GASTROINTESTINAL HORMONES

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GI Hormone

❑The gastrointestinal hormones (or gut 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.

❑Enteroendocrine cells do not form endocrine glands but are spread throughout the digestive tract. They exert their autocrine and paracrine actions that integrate all of gastrointestinal function.

Regulation of GI function

- **Endocrine regulation** : Enteroendocrine cells (EEC) secretes regulatory peptide or hormones that travel via blood stream to remote target organ. Ex. gastrin, secretin

- **Paracrine regulation** : Regulatory peptide secreted by EEC acts on a nearby target cell by diffusion through interstitial space. Ex. histamine, 5-HT

Classification of GI hormones

The gastrointestinal hormones can be divided into the following groups based upon their chemical structure.

- **Gastrin-cholecystokinin family: gastrin and cholecystokinin**
- **Secretin family: secretin, glucagon, vasoactive intestinal peptide (VIP) and gastric inhibitory peptide (GIP)**
- **Somatostatin family**
- **Motilin family**
- **Substance P**

STRUCTURE AND FUNCTIONS OF GASTRO-INTESTINAL (GI) TRACT

The GI tract is derived from the **endoderm**, the innermost of the three layers forming the developing embryo. During fetal life, it is divided into three segments described as the **foregut** (with blood supply derived from the coeliac trunk), **midgut** (supplied by the superior mesenteric artery) and **hindgut** (supplied by the inferior mesenteric artery). These parts develop into the characteristics of the definitive GI tract. The foregut extends from the oesophagus down to the second part of the duodenum, where the common bile duct enters the GI tract. The midgut extends to the junction of the middle and distal thirds of the transverse colon (known as **Cannon's point**), and the more distal structures are derived from the hindgut.

Gastrointestinal system consists of the Gastrointestinal (GI) tract and accessory glandular organs. GI tract includes mouth, pharynx, esophagus, stomach, small intestine, large intestine, anus. Salivary glands, liver, gallbladder, pancreas constitute accessory glandular organs.

From esophagus to the anus, the GI tract has the same basic arrangement of 4 layers in its tissues. These are mucosa, submucosa, muscularis and serosa (Fig. 8.2).

In the GI tract, digestion of food occurs through well-defined process. An important feature of digestion and endocrine activity of the gut is that these must be highly coordinated. If in the absence of enough foodstuffs, there is the secretion of gastric acid and pepsin in the stomach, the enzymes and acid will begin to attack the gastric mucosa resulting in gastric ulceration. Similarly, if the contents of the stomach enter the duodenum before the pancreatic secretions are released, the acidity of the chyme results in duodenal damage. If there is an increased rate of peristalsis in the colon, it results in insufficient removal of water from the gut contents, which produces diarrhoea; decreased peristalsis culminates in constipation. It is because of this need for coordination that the integrated gastrointestinal endocrine system is so important.

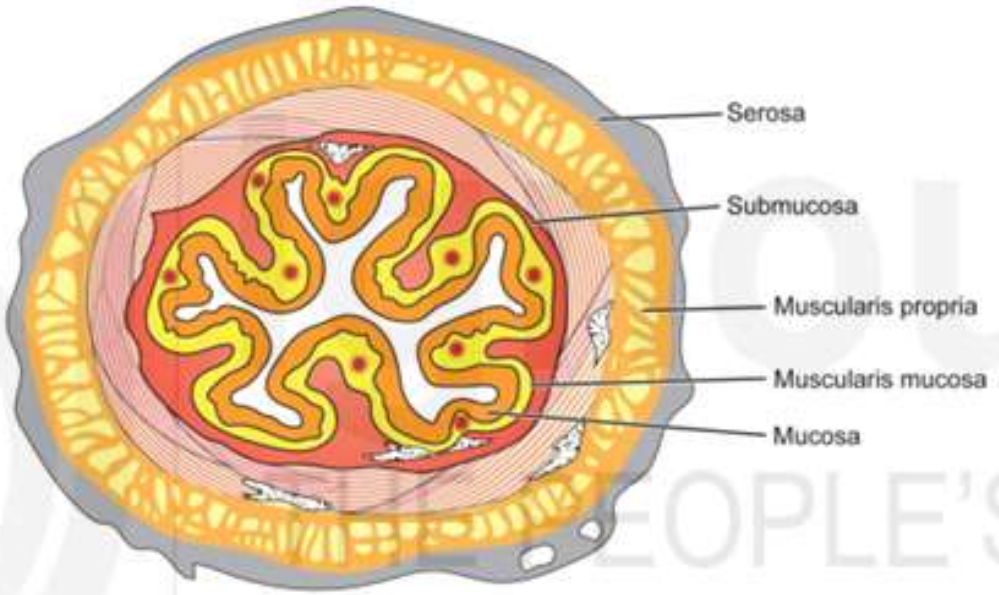

Fig. 8.2: Structural organization of tissues of GI tract.

GI TRACT HORMONES

The gastrointestinal hormones are synthesized by a group of cells known as clear cells, enterochromaffin cells, argentaffin cells or agyrophil cells. These cells are distributed along the whole length of the gut, although their density varies between regions. Because of the diffuse distribution of these hormones secreting cells, the system is sometimes referred to as the dispersed endocrine system (DES).

Based upon the chemical structures of the GI hormones, they may be divided into different categories

1. Gastrin-Cholecystokinin Family: consists of **gastrin** and **cholecystokinin**
2. Secretin Family: consists of **secretin**, glucagon, **vasoactive intestinal peptide** and **gastric inhibitory peptide**
3. Peptide Family: consists of peptides such as somatostatin, **motilin**, **substance P**, **Neurotensin**

Gastrin-Cholecystokinin Family: This family of GI hormones consists of Gastrin and cholecystokinin based on the fact that they both possess an identical sequence of the terminal five amino acids at the C-terminal.

Gastrin

Gastrin is secreted by the specialized endocrine G-cells located in the antral part of the gastric mucosa. Gastrin exists in several forms, however, the predominant form in the circulation is comprised of 34 amino acids (G34) (Fig. 8.9).

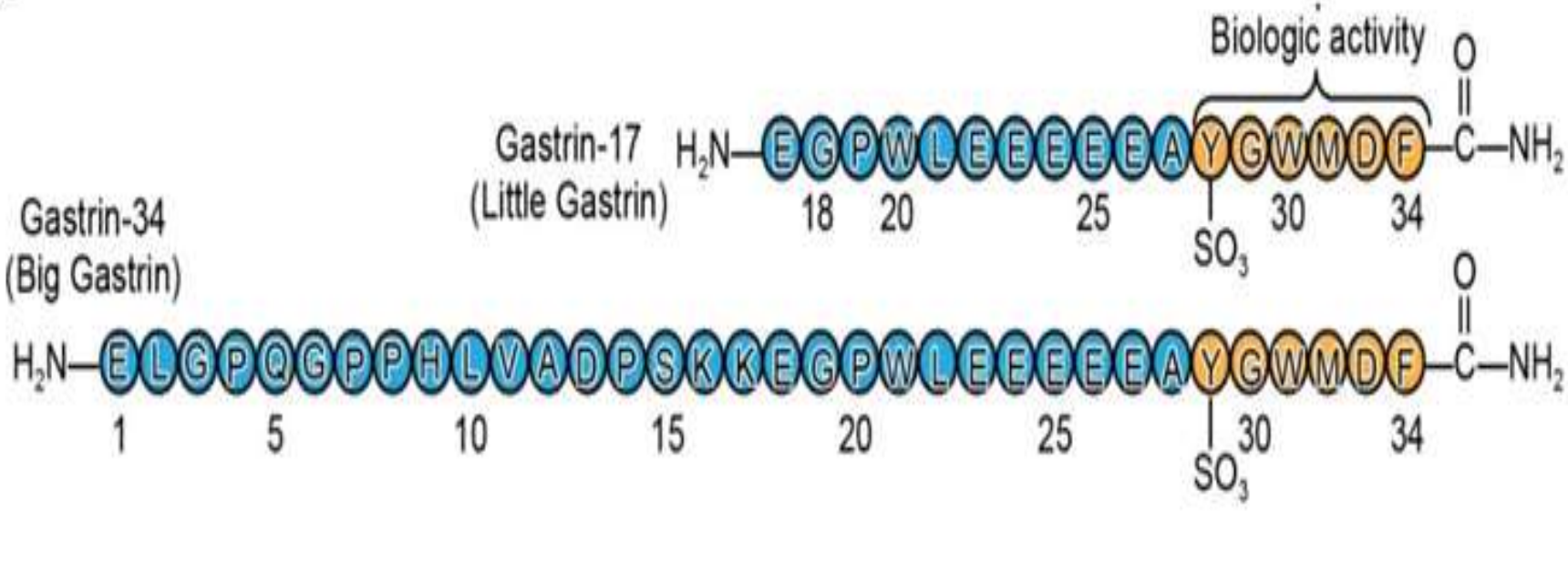

Fig. 8.9: The amino acid structure of Gastrin.

A larger form, G45, is believed to be a precursor molecule for other gastrins. The form with the greatest physiological significance is probably G17 (17 amino acids long). Another form of gastrin reported is G14 (14 amino acids long), which is thought to be a breakdown product. Gastrin 34, 17 and 14 are the ones found in circulation (Fig. 8.10).

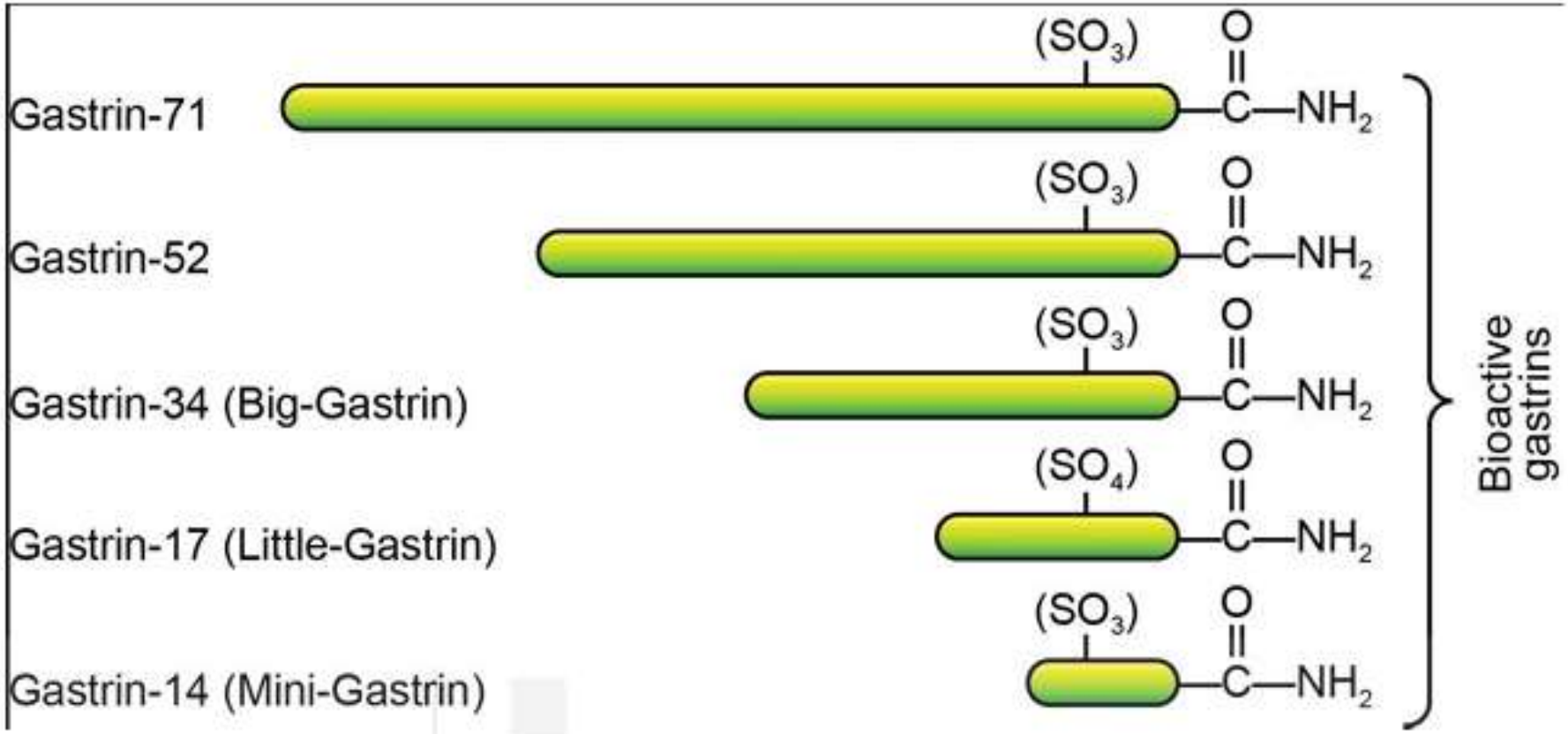

Fig. 8.10: The 101 amino acid long progastrin is enzymatically processed into at least five major peptides shown in the figure.

Gastrin Synthesis and Release

Gastrin (G17) is synthesized in the antral portion of the stomach by the G Cells, while in the duodenum, gastrin is synthesized as G34.Gastrin secretion is stimulated by the presence of food in the stomach, most notably peptides or amino acids and to a lesser extent fatty acids and also the thought, sight, smell and taste of the food as well as chewing and swallowing, distension of stomach, through activation of the vagus nerve and adrenaline.

Mechanism of Action of Gastrin

The main action of gastrin is to increase the secretion of gastric acid. This is via a direct effect on the parietal cells, or it can involve the potentiation of histamine-induced gastric acid secretion. As a result of the increased acid secretion, gastrin increases pepsin activity.

Functions of Gastrin

- Gastrin increases the blood flow to the gastric mucosa and has a direct effect on the gastric glands.
- Gastrin increases the secretion of pancreatic enzymes in readiness for the movement of the stomach contents into the duodenum, and the secretion of the pancreatic hormones insulin and glucagon.
- It facilitates the movement of the stomach contents into the duodenum by increasing both gastric and intestinal motility and by relaxing the pyloric sphincter.
- It also stimulates the contraction of the gallbladder which results in the addition of bile salts to the gut contents.

- It acts in multiple ways to increase the secretion of HCl and pepsinogen, which are required for the initiation of digestion of the protein.
- Gastrin also influences peristalsis and gastric motility- functions that are aimed at keeping the contents moving through the tract.
- Gastrin acts a growth factor. It is also not only trophic to stomach mucosa but also to the small intestine, helping in maintaining functionally viable GI tract lining.
- Gastrin secretion is inhibited by the accumulation of acid in the stomach. When the pH of the gastric content falls below 2.5, the release of gastrin is inhibited.
- The secretion of gastrin is under feedback control and is inhibited by an increased acid concentration within the stomach and by other gastrointestinal hormones such as vasoactive intestinal peptide, somatostatin and glucagon.

Gastrin (G17 and G34) has been identified in the brain, and administration of the terminal four amino acids has been shown to stimulate growth hormone by the anterior pituitary gland and thus it has been suggested that gastrin may play a role as a neurohormone.

Cholecystokinin (CCK)

Cholecystokinin is another hormone that acts on the pancreas. It stimulates the release of pancreatic enzymes and also contract the gallbladder. The most common form of CCK is comprised of 33 amino acids, the terminal five amino acids of which are identical to those of gastrin. Other forms of CCK have also been reported, all with the same terminal amino acid sequence. Forms with 8,12 and 58 amino acids can be found in the I-cells of the intestinal tract, while in the blood, the predominant forms are 8,33 or 58 amino acids (Fig. 8.11). CCK is secreted by the I-cells in response to the passage of gastric acid or products of digestion such as amino acids and fatty acids into the duodenum.

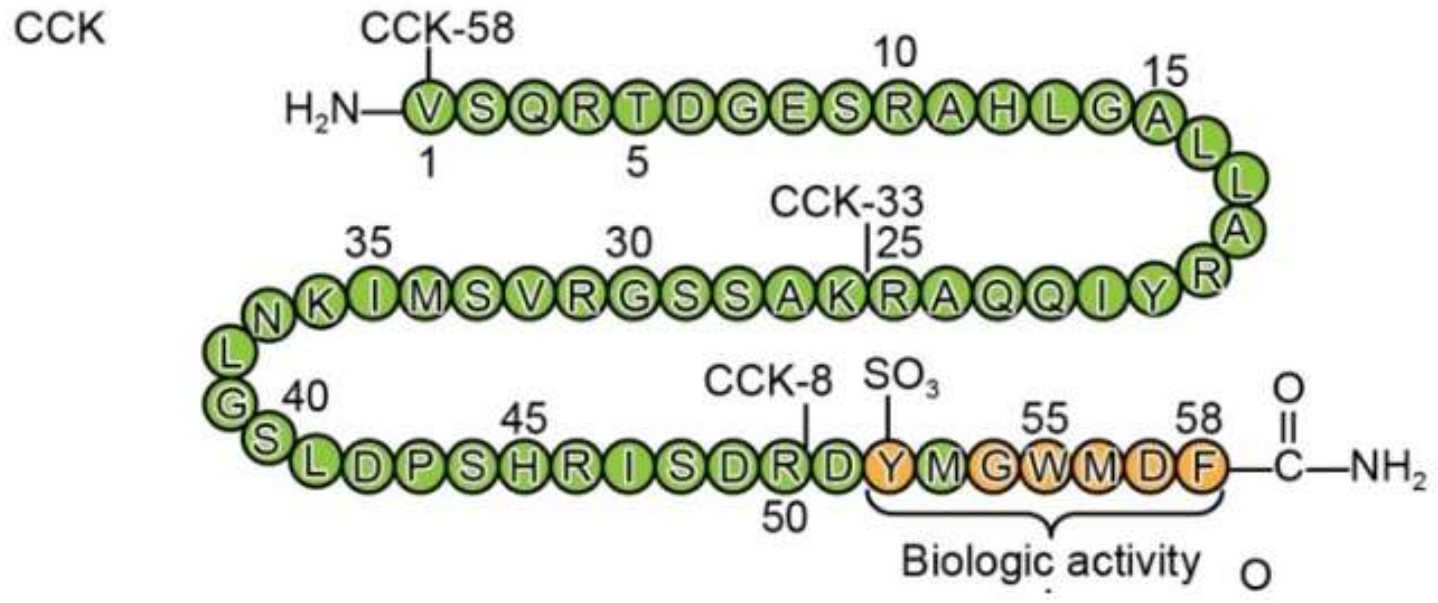

Fig. 8.11: Primary structure of CCK.

CCK Synthesis and Release

Its release is stimulated by the fat and protein present in the meal. Once secreted, the most notable action of CCK is to cause increased production of hepatic bile and contraction of the gall bladder to cause the addition of bile salts to the duodenal contents.

Another important action of CCK is stimulating the secretion of pancreatic digestive enzymes, insulin, glucagon and pancreatic polypeptide. The secretion of CCK ceases when the products of digestion leave the duodenum and enter the jejunum.

Functions of CCK

- CCK stimulates the release of pancreatic juice rich in enzymes like amylase, or inactive enzyme precursors like trypsinogen.These enzymes are then used in hydrolysing the nutrients carbohydrates and proteins.
- It induces the contraction and evacuation of the gall bladder.
- It is involved in inhibiting gastric motility and closure of the pyloric sphincter to prevent the emptying of bile into the duodenum from being too rapid. The closure of the sphincter also prevents the reflux of duodenal contents into the stomach.
- It stimulates the peristalsis of the duodenum, jejunum, ileum and colon.
- It is the most powerful stimulator of pancreatic growth, causing an increase in the pancreatic weight, DNA and enzyme content; however, unlike gastrin, CCK has no effect on the growth of the gut mucosa.
- It may also produce a sensation indicating enough food has been taken. It determines satiety and appetite.
- CCK may have a role in intestinal transport; both of sodium and water absorption have been found to increase in response to CCK.

CCK is also found in the brain, predominantly in the 8 amino acid form, though 58 amino acid form has also been reported. In the brain, CCK acts as a neurotransmitter or neuromodulator.

Secretin Family

Secretin, glucagon, vasoactive intestinal peptide and gastric inhibitory peptide are classed together because of the degree of homology in their amino acid sequences; however, unlike the gastrins and CCK, this homology is not in a distinct portion of the molecules, but is rather, in diffuse singlets, doublets and triplets of amino acids.

Secretin

Secretin is secreted by the S cells which are found in the duodenum and to alesser extent in the jejunum and ileum. The stimulus for the secretion of secretin is the presence of gastric acid in the duodenum. Following its secretion, secretin acts via cAMP to stimulate the secretion of a pancreatic juice with a high concentration of bicarbonate ions, an action which possibly involves interaction with CCK.

Structure of Secretin

It is comprised of 27 amino acids long peptide, of which 14 are homologous to the sequence of glucagon.

Release of Secretin

It is released mainly in response to the low pH of the gastric contents coming from the stomach to the small intestine. The release from the small intestine is especially strong when the pH drops below 4.5. The secretion of secretin ceases when the pH of the duodenal contents rises above 4.5 because of the alkaline pancreatic secretion.

Functions of Secretin

- The primary action of the secretin is to stimulate the pancreas for the secretion of pancreatic fluids and bicarbonates into the duodenum.
- Along with cholecystokinin, secretin stimulates the growth of the exocrine pancreas and the secretion of biliary fluid and bicarbonates.
- Secretin also increases the secretion of insulin and bile and causes constriction of the pyloric sphincter and a decrease in gastric acid secretion.
- It inhibits the secretion of HCl, motility of the stomach and the tonus of the lower oesophageal sphincter.
- It supports chemically induced carcinogenesis in the pancreas.
- Its level decreases in coincidence with peptic ulcers (Fig. 8.12).

Glucose-dependent insulinotropic peptide or Gastric inhibitory peptide (GIP)

Gastric inhibitory polypeptide (GIP) is produced by endocrine K cells of the duodenum and jejunum (upper small intestine) and can stimulate the release of insulin if the blood glucose level is raised. The greatest density of K cells is in the jejunum. The original term (GIP) which referred to its ability to inhibit the secretion of HCl was due to its function – stimulation of insulin secretion changed into the term the glucose-dependent insulinotropic peptide.

Structure and Release of GIP

GIP is a 43 amino acid peptide, having structural similarity to the other members of the secretin family. 7 amino acids of GIP are homologous with secretin. Glucose and fat (triglycerides) in the lumen of the duodenum and proximal jejunum of the intestine can stimulate the release of GIP.

Function

- The predominant effect of GIP is the stimulation of insulin secretion by the β cells of the islets of Langerhans, although glucose must also be present for this effect to occur as elevation of GIP concentration by the administration of triglycerides alone has no effect on insulin secretion.
- As GIP has a stimulatory effect on insulin, it has an important role in signaling the pancreas that a significant carbohydrate and fat load is present in the gut that will require metabolic disposal.
- GIP also inhibits the secretion of gastrin and gastric acid, and it stimulates the release of digestive juices from the mucosal glands of the duodenum and ileum.
- GIP also has a direct metabolic effect on the other tissues and organ such as adipose tissue, liver, muscle, GI tract and brain, where it potentiates the actions of insulin and acts in a manner contrary to that of glucagon.

Vasoactive intestinal peptide (VIP)

Vasoactive intestinal polypeptide (VIP) is secreted from the nerve endings of the entire GIT. In both gut and the brain, this peptide is found mainly in neurons and their synapses. In the gut, these neurons are found between the muscle layers in the submucosa and the Meissner plexus. Its secretion is not increased in response to food intake.

Structure of VIP

This peptide contains 28 amino acid residues and is structurally related to secretin, glucagon and GIP. The structure of VIP is relatively well conserved throughout the animal kingdom.

Functions of VIP

- It has potent vasodilator and hypotensive effects. It relaxes a variety of smooth muscles and antagonizes the effect of smooth muscle constrictor agents.
- VIP can cause the release of glucose from the liver and inhibit gastric acid production and insulin secretion. These actions are normally expressed by the hormones glucagon, secretin and GIP.
- It has a role in relaxing the cardio-oesophageal sphincter and the stomach during gastric filling.

- VIP also effects intestinal blood flow during digestion.
- The histidine-methionine (PHM) peptide yields a similar effect.
- It relaxes the lower oesophageal sphincter and causes vasodilatation in the intestine and brain.
- It inhibits the secretion of HCl, pepsin, gastrin, bicarbonates in the pancreatic juice and resorption of sodium.
- It stimulates the secretion of chlorine in the intestine and releases insulin, glucagon and SMS.
- A decrease in the number of nervous fibers producing VIP brings about increased tonus of sphincters and motility impairments

Peptide Family

This is a heterogeneous group of peptide hormones that have been shown to be secreted in the gut, and usually the brain, and which have some effect on gastrointestinal function. Some of the examples of this family of hormones are motilin, substance P (SP); neurotensin, Adiponectin, leptin, ghrelin etc.

Adiponectin

Adiponectin, a protein hormone, is an adipokine that is solely produced by the adipocyte and has an insulin sensitizing factor. The major site of adiponectin's insulin sensitizing action has been found to be the hepatocytes.Monomeric subunits (30 kDa) form trimers, which further associate to form polymeric complexes of higher structure, including low-molecular-weight (LMW) hexamers (approximately 180 kDa) and high-molecular-weight (HMW) polymers containing 16–18 monomeric subunits (approximately 400–600 kDa). These complexes are the predominant forms of adiponectin in human blood. It seems that oligomerization of adiponectin is essential for some biological effects of this protein.

Functions of Adiponectin

1. Adiponectin is an endogenous insulin-sensitizing factor. In animal models of obesity, adiponectin can reverse insulin resistance.

2. It also appears to exert central catabolic effects, as cerebroventricular injection of the hormone causes weight loss and reduced glucose and lipid levels.

3. Moreover, in contrast to leptin, there is a strong negative correlation in human beings between plasma concentration and BMI. Obese subjects have lower plasma adiponectin concentrations (despite higher fat mass) than non-obese subjects. Weight reduction in obese patients leads to an increase in plasma adiponectin concentration. Men have significantly lower plasma adiponectin concentrations than women.

4. Experimental and clinical studies suggest that adiponectin contributes to the pathogenesis of diabetes, metabolic syndrome, and cardiovascular disease. Low circulating adiponectin concentrations are associated with obesity, insulin resistance, dyslipidemia, atherosclerosis, cardiovascular disease, essential hypertension, metabolic syndrome, and type-2 diabetes.

5. The administration of adiponectin to rodents decreases fat mass by stimulation of fatty acid oxidation in muscle. Moreover, chronically elevated serum adiponectin concentration leads to reduced food intake and amelioration of obesity and glycemic and lipid parameters in obese rats.

Leptin

Leptin, a peptide, is a hormonal product of adipose tissue whose expression reflects the body's state of nutritional reserves (fat). Leptin is believed to act as a metabolic signal to the brain to regulate feeding behaviour and metabolism to allow the body to maintain a normal weight.Recently, the stomach has been identified as an important source of leptin and growing evidence show diverse functions for leptin in the gastrointestinal tract.

Structure of Leptin

Leptin is a product of the obese(OB) gene, acts through its receptor OB-R and is a helix bundle protein. Leptin contains 167 amino acid residues and is mainly produced by the white adipose tissue; however,the stomach is also reported to produce leptin.

Functions of Leptin in GI Tract

- Leptin interacts with the vagus nerve and cholecystokinin to delay gastric emptying and has a complex effect on the motility of the small bowel.
- Leptin modulates absorption of macronutrients in the gastrointestinal tract differentially in physiologic and pathologic states.
- In physiologic states, exogenous leptin has been shown to decrease carbohydrate absorption and to increase the absorption of small peptides by the PepT1 di-/tripeptide transporter.
- In certain pathologic states, leptin has been shown to increase the absorption of carbohydrates, proteins, and fat.
- Leptin has been shown to be upregulated in the colonic mucosa in patients with inflammatory bowel disease.
- Leptin stimulates gut mucosal cell proliferation and inhibits apoptosis. These functions have led to speculation about the role of leptin in tumorigenesis in the gastrointestinal tract, which is complicated by the multiple immunoregulatory effects

Ghrelin

The gastric fundus is the most abundant source of ghrelin, although smaller amounts are found in the intestine, pancreas, pituitary, kidney, and placenta. Ghrelin is produced by distinctive endocrine cells known as P/D1 cells that are of two types, "open" and "closed." The open type is exposed to the lumen of the stomach where it comes into contact with gastric contents, whereas the closed type is not open to the lumen of the stomach but rather lies in close proximity to the capillary network of the lamina propria.Both cell types secrete hormone into the bloodstream. Based on its structure, it is a member of the motilin family of peptides, and, like motilin, ghrelin stimulates gastric contraction and enhances stomach emptying.

Structure of Ghrelin

Ghrelin is a 28 amino acid peptide with a fatty acid chain on the N-terminal of the third amino acid produced by the stomach and is the natural ligand for the growth hormone secretagogue (GHS) receptor (Fig. 8.13).

Functions of Ghrelin

- Ghrelin increases gastric acid secretion and gastric motility.
- It has been found to be a potent appetite stimulantand is involved in the control of energy homeostasis.
- The administration of ghrelin centrally or peripherally stimulates growth hormone secretion, increases food intake, and produces weight gain.
- Circulating ghrelin levels increase during periods of fasting or under conditions associated with negative energy balance such as starvation or anorexia.
- Ghrelin levels are low after eating and in obesity. Ghrelin appears to play a central role in the neurohormonal regulation of food intake and energy homeostasis.
- Ghrelin released from the stomach acts on the vagus nerve to exert its effects on feeding.

Table : Role of some major gastrointestinal hormones in digestion

S.No.	Hormone	Source	Target organ	Action
1.	Gastrin	Stomach	Stomach	Stimulate the gastric gland to secrete & release of gastric juice.
2.	Enterogastrone (=Gastric Inhibitory Peptide-GIP)	Duodenum	Stomach	Inhibits gastric secretion and motility (slows gastric contraction).
3.	Secretin (First hormone discovered by scientists)	Duodenum	Pancreas, Liver, Stomach	Releases bicarbonates in the pancreatic juice . Increases secretion of bile. Decreases gastric secretion and motility.
4.	Cholecystokinin-Pancreozymin (CCK-PZ)	Small Intestine	Gall bladder and Pancreas	Contracts the gall bladder to release bile. Stimulates pancreas to secrete and release digestive enzymes in the pancreatic juice.
5.	Duocrinin	Duodenum	Duodenum	Stimulates the Brunner's glands to release mucus and enzymes into the intestinal juice.
6.	Enterocrinin	Small intestine	Small intestine	Stimulates the Crypts of Lieberkuhn to release enzymes into the intestinal juice.
7.	Vasoactive Intestinal Peptide (VIP)	Small intestine	Small intestine and stomach	Dilates peripheral blood vessels of gut. Inhibits gastric acid secretion.
8.	Villikinin	Small intestine	Small intestine	Accelerates movements of villi.
9.	Somatostatin (SS)	Delta cells of islets of Langerhans of pancreas Argentaffin cells of gastric and intestinal glands	Pancreas, Gastrointestinal tract Gastrointestinal tract.	Inhibits the secretion of glucagon by alpha cells and insulin by beta cells. It also inhibits absorption of nutrients from the gastrointestinal tract Suppresses the release of hormones from the digestive tract.
10.	Pancreatic Polypeptide (PP)	Pancreatic Polypeptide cells	Pancreas	Inhibits the release of pancreatic juice from the pancreas.