6.1 INTRODUCTION

In mammals, the integration of the activities of various parts of the digestive system in dealing with ingested food is partly endocrine in character. The sustainability of life depends on the continuous supply of food. The digestion of food is the first physiological event in the nutritional process. Food is usually broken down to simpler chemical compounds in the presence of acids, alkalis and various digestive enzymes, which are secreted by glands in the wall of the stomach and intestine as well as the acini of pancreas. Finally the digested food is absorbed through the wall of the intestine.

The secretory and motor activities of the gastrointestinal tract in mammals is not only controlled by the autonomic nervous system but also by various hormones that are secreted by the localized areas of the alimentary canal. More than 15 types of hormone-secreting enteroendocrine cells have been

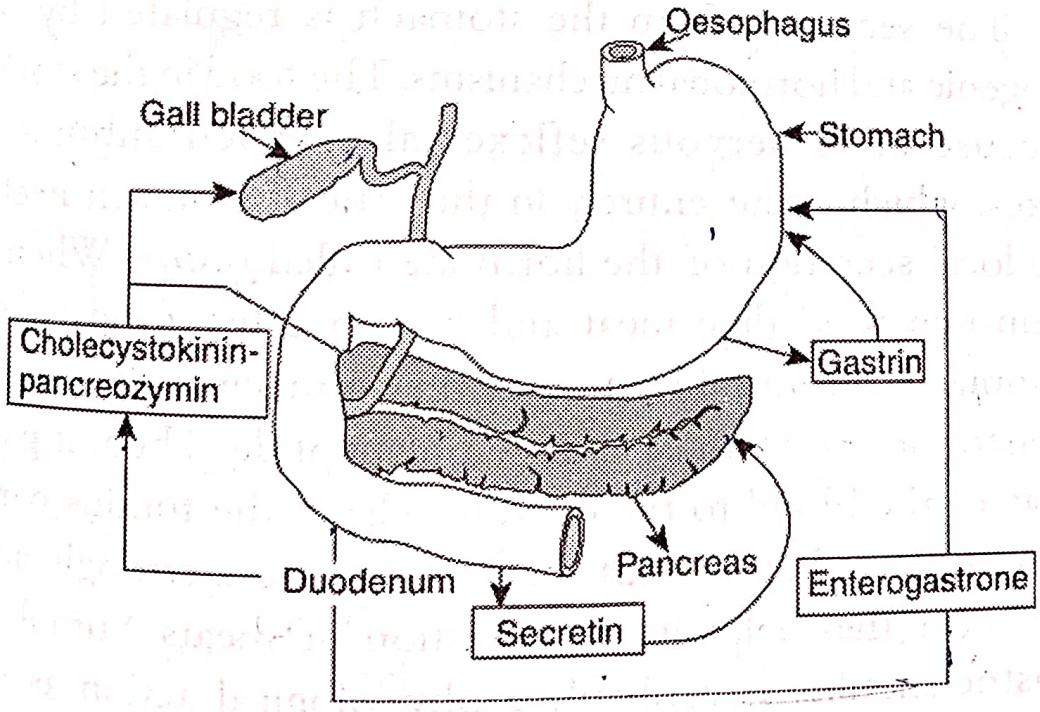

Figure 6.1 Diagrammatic representation of the action of some hormones secreted by gastrointestinal tract with their sites of secretion and action.

identified in the mucosa of the stomach, small intestine and colon. The major hormones and their general sites of formation and regions of action are shown in figure 6.1. The gastrointestinal hormones include *gastrin, secretin, cholecystokinin-pancreozymin, enterogastrone, glucose-dependent insulinotropic polypeptide (GIP), vassoactive intestinal peptide (VIP), motilin.* The release of these hormones is mainly regulated by the presence or absence of particular food in the lumen of the gastrointestinal tract. All the gastrointestinal hormones are protein in nature and play a significant role in regulating the interconversions of nutrients to metabolic substances and their stored forms.

6.2 GASTRIN

The wall of the stomach secretes hydrochloric acid and pepsinogen mainly for the digestion of proteins present in the food. The secretion from the stomach is regulated by both neurogenic and hormonal mechanisms. The food in the stomach can cause local nervous reflexes also called submucosal reflexes, which occur entirely in the wall of stomach itself to cause local secretion of the hormone called *gastrin.* When the protein-rich food (like meat and certain other foods) enters the stomach, the antral portion of the stomach starts secreting the gastrin in the form of a large polypeptide. Then, it passes by way of the blood to the oxyntic cells in the fundus part of the stomach and stimulates them to secrete a strongly acidic gastric juice that helps in the digestion of meats. Stimulation of gastric motility is probably a physiological action as well. The vagus nerve also sensitizes the oxyntic cells to the action of gastrin. The complex reflex arc that is initiated by feeding,

initially involves nerve stimulation along cholinergic nerves to the pyloric cells that release the gastrin.

As mentioned earlier, gastrin is a polypeptide hormone that shows differences in molecular structure due to derivatization of single amino acid residues. Its inactive form is called *preprogastrin*, which is processed into fragments of polypeptide chains of various sizes. There are three forms of gastrin called G 34, G 17, and G 14, in which the figures indicate the number of amino acid residues in its polypeptide chain. G 17 is the principal form of gastrin with respect to the gastric acid secretion. G 14 and G 17 have half-lives of 2–3 minutes in the circulation, whereas G 34 has a half-life of 15 minutes. Gastrins are inactivated primarily in the kidney and small intestine.

6.3 SECRETIN

In 1902, Bayliss and Starling first demonstrated that the excitatory effect of duodenal stimulation on pancreatic secretion was due to blood-borne factor. This factor was then identified as *secretin*. When the food (chyme) enters the upper part of the small intestine, it causes a hormone secretin to be released from the glands of the mucosa of the upper portion of the small intestine. Secretin is a linear polypeptide of 27 amino acid residues, having a molecular weight of 3200. The quantity of the secretin released is especially abundant when the chyme is highly acidic. The secretin in turn is absorbed into the blood and then carried to the glandular cells of the pancreas where it causes the cells to secrete large quantities of the fluids containing extra large amount of sodium bicarbonate. This action of secretin on the pancreatic duct

cells is mediated via cAMP. The bicarbonate then reacts with the acid of the chyme to neutralize it. Thus, the secretin mechanism is an automatic process to prevent excess acid in the upper part of the small intestine.

The product of protein digestion and acid present in the food that bathes the intestinal mucosa stimulates the upper small intestine to release secretin. This is another example of feedback control. In response to secretin the alkaline pancreatic juice floods into the duodenum, neutralizes the acid from the stomach and thus prevents the release of secretin.

6.4 CHOLECYSTOKININ-PANCREOZYMIN (CCK-PZ)

There is another hormone that is liberated from intestinal mucosa; initially it was called pancreozymin, which promotes secretion of pancreatic enzymes. Also, concentration of the gall bladder to liberate bile is caused by an intestinal hormone, cholecystokinin. It is considered that these activities are due to the same substance and hence considered as a single hormone called CCK-PZ or most commonly CCK. Like gastrin, CCK also exhibits in Prepro-CCK that is processed into many fragments, like CCK 58, CCK 39, CCK 12, CCK 8, and CCK 4, where the figures indicate number of amino acid residues in the polypeptide chain. The half-life of the circulating CCK is about 5 minutes.

The presence of fat in intestine initiates the release of bile from the gall bladder, and it also involves an endocrine reflex due to release of CCK. This hormone has several functions in the body and, apart from its action on gall bladder, endocrine and exocrine pancreas and intestinal motility, it can elicit a sensation of satiety. It was experimentally proved that CCK-

injected rats showed reduced feeding. Some of the forms of CCK are also found in the brain where they may be related to production of anxiety and analgesia. In addition to the above-mentioned functions, CCK also inhibits gastric emptying, exerts a trophic effect on pancreas, and may enhance the motility of the small intestine and colon.

It is also evident that along with secretin, it promotes the contraction of the pyloric sphincter and prevents the reflex of duodenum into the stomach. There is a sort of positive feedback mechanism for controlling the secretion of CCK from the small intestine since its secretion is increased when the intestinal mucosa comes in contact with the products of digestion, particularly peptides and amino acids, and also by presence of fatty acids. In response to CCK, bile and pancreatic juice enter the duodenum and digest the protein and fatty food so that more amino acids and fatty acids are formed, which in turn stimulate the intestinal mucosa to secrete more CCK.

6.5 ENTEROGASTRONE

The gastrointestinal hormones with inhibitory effects have also been described. Enterogastrone is one such hormone that is produced in the small intestine in the presence of fatty substances in the duodenum but acts on the stomach by inhibiting its movements and HCl secretion. The ingestion of fatty meals thus retards gastric activity. The action of enterogastrone appears to be principally antisecretory, and since in the presence of enterogastrone the gastric juice produced under the influence of gastric stimulants such as histamine is low in acid content and rich in pepsin, it would appear that enterogastrone preferentially inhibits the acid-secreting parietal cells of the stomach.

6.6 GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP)

It is the hormone secreted by the mucosa of the duodenum and jejunum. It contains 43 amino acid residues. The secretion of GIP is stimulated by the glucose and fat in the duodenum. Previously this hormone was known as gastric inhibitory peptide because in large doses it inhibits the gastric secretion and motility. However, it is now evident that it does not inhibit gastric motility when administered in smaller doses and raises the blood glucose level as seen after a meal. GIP also stimulates β-cells in pancreatic islets for insulin secretion when administered in doses that produce blood levels comparable to those produced by oral glucose. For this reason, it is often called glucose-dependent insulinotropic polypeptide.

6.7 VASSOACTIVE INTESTINAL PEPTIDE (VIP)

It is the hormone present in nerves in the gastrointestinal tract, containing 28 amino acid residues in its polypeptide chain. VIP is also found in blood, in which it has a half-life of 2 minutes. The principal action of VIP in intestine is to promote the intestinal secretion of electrolytes and hence of water. In addition, it also relaxes intestinal smooth muscle, including sphincters, dilates peripheral blood vessels, and inhibits gastric acid secretion.

Other gastrointestinal chemical coordinators have been proposed on the basis of brief experiments, but these appear to have a more questionable existence.

6.8 MOTILIN

It is a polypeptide hormone containing 22 amino acid residues and is secreted by stomach, small intestine and colon. It acts on G protein-coupled receptors on enteric neurons in the duodenum and colon and upon injection it causes contraction of smooth muscles in the stomach and intestine.

6.9 OTHER GASTROINTESTINAL HORMONES

In addition to the above-mentioned hormones, other gastrointestinal hormones are:

i. *Ghrelin* It is the hormone secreted by stomach with secretion decreased by feeding and increased by fasting. It may control the food intake.

ii. *Neurotensin* It is a polypeptide hormone containing 13 amino acid residues that is secreted by neurons and mucosa of the ileum in response to fatty acids. It inhibits gastrointestinal motility and increases ileal blood flow.

iii. *Substance P* It is found in endocrine and nerve cells in the gastrointestinal tract and may enter the circulation. It increases intestinal motility.

iv. *Somatostatin* In addition to hypothalamus and pancreatic islets, gastrointestinal mucosa also secretes this hormone, which exists in tissues in two forms, somatostatin 14 and somatostatin 28. It inhibits gastric acid secretion and motility, pancreatic exocrine secretion, gall bladder contraction, and the absorption of glucose, amino acids and fatty acids.

v. *Glucagon* The hormone from gastrointestinal tract may be responsible for the hyperglycemia after pancreatectomy.

vi. *Guanylin* It is a gastrointestinal hormone secreted by the cells of intestinal mucosa and contains 15 amino acid residues in its polypeptide chain that binds guanylyl cyclase. As a consequence, there is increase in intracellular concentration of cGMP and secretion of Cl^- into the intestinal lumen.