expressed in the terminal small intestine and large intestine, where it is cleaved into a number of peptides other than glucagon.** This alternative pathway for processing of proglucagon occurs in gut endocrinocytes called L cells. Because these peptides were discovered by cross reactions with antisera against glucagon, they were originally given the name "enteroglucagon", and are sometimes referred to collectively as "proglucagon-derived peptides".

The major, characterized patterns of proglucagon processing are depicted in the figure below. In both pancreas and gut, three types of products are generated:

- **Peptides with known biological activity** (*yellow color*): glucagon and glucagon-like peptide-1 (GLP-1)
- **Peptides that may have biological activity**, but which are poorly characterized or active only at what are considered non-physiologic concentrations (*cyan color*): glucagon-like peptide-2 (GLP-2) and oxyntomodulin
- **Peptides without apparent biological activity** (*gray color*): glicentin, glicentin-related pancreatic peptide, major proglucagon fragment.



Regardless of activity, each of these peptides is secreted into blood after ingestion of a meal containing carbohydrates or lipids.

**Glucagon-like peptide-1** has a major effect of enhancing the release of [insulin](#) in response to a glucose stimulus, and coincidentally, suppressing secretion of glucagon. As a result, injections of this hormone lower blood glucose levels, not only in normal people, but in those having insulin-dependent and non-insulin-dependent diabetes mellitus. For this reason, GLP-1 is being investigated for its utility in the therapy of diabetes.

GLP-1 has been shown to potently inhibit several aspects of digestive function, including gastric emptying, gastric secretion and pancreatic secretion. Like many gut peptides, GLP-1 is also synthesized in the brain, and may play a role in [control of food intake](#).

**Glucagon-like peptide-2** is not well characterized, but some reports suggest that it stimulates proliferation of intestinal epithelial cells.

**Oxyntomodulin** is identical to glucagon, but with an 8 amino acid extension on the C-terminus. Experimentally, it has glucagon-like activity, but this is of doubtful physiologic significance, as it binds the glucagon receptor with low affinity relative to glucagon. Other effects that have been demonstrated include inhibition of gastric secretion and motility, and inhibition of pancreatic secretion.



## References and Reviews

- Ahren B: Glucagon-like peptide-1 (GLP-1): a gut hormone of potential interest in the treatment of diabetes. *Bioessays* 20:642-651, 1998.
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# Enteroglucagon and Glucagon-Like Peptides

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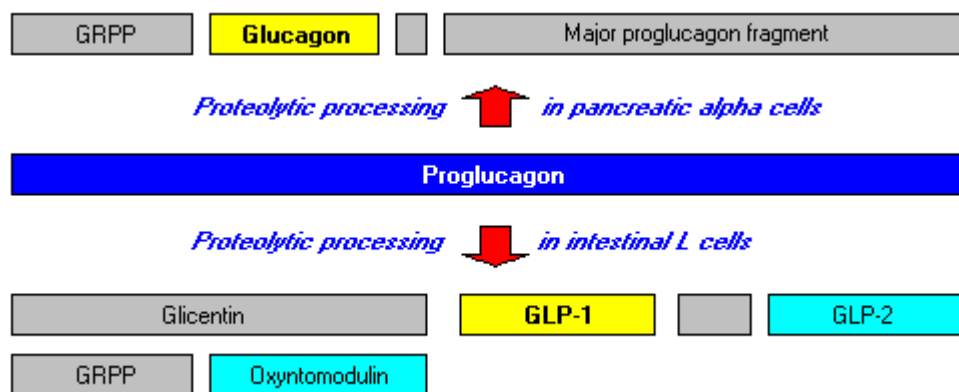
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## Gastric Inhibitory Peptide

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Gastric inhibitory peptide (GIP) is a member of the secretin family of hormones. It was discovered as a factor in extracts of intestine that inhibited gastric motility and secretion of acid, and initially called *enterogastrone*. Like secretin, it is secreted from mucosal epithelial cells in the first part of the small intestine.

Another activity of GIP is its ability to enhance the release of insulin in response to infusions of glucose. For this action, it has also been referred to as *glucose-dependent insulinotropic peptide*.

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## Vasoactive Intestinal Peptide

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VIP is a 28-amino acid peptide structurally related to [secretin](#). It was originally isolated from intestinal extracts and shown to be a potent vasodilator. Subsequent work demonstrated that VIP is very widely distributed in the peripheral and central nervous systems, and probably should not be considered a true GI hormone.

A huge number of biological effects have been attributed to VIP. With respect to the digestive system, VIP seems to induce smooth muscle relaxation (lower esophageal sphincter, stomach, gallbladder), stimulate secretion of water into pancreatic juice and bile, and cause inhibition of gastric acid secretion and absorption from the intestinal lumen.

Certain tumors arising from the pancreatic islets or nervous tissue (called VIPomas) secrete excessive quantities of VIP, and are associated with chronic, watery diarrhea.

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