

Gastrointestinal Hormones

Defn.: Gastrointestinal (GI) hormones are internal or endocrine secretions of the gut released from special cells of the GI system that participate in modulating the functions of the gut or extragut tissues and organs.

1. The gastrointestinal hormones constitute a group of hormones secreted by enteroendocrine cells in the stomach, pancreas, and small intestine that control various functions of the digestive organs.
2. Most of the gut peptides, such as secretin, cholecystokinin or substance P, were found to play a role of neurotransmitters and neuromodulators in the central and peripheral nervous systems.
3. Enteroendocrine cells do not form glands but are spread throughout the digestive tract.
4. They exert their autocrine and paracrine actions that integrate gastrointestinal function.

Hormone	Major actions
Gastrin	↑Acid and pepsin secretion from gastric mucosa; ↑ECL proliferation; ↓cholangiocyte HCO ₃ ⁻ secretion
CCK	↑Pancreatic enzyme secretion and gallbladder contraction
Secretin	↑Pancreatic bicarbonate and H ₂ O secretion; ↑cholangiocyte HCO ₃ ⁻ secretion
Motilin	↑Intestinal motility
Enteroglucagon	↑Enterocyte proliferation
Somatostatin	↓Gastric acid secretion and gastric motor activity; ↓cholangiocyte HCO ₃ ⁻ secretion
Gastric inhibitory peptide	↑Glucose-stimulated insulin secretion and ↓gastric acid secretion
Pancreatic polypeptide	↓Pancreatic bicarbonate secretion
Peptide YY	↓Gastric motor activity and acid secretion

ECL – Entero Chromaffin-like cell (a type of neuroendocrine cell found in stomach)

CCK – Cholecystokinin (a peptide hormone of GI system)

Neuropeptide	Major actions
Bombesin (gastrin-releasing peptide)	↑ Gastrin release
Substance P	↑Smooth muscle contraction mediates inflammatory response
Vasoactive intestinal peptide	↑Smooth muscle relaxation and pancreatic bicarbonate secretion
Calcitonin gene-related peptide	↑Somatostatin release and smooth muscle contraction; regulates cholangiocyte proliferation

Hormone	Source of secretion	Actions
1. Gastrin	1. G cells in stomach 2. TG cells in GI tract 3. Islets in fetal pancreas 4. Anterior pituitary 5. Brain	1. Stimulates gastric secretion and motility 2. Promotes growth of gastric mucosa 3. Stimulates release of pancreatic hormones 4. Stimulates secretion of pancreatic juice
2. Secretin	S cells of small intestine	1. Stimulates secretion of watery and alkaline pancreatic juice 2. Inhibits gastric secretion and motility 3. Constricts pyloric sphincter 4. Increases potency of cholecystokinin action
3. Cholecystokinin	I cells of small intestine	1. Contracts gallbladder 2. Stimulates pancreatic secretion with enzymes 3. Accelerates secretin activity 4. Increases enterokinase secretion 5. Inhibits gastric motility 6. Increases intestinal motility 7. Augments contraction of pyloric sphincter 8. Suppresses hunger 9. Induces drug tolerance to opioids
4. GIP	1. K cells in duodenum and jejunum 2. Antrum of stomach	1. Stimulates insulin secretion 2. Inhibits gastric secretion and motility
5. VIP	1. Stomach 2. Small and large intestines	1. Dilates splanchnic (peripheral) blood vessels 2. Inhibits HCl secretion in gastric juice 3. Stimulates secretion of succus entericus 4. Relaxes smooth muscles of intestine 5. Augments acetylcholine action on salivary glands 6. Stimulates insulin secretion
6. Glucagon	1. α cells in pancreas 2. A cells in stomach and intestine	Increases blood sugar level
7. Glicentin	L cells in duodenum and jejunum	Increases blood sugar level
8. GLP – 1	1. α cells in pancreas 2. Brain	1. Stimulates insulin secretion 2. Inhibits gastric motility
9. GLP – 2	1. L cells in ileum and colon	Suppresses appetite

GIP - Gastric inhibitory polypeptide

VIP - Vasoactive intestinal peptide

GLP - Glucagon-like peptide 1 & 2

Hormone	Source of secretion	Actions
10. Somatostatin	1. Hypothalamus 2. D cells in pancreas, 3. D cells in stomach and small intestine	1. Inhibits secretion of GH and TSH 2. Inhibits gastric secretion and motility 3. Inhibits secretion of pancreatic juice 4. Inhibits secretion of GI hormones
11. Pancreatic polypeptide	1. PP cells in pancreas 2. Small intestine	1. Increases secretion of glucagon 2. Decreases pancreatic secretion
12. Peptide YY	L cells of ileum and colon	1. Inhibits gastric secretion and motility 2. Reduces secretion of pancreatic juice 3. Inhibits intestinal motility and bowel passage 4. Suppresses appetite and food intake
13. Neuropeptide Y	1. Ileum and colon 2. Brain and ANS	1. Increases blood flow in enteric blood vessels 2. Stimulates food intake
14. Motilin	1. Mo cells in stomach and intestine 2. Enterochromaffin cells in intestine	1. Accelerates gastric emptying 2. Increases movements of small intestine 3. Increases peristalsis in colon
15. Substance P	1. Brain 2. Small intestine	Increases movements of small intestine
16. Ghrelin	1. Stomach 2. Hypothalamus 3. Pituitary 4. Kidney 5. Placenta	1. Promotes GH release 2. Induces appetite and food intake 3. Stimulates gastric emptying

The digestive system is the primary site of action for most GI hormones and related polypeptides.

The stomach is the primary site of gastrin production with some D-cells also populating the duodenum.

Somatostatin and histamine are also produced in the stomach by enterochromaffin-like (ECL) cells, which is an enteroendocrine cell subtype.

The small intestines, namely the duodenum and jejunum handle secretion of CCK, secretin, GIP, and motilin.

Functions:

The main actions of the gastrin-CCK family and the secretin family of hormones are listed below.

Gastrin

- Stimulates H⁺ (acid) secretion by parietal cells in the stomach
- Trophic (growth) effects on the mucosa of the small intestine, colon, and stomach
- Inhibits the actions of Secretin and GIP
- Inhibited by H⁺

CCK

- Contraction of the gallbladder with simultaneous relaxation of the sphincter of Oddi.
- Inhibits gastric emptying
- Stimulates secretion of pancreatic enzymes: lipases, amylase, and proteases
- Secretion of bicarbonate from the pancreas
- Trophic effects on the exocrine pancreas and gallbladder

Secretin

- Inhibits gastrin, H⁺ secretion, and growth of stomach mucosa
- Stimulates biliary secretion of bicarbonate and fluid
- Secretion of bicarbonate from the pancreas
- Trophic effect on the exocrine pancreas

GIP

- Stimulation of insulin secretion
- Induces satiety
- In large doses, decreases gastric acid secretion
- In large doses, decreases the motor activity of the stomach and therefore slows gastric emptying when the upper small intestine is already full of food products.
- Stimulates the activity of lipoprotein lipase in adipocytes
- Protects beta-cells of the pancreas from destruction by apoptosis

GLP-1

- Decreases gastric emptying
- Induces satiety
- Increases sensitivity of pancreatic beta-cells to glucose.

Motilin

- Increases gastrointestinal motility by stimulating the “migrating motility” or “myoelectric complex” that moves through the fasting stomach and small intestines every 90 minutes. This cyclical release

and action get inhibited by the ingestion of food. Not much is known about this peptide, except for this essential function.

Mechanism:

The release of GI hormones is in response to input from G-protein-coupled receptors that detect changes in luminal contents. Some of these receptors only respond to selective luminal substances and subsequently release GI hormones from their respective enteroendocrine cells through unknown mechanisms. Overall, gastrointestinal hormones manage a diverse set of actions in the body including:

- Contraction and relaxation of smooth muscle wall and sphincters
- Secretion of enzymes for digestion
- Secretion of fluid and electrolytes
- Trophic (growth) effects on tissues of GI tract
- Regulating secretion of other GI peptides (i.e., somatostatin inhibits secretion of all GI hormones)

Gastrin is an interesting hormone because it acts through two mechanisms that ultimately increase the secretion of gastric acid (hydrogen ions) into the stomach.

The first mechanism involves gastrin binding to CCK-2 receptors on parietal cells, causing increased expression of K/H ATPase enzymes that are directly responsible for increased hydrogen ion secretion into the stomach.

The second mechanism is mediated by enterochromaffin-like cells, which secrete histamine in response to activation by gastrin.

Histamine then binds H₂ receptors on nearby parietal cells, which further stimulates secretion of hydrogen ions.

In addition to stimulating ECL cells to produce acid, gastrin also stimulates these parietal cells and ECL cells to proliferate.