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CONTENTS 15.9.1 Hormones and the gastrointestinal tract 2862 Rebecca Scott, T.M. Tan, and S.R. Bloom 15.9.2 Carcinoid syndrome 2870 B. Khoo, T.M. Tan, and S.R. Bloom 15.9.1 Hormones and the gastrointestinal tract Rebecca Scott, T.M. Tan, and S.R. Bloom ESSENTIALS The gastrointestinal tract is the largest endocrine organ in the body, with its component cells dispersed along its length rather than being clustered in glands. More than 20 gut peptides integrate gastrointestinal function by regulating the actions of the epithe- lium, muscles, and nerves; they also affect the growth and devel- opment of the gut and have a major role in appetite control. They mostly work in an autocrine or paracrine manner. Gastrointestinal hormones include the gastrin–cholecystokinin family, the secretin superfamily, preproglucagon derivatives, the motilin–ghrelin family, the pancreatic polypeptide-fold family, and various other gut peptides. Gastrointestinal and other diseases may cause abnormalities of these gut peptides, for example: (1) achlorhydria (from atrophic gastritis or drug-induced) causes elevation of circulating gastrin; (2) malabsorptive conditions are associated with a decrease in the amount of peptides produced in the affected region, and a com- pensatory elevation of other peptides; and (3) obesity is associated with an imbalance of orexigenic (appetite-stimulating) versus less satiating hormonal changes, and the beneficial effects of bariatric surgery are partly explained through alterations in gut hormones. Introduction William Bayliss and Ernest Starling discovered secretin, the first recognized hormone, from a section of dog jejunum in 1902. The gastrointestinal tract is now recognized as the largest endocrine organ in the body. It produces more than 20 substances that act as hormones or neurotransmitters within the gastrointestinal tract and its associated nervous system. These substances have a diverse range of roles, from gastrointestinal motility, absorption, and growth to control of glucose homeostasis, appetite, and metabolism. Recent advances, such as the identification of REG4 and NEUROG3 genes as markers of hormone-producing enteroendocrine cells, will help identify further hormone-secreting cells and possibly new gastro- intestinal hormones. This chapter will describe the gut peptide hormones and neuro- transmitters in terms of their structure and function. It will then look at the effects of gastrointestinal disease on gut hormones. The end of the chapter will focus on alterations of gut hormones after bariatric surgery, and their potential therapeutic uses. Gut peptides The enteroendocrine cells that secrete gut

hormones are widely dis- persed throughout the gut and pancreas (Fig. 15.9.1.1). Traditionally, enteroendocrine cells have been characterized by their location, morphology, and the hormones they secrete. Recent studies have suggested that there is greater overlap between cells, with multiple hormones being transcribed in each cell. This may provide the in- testine with a degree of adaptability. Nevertheless, as individual cells tend to produce one hormone in greater quantities than others, and cells that produce the same hormone typically cluster together, the traditional delineation of which enteroendocrine cell produces which hormone will be used here. Electron microscopy demonstrates that hormones are stored in specific peptide storage granules within cells, which are subse- quently released by exocytosis (Fig. 15.9.1.2). Enteroendocrine cells can be divided into two types: open-type and closed-type cells. The open-type cells have direct contact with the intestinal lumen via ap- ical cytoplasmic processes, while the closed-type cells do not directly 15.9 Hormones and the gastrointestinal tract

15.9.1 Hormones and the gastrointestinal tract 2863 contact the intestinal lumen. The interplay of luminal, hormonal, and neural signals affects the function of both of these cell types. Molecular cloning techniques have shown that many peptides originate from the same precursor or family. The gut peptides will now be classified according to their common structure or precursor. Gastrin–cholecystokinin family Gastrin Gastrin is made in G cells of the gastrointestinal tract. Most G cells are found in the antrum of the stomach. Gastrin is initially pro- duced as 101-amino acid preprogastrin, but subsequently cleaved to a number of active peptides. These include G6, G14, G17, G34, G54 and G71, though G17 and G34 are the predominant forms in the circulation. The biological activity resides in the four C-terminal amino acids of all these forms. Gastrin release is stimulated by several factors including gas- tric distension, luminal contents (in particular amino acids and calcium), vagal stimulation, and the presence of gastrin-releasing peptide. Release is inhibited by somatostatin and secretin. Gastrin activates the cholecystokinin (CCK)-2 receptor, found mainly on enterochromaffin-like cells and parietal cells. It simulates gastric acid secretion, mainly via a paracrine effect on the enterochromaffin-like cells, which then release histamine that activates the parietal cells. Additionally, gastrin has proliferative effects on the gastric mucosa, and also causes gastric remodelling, which may be involved in the development of gastric cancers. Cholecystokinin CCK is produced by I cells in the duodenum, jejunum, and proximal ileum, and also the myenteric plexus and brain. CCK and gastrin contain five identical amino acids at the C-terminus, but the speci- ficity of CCK is determined by the adjacent three amino acids, such that the octapeptide is the biologically active form (Fig. 15.9.1.3). Like gastrin, CCK refers to a family of biologically active peptides. It is initially produced as prepro-CCK, a 115-amino acid polypep- tide, but cleaved to peptides 58, 39, 33, 22, 12, and 8 amino acids in length. Release is stimulated by luminal products of the digestion of fat and protein, and by the pancreatic secretory trypsin inhibitor-1 (monitor peptide). CCK is a ligand for CCK-1 and CCK-2 receptors. These are widely distributed, being found in the intestine, pancreas, gallbladder, oe- sophagus, brain, and peripheral nerves. CCK has multiple func- tions. These include stimulation of pancreatic enzyme secretion, trophic effects on the pancreas, potentiation of secretin-induced bicarbonate production, contraction of the gallbladder, relaxation of the sphincter of Oddi, inhibition of gastric acid secretion, regu- lation of bowel motility, and delay in gastric emptying. Clinically it is used to measure pancreatic exocrine secretion, sphincter of Oddi manometry, and in radiological examination of the gallbladder. CCK rises postprandially and acts as a satiety signal; however, clinical trials of CCK analogues as an antiobesity therapy have not been successful. Secretin superfamily The secretin superfamily includes secretin, vasoactive intestinal peptide (VIP), glucose-

dependent insulinotropic peptide/gastric inhibitor peptide (GIP), peptide histidine-isoleucine amide/peptide GLP-1 GLP-2 Oxyntomodulin Glicentin PYY(3–36) Somatostatin Large intestine Cholecystokinin Secretin GIP Motilin Somatostatin Small intestine Ghrelin Gastrin Obestatin Stomach Insulin Glucagon Pancreatic polypeptide Amylin Somatostatin Pancreas Fig. 15.9.1.1 The gastrointestinal tract releases a number of hormones from different areas. These hormones signal to the periphery and to the central nervous system to affect a number of biological functions. Fig. 15.9.1.2 Electron micrograph showing the typical morphology of an endocrine cell of the gut mucosa, with well-developed microvilli at the luminal border and secretory granules grouped towards the basal membrane (magnification ×5500). Gastrin (G-17) (pyro) E-G-P-W-L-E-E-E-E-E-A-Y-G-W-D-F-NH2 K-A-P-S-G-R-V-S-M-I-K-N-L-Q-S-L-D- P-S-H-R-I-S-D-R-D-Y-M-G-W-M-D-F-NH2 SO3H SO3H Cholecystokinin Fig. 15.9.1.3 Amino acid sequences of gastrin (G-17) and cholecystokinin, demonstrating the shared pentapeptide tail, and the three additional amino acids that confer activity to cholecystokinin.

SECTION 15 Gastroenterological disorders 2864 histidine methionine amide, orexins, growth hormone-releasing factor, pituitary adenylate cyclase-activating polypeptide (PACAP), and preproglucagon derivatives. Secretin Secretin is a 27-amino acid polypeptide produced by S cells scattered through the duodenum and jejunum. Secretin-immunoreactive cells are also found in the brain. Secretin acts on a G protein-coupled receptor found in the brain, pancreas, intestine, kidney, and biliary epithelium. Hydrochloric acid potently stimulates secretin release, and a duodenal pH less than 4.5 causes significant secretin production. Additional stimulants to release are bile and the products of fat di- gestion. Secretin reduces gastric acid production and stimulates the release of a bicarbonate-rich, alkaline pancreatic fluid. It also re- duces gastric motility, stimulates bile secretion, and induces insulin release. Secretin may play a role in the developing gastrointestinal tract, with high concentrations in the early postnatal period. Glucose-dependent insulinotropic peptide GIP is a 42-amino acid peptide secreted from intestinal K cells that are found most abundantly in the proximal small intestine. GIP re- lease is stimulated by food consumption, particularly glucose, long- chain fatty acids, and their monoglycerides. At pharmacological doses, GIP inhibits gastric secretions, hence its original name of gastric inhibitor peptide. However its predominant physiological role is as an incretin, enhancing glucose- stimulated insulin secretion (Fig. 15.9.1.4). The incretin effect in type 2 diabetes is reduced in part due to a reduction in the effect of GIP. GIP increases insulin production and pancreatic beta-cell proliferation, and reduces beta-cell apoptosis; but it also causes glucagon secretion, and subsequent hyperglycaemia, preventing it being a diabetes treatment. The additional physiological effects of GIP are still debated. GIP receptors are found on adipose tissues, but studies have shown GIP to both promote fat deposition and to cause lipolysis. GIP reduces bone resorption, and a common mutation in the GIP receptor increases bone fracture risk. GIP receptors are also widely expressed in the brain, and may have a role in memory. There is increasing evidence suggesting drugs that are combined agonists at the GIP, glucagon-like peptide (GLP)-1, and glucagon receptors may be effective treatments for diabetes and obesity. Vasoactive intestinal polypeptide VIP is a 28-amino acid neurotransmitter widely produced in the in- testine, as well as the nervous, respiratory, and reproductive systems. It acts on VIP receptors type 1 and 2 (VPAC1 and VPAC2), which are widely expressed, reflecting the diverse actions of VIP. Within the gastrointestinal tract it stimulates secretion of water and electrolytes in the gastrointestinal lumen, and increases gastrointestinal motility. It has insulinotropic and antiapoptotic effects on the pan- creas. VIP affects food intake and fat deposition, and affects release of other gastrointestinal hormones including GLP-1 and peptide tyrosine-tyrosine (PYY).

Peptide histidine isoleucine amide This 27-amino acid peptide derives its name from an N-terminal his- tidine, and a C-terminal isoleucine amide. It is produced throughout the intestine, with highest concentrations in the colon, but is also found in the brain, respiratory system, and reproductive system. It colocalizes with VIP and has a range of actions, including stimu- lating the secretion of pancreatic juice and amylase, the release of glucagon, and augmenting water and electrolyte transport in the jejunum. Neurotransmitters of the secretin family: orexins, GHRF, and PACAP PACAP is a neurotransmitter of 38 amino acids, which has signifi- cant homology to VIP. PACAP is present in several peripheral tis- sues, including the gastrointestinal tract, adrenal gland, and testes. It acts on VIP receptors and PAC1 receptors. PACAP stimulates salivary, gastrointestinal and pancreatic secretions; relaxes gastro- intestinal smooth muscle; and suppresses food intake. It is also in- volved in the control of circadian rhythm, learning, memory, and anxiety. Orexins A and B (also known as hypocretins) are, respectively, 33- and 28-amino acid peptides, formed from post-translational processing of the same precursor. Their highest concentration is in the hypothalamus, but they are widely expressed, including in the gastrointestinal tract. Orexin B has an appetite-stimulating effect, while orexin A is involved in sleep control, with defects being asso- ciated with narcolepsy. CCK downregulates orexin expression, and may reduce food intake in this way. Growth hormone-releasing factor, a 44-amino acid peptide, is found predominantly in the hypothalamus. At low doses it stimu- lates feeding, while at high doses it suppresses feeding. Preproglucagon derivatives The preproglucagon gene is found on chromosome 2. The trans- lated 180-amino acid polypeptide is expressed in the alpha-cells of the pancreas, L-cells of the intestine, and within the brain. Within the pancreas, the enzyme proconvertase 2 converts this polypep- tide into glucagon, glicentin-related pancreatic peptide, and major proglucagon fragment. In the intestine and brain, proconvertase 1/3 cleaves the prohormone into a number of related peptides: glicentin Blood glucose Plasma insulin Time Plasma insulin after oral administration of glucose Plasma insulin after oral administration of glucose Blood glucose after oral administration of glucose Blood glucose after IV administration of glucose Fig. 15.9.1.4 Representation of the incretin effect. Administration of the same amount of glucose as an oral dose (green lines) compared to an intravenous dose (blue lines) causes a similar change in plasma glucose level (solid lines), but a relatively greater increase in insulin releases (dashed lines). This is due to glucose within the intestine leading to GLP-1 and GIP release, which stimulate insulin secretion.

 (also known as enteroglucagon), GLP-1, GLP-2, and oxyntomodulin (Fig. 15.9.1.5). Glicentin This is a 69-amino acid peptide, containing a glucagon molecule with an N-terminal extension (glicentin-related pancreatic polypep- tide). It is released from the L cells of the intestine after a mixed meal, particularly of carbohydrate and long-chain fatty acids. The amount of glicentin secreted is proportional to the amount of unabsorbed food entering the colon, so high glicentin concentrations are found in conditions where the absorptive capacity of the small intestine is lost. It acts to reduce digestive secretions, delay gastric emptying, and increase insulin secretion, and it has a trophic effect on the gut. Glucagon-like peptide-1 GLP-1 is secreted as GLP-11–37, GLP-1 (7-36) amide and GLP-17–37. The GLP-1 (7-36) amide and GLP-17–37 moieties have biological activity, and are rapidly degraded in the plasma by the enzyme dipeptidylpeptidase-4 (DPP-4). GLP-1 is secreted following direct contact of nutrients with the intestinal lumen, and by a neuroendo- crine circuit involving the vagus nerve and the hormone GIP. GLP-1 stimulates insulin release and lowers blood sugar. Endo genous GLP-1 is an incretin, enhancing insulin release following oral consumption of glucose. Long-acting analogues of GLP-1 are widely used to treat type 2 diabetes, as are DPP-4 inhibitors, which act by enhancing the action

of endogenous GLP-1. GLP-1 has additional effects in the pancreas, enhancing beta-cell proliferation, inhibiting glucagon secretion, and reducing apoptosis. Evidence that GLP-1 analogues may lead to acute pancreatitis and pancreatic cancer has been equivocal, hence clinical vigilance is suggested. GLP-1 induces satiety through actions on the vagus nerve and the central nervous system (Fig. 15.9.1.6), and GLP-1 analogues are now being used to treat obesity by reducing appetite. GLP-1 is found in the taste cells of the gastrointestinal tract, and modulates preference for sweet food. Glucagon-like peptide-2 GLP-2 has trophic effects on the intestine, enhancing crypt cell pro- liferation and reducing enterocyte apoptosis. It also enhances nutrient absorption and increases intestinal blood flow, and GLP-2-based drugs are used clinically to enhance nutrient absorption in patients with short bowel syndrome. Oxyntomodulin Oxyntomodulin is a 37-amino acid polypeptide that consists of a glucagon molecule with a C-terminal extension. There is no known oxyntomodulin-specific receptor, but it activates both the GLP-1 and glucagon receptors, though to a lesser extent than either cog- nate ligand. It is released postprandially, and is a potent inhibitor of gastric motility and gastric acid secretion. Its actions on the GLP-1 receptor mean it induces satiety, while activation of the glucagon receptor increases energy expenditure. In humans, the increase in energy expenditure caused by oxyntomodulin may be via increased physical activity, whereas animal data suggests it increases resting energy expenditure. Drugs that mimic the actions of oxyntomodulin are in development as potential treatments for obesity. PS GRPP GRPP GRPP Glucagon Glucagon Glucagon Glucagon IP1 IP1 Oxyntomodulin Glicentin IP1 GLP-1 GLP-1 GLP-1 Major Proglucagon Fragment Pancreas (proconvertase 2) Brain/intestine (proconvertase 1/3) GLP-2 GLP-2 GLP-2 IP2 IP2 Fig. 15.9.1.5 Major active derivatives of the preproglucagon gene. In the pancreas, proconvertase 2 predominantly produces glucagon; additional fragments include glicentin-related polypeptide (GRPP) and the major proglucagon fragment (GRPP + glucagon + IP1). In the central nervous system and the intestine, alternative processing by proconvertase 1/3 produces GLP-1, GLP-2, oxyntomodulin, and glicentin.
Fig. 15.9.1.6 Section showing c-fos staining of the paraventricular nucleus in mice after administration of the GLP-1 analogue Exendin-4.

 Motilin–ghrelin family Preproghrelin is subsequently processed into either the 28-amino acid peptide ghrelin, or the 23-amino acid amidated peptide obestatin. Motilin is a 22-amino acid peptide that shares 50% hom- ology with ghrelin. Ghrelin and motilin act on receptors that are part of the same G protein-coupled receptor family. The receptor for obestatin remains uncertain, and early reports of it acting on the GPR39 receptor have not been replicated. Motilin Motilin is a 22-amino acid peptide produced by intestinal M cells. These are found in the jejunum, duodenum, and to a lesser degree the stomach antrum. Motilin is released in the interdigestive period, in as- sociation with period 3 of the migrating motor complex that controls gastrointestinal motility. After meals, it is released in response to duo- denal acidification, and also to mechanical influences on the gastro- intestinal tract. Motilin acts to enhance gastrointestinal motility. Erythromycin activates the motilin receptor and is the basis for its role in gastric motility, helping those with delayed gastric emptying. Motilin agonists are in phase II trials in the treatment of gastroparesis. Ghrelin Ghrelin is a 28-amino acid peptide that is n-octanoylated on the third residue by the enzyme Ghrelin-O-acyltransferase (GOAT). It is produced predominantly by the X/A-like cells of the stomach, though is found in small amounts in the intestine, pancreas, kid- neys, pituitary, and hypothalamus. Ghrelin was first characterized as a growth hormone secretagogue, but its major action is to stimu- late food intake. Ghrelin is the only known orexigenic (appetite- stimulating) hormone (as opposed to an autocrine or paracrine agent), with

endogenous levels rising during fasting and falling postprandially. The rise in ghrelin also stimulates growth hormone release which protects blood glucose levels during fasting. Ghrelin has potential to stimulate appetite in chronic conditions associated with anorexia such as cancer, renal failure, and dialysis; antagonists have been trialled as obesity therapies, but have not been successful. Ghrelin causes a preference for sweet food, though the mechanism by which this happens is not yet understood. Additionally, ghrelin inhibits nausea and increases gastric emptying. Obestatin Obestatin is 23-amino acid amidated peptide produced by the stomach. Initial rodent studies found obestatin suppresses food in- take and reduces body weight, but subsequent studies refuted this. Obestatin may be involved in processes such as sleep, memory, and anxiety; it may also have protective effects in the gastrointes- tinal tract, reducing development of acute pancreatitis, colitis, and helping the healing of gastric ulcers. Pancreatic polypeptide-fold family The pancreatic polypeptide-fold (PP-fold) family includes the gut hormone peptide tyrosine-tyrosine (PYY), the neurotransmitter neuropeptide Y, and pancreatic polypeptide found in pancre- atic islets. All are 36-amino acid peptides that require C-terminal amidation for bioactivity, and share the PP-fold structural motif. They interact with the Y family of receptors that couple to inhibitor G proteins and are probably derived from a common ancestral gene. Peptide tyrosine-tyrosine PYY is secreted as PYY1–36 by the L cells of the intestine, and is con- verted to the biologically active PYY3–36 by dipeptidylpeptidase 4 in plasma. PYY3–36 is a specific agonist for the Y2 receptor, which is densely expressed in the arcuate nucleus of the hypothalamus. It is released following a meal in proportion to energy content con- sumed; protein stimulates PYY release more than other macronutri- ents. PYY is a satiety signal, with levels falling during fasting. It also delays gastric emptying, decreases intestinal motility, and inhibits gastric acid secretion. PYY modulates the rewarding properties of food, and higher endogenous levels are associated with disordered eating. Neuropeptide Y Neuropeptide Y (NPY) is a widely expressed neurotransmitter, often colocalized with noradrenaline. It is found in the extrinsic adren- ergic nerves of the myenteric plexus, and in the intrinsic nerves of the myenteric and submucosal plexi, with highest concentrations in the upper intestine and distal colon. In the gut it is a potent vasocon- strictor, it inhibits intestinal secretion, and it depresses colonic mo- tility. NPY is an important neurotransmitter in the central nervous system, and expression within the hypothalamus stimulates feeding. Pancreatic polypeptide Pancreatic PP is secreted by PP cells of the endocrine pancreas, and in small amounts by the distal intestine. It binds to the Y4 receptor, which is widely distributed in the central nervous system. PP is released in response to oral nutrients, and through vagal stimula- tion during the cephalic phase of ingestion. PP inhibits pancreatic exocrine secretion of enzymes and bicarbonate, and enhances the insulin-induced decrease in hepatic glucose output. It acts as a sa- tiety signal and slows gastric emptying. Other gut peptides Bombesin and the gastrin-releasing peptides Bombesin is a 1620-Da peptide of 14 amino acids, isolated from amphibian skin. It stimulates gastrin release and hence gastric acid secretion. Mammalian bombesin has not been isolated, but a number of peptides which share the biologically active C-terminal sequence have been found. These include gastrin-releasing pep- tide, neuromedin B, and neuromedin C. Gastrin-releasing peptide (GRP) is 27 amino acids long and found in the intrinsic neurons of the myenteric and submucosal plexi, particularly in the stomach and pancreas, and also in the mammalian central nervous system. It reduces food intake, and affects circadian rhythm, the sensation of itch, memory, smooth muscle contractions, and sexual behaviour. Neuromedin B is expressed in the hypothalamus and controls the stress, thyroid, and reproductive axes. It also reduces food intake. Neuromedin B and GRP work on the BB1 and BB2 receptors re- spectively. A BB3 receptor has been cloned, though its endogenous ligand has not been isolated; however, the receptor may have a role in glucose homeostasis. Neuromedin C

affects pancreatic exocrine and endocrine secretion. Opioids The opioids met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin are found in enteric neurons and mucosal endocrine

15.9.1 Hormones and the gastrointestinal tract 2867 cells. The μ, κ, and δ-opioid receptors are found throughout the gastrointestinal tract. Their effects include delaying transit through the small and large intestine, inhibiting gastric emptying, and inhibiting fluid and electrolyte secretion. These combine to cause constipation: opioids have been used to treat diarrhoea for centuries. Endogenous opioids reduce inflammation within the gastrointes- tinal tract, and maintain gastric mucosal integrity, so modulation of this system may be useful in inflammatory bowel disease. Endocannabinoids Humans produce a large number of endogenous endocannabinoids. These act on CB1 and CB2 receptors. The CB1 receptor is important in energy homeostasis, as activation increases food intake. Some obese people have been shown to have mutations in the gene coding for the FAAH enzyme, which leads to increased activity of the CB1 receptor. The inverse agonist for the CB1 receptor, rimonabant, has been used as a treatment for obesity. Endocannabinoids also regu- late gut motility, inflammation, and pain. Tachykinins There are two tachykinin genes: preprotachykinin A (TAC1) which encodes substance P and neurokinin A, and preprotachykinin B (TAC3) which encodes neurokinin B. These are excitatory neuro- transmitters which are released in response to inflammation and in- fection, and regulate pain, secretion, and motility. The tachykinins are responsible for the diarrhoea and gastrointestinal side effects seen after chemotherapy, radiotherapy, and certain infections. NK1- R receptor antagonists have been approved to treat nausea associ- ated with chemotherapy and radiotherapy. Neurotensin Neurotensin is a 13-amino acid peptide found in the CNS, en- teric neurons, and N cells of the gastrointestinal tract. N cells are predominantly found in the ileum, but are spread throughout the gastrointestinal tract. Release is stimulated by intestinal fatty acids. Central and peripheral administration of neurotensin reduces appetite in rodent models. It helps protect the gastric mucosa by stimulating growth and preventing apoptosis, reducing acid secre- tion, and decreasing gastric motility. It also enhances pancreatic secretion and insulin release, and prevents apoptosis in pancreatic acinar cells. Somatostatin Somatostatin is cleaved from a 122-amino acid precursor to a number of different forms. The 28-amino acid form is secreted by D cells that are widely distributed in the gastrointestinal tract and pancreas; in enteric neurons the 14-amino acid form predomin- ates. Release is stimulated by food consumption, particularly fat and proteins. Somatostatin has a wide range of roles, but importantly it suppresses all the activities of the gastrointestinal tract. It reduces secretions from the salivary glands, biliary tree, the stomach, and pancreas. It suppresses hormone release, including gastrin, secretin, motilin, enteroglucagon, CCK, VIP, GIP, intrinsic factor, pepsin, neurotensin, insulin, PP, and glucagon. It inhibits gastrointestinal motility, reduces visceral blood flow, and limits cell growth and re- newal within the gastrointestinal tract. Somatostatin analogues have a number of clinical uses, including the treatment of acromegaly and imaging of neuroendocrine tumours. Amylin Also known as islet amyloid polypeptide, amylin is a 37-amino acid peptide released from pancreatic beta-cells in response to food consumption. Amylin primarily reduces blood glucose levels, but pharmacological dosing leads to reduced food intake. Synthetic amylin has been approved in for use in the United States of America in diabetic patients treated with insulin and trials of amylin com- bined with other potential weight loss drugs, including leptin and sibutramine, continue. Peptide neurotransmitters Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide formed by alternative processing of the calcitonin gene transcript, and is related to amylin. It is found in the extrinsic sensory neurons and intrinsic neurons of the intestine. It reduces food intake, gastric acid and pancreatic secretion,

protects against gastric ulcers, and af- fects gastrointestinal motility. It also plays a role in detection of co- lonic pain and inflammation. Nesfastin-1 is an 82-amino acid peptide produced from the pre- cursor nucleobindin-2 in the pancreas and gastric mucosa, and is also expressed in the brain. It reduces food intake and controls gastrointestinal motility. Galanin is a 30-amino acid peptide in humans, found in enteric neurons. It acts through three distinct G-coupled protein recep- tors, and within the gastrointestinal tract, stimulates feeding, re- duces gastric acid secretion, influences gastric emptying, and affects gastrointestinal motility. Endothelins comprise three different peptides: ET-1, ET-2, and ET-3. ET-1 is expressed in multiple gastrointestinal tissues including vascular endothelium, submucosal stroma, and muscle. It causes both contraction and relaxation of the gastrointestinal tract depending on which receptor is activated, and has effects on vascular tone and perfusion. ET1 is elevated in a number of inflammatory conditions, including inflammatory bowel disease and peptic ulcer disease, and this may reduce perfusion to the intestinal mucosa and slow healing. Alterations in hormones in gastrointestinal and other diseases Gastric pathology and hypergastrinaemia Achlorhydria refers to a condition of low or absent secretion of hydrochloride acid within gastric secretions. It has a number of causes, including atrophic gastritis, bacterial overgrowth, intes- tinal metaplasia, pernicious anaemia, uraemia, long-term use of proton pump inhibitors, and H2 inhibitors. The lack of feedback from acid secretion causes hyperplasia of gastrin-secreting G cells. The subsequent elevation in gastrin levels causes hyperplasia of enterochromaffin-like cells (Fig. 15.9.1.7), which leads to carcinoid tumours; there is also an increased risk of gastric cancer. To date, there is no evidence that long-term proton pump inhibitor or H2 inhibitor use causes gastric carcinoids. Peptic ulcer disease is not normally associated with abnormal- ities in gut peptide secretion. However, in some studies, gastrin release is increased by Helicobacter pylori infection. CCK-B re- ceptor antagonists, which block the effects of gastrin, may be useful in the treatment of gastric ulcers. Additionally, reduced

 somatostatin levels in patients infected with H. pylori may influ- ence the paracrine regulation of gastric function. Dumping syndrome Subsequent to vagotomy or gastrectomy, there is increased speed of gastric emptying and food enters the small intestine rapidly. This may manifest itself as the symptoms of ‘dumping syndrome’, with sweating, fainting, flushing, weakness, feelings of hunger, and rapid heart rate. In those with dumping syndrome, there is a concurrent alteration in gut hormone response, with VIP, glicentin, and neurotensin all rising above the levels expected after a meal, while motilin release is reduced. The increase in VIP and neurotensin may contribute to the postprandial hypotension associated with dumping syndrome. Inflammatory bowel disease Altered levels of gut hormones are found in inflammatory bowel dis- ease. In ulcerative colitis, colonic PYY levels are reduced, in favour of the L-cells producing higher levels of enteroglucagon and GLP-1. There is increased release of GIP, gastrin, glicentin, ghrelin, motilin, and pancreatic polypeptide. In contrast, tachykinin levels are reduced. In Crohn’s disease, there are increased numbers of terminal ileal cells containing GLP-1, but no increase in plasma GLP-1. However, there are raised levels of GIP, ghrelin, motilin, and enteroglucagon, while PYY is reduced. Changes in gastrointestinal hormones may be re- sponsible for altered appetite and nutrient handling in inflammatory bowel disease. Elevated levels of endothelin have been reported in both ulcerative colitis and Crohn’s disease, and oral administration of an endothelin receptor antagonist in a model of colitis has been found to ameliorate diarrhoea and tissue damage. Endocannabinoids reduce inflammation, and research continues as to their therapeutic value in inflammatory bowel disease. Irritable bowel syndrome Irritable bowel syndrome is characterized by diarrhoea, constipation, bloating, and abdominal

discomfort. Levels of enteric hormones do change, but the exact pattern varies in patients depending on the predominant phenotype. In most, CCK and VIP levels are raised, while PYY and NPY are reduced. However motilin and gastrin immunoreactivity appear higher in those with diarrhoea- predominant irritable bowel syndrome. Malabsorption Malabsorptive conditions are associated with a decrease in the amount of peptides produced in the affected region, and a compensatory elevation in other peptides, particularly those trophic peptides implicated in the bowel's adaptation to loss of absorptive surface, such as enteroglucagon (Fig. 15.9.1.8). In coeliac disease, PYY, ghrelin, enteroglucagon, and neurotensin are elevated while GLP-1, amylin, secretin, and GIP are reduced. Elevated enteroglucagon has a trophic effect on the small intestinal mucosa, while increased PYY may affect pancreatic and biliary se- cretion. In tropical sprue, PYY and enteroglucagon are also elevated, as are motilin levels, but the other hormone levels are normal. In both sprue syndromes, treatment normalizes gut hormones. The malabsorption associated with pancreatic exocrine insuf- ficiency of any cause leads to an excess of nutrients in the colon, and as a result, the concentrations of enteroglucagon, PYY, and neurotensin are raised. The gut adaptation resulting from the effects of these peptides may contribute to the improvement in absorptive function with age in patients with cystic fibrosis. Neuropathic disease In conditions where there is destruction of intrinsic enteric nerves, neuroendocrine peptides are also affected. In Hirschsprung's disease, where children have aganglionic bowel segments, VIP, substance P, PACAP, and neurotensin levels are reduced, while NPY- containing neurons are not. These changes may contribute to the defect in intestinal relaxation. There are also increased numbers of neuroendocrine cells producing PYY, somatostatin, and serotonin, which contribute to sustained intestinal contraction. Fig. 15.9.1.7 Histological section of gastric fundus (oxyntic mucosa) from a patient with pernicious anaemia. Long-standing achlorhydria has led to hyperplasia of enterochromaffin-like cells, demonstrated by immunostaining of the general endocrine cell marker chromogranin. In addition to the abnormally high number of cells in the mucosa, small nodules (microcarcinoids) have formed in the submucosa (magnification ×180). % 1400 1200 1000 800 600 400 200 Normal Gastrin HPP Insulin GIP Secretin Motilin Neurotensin Enteroglucagon Fig. 15.9.1.8 The percentage incremental rise in gut hormones following a standard test breakfast in patients with coeliac disease compared with normal controls.

 In Chagas' disease there is destruction of enteric nerves due to chronic infection with Trypanosoma cruzi. There is a general re- duction in neural innervation, and greatly reduced levels of sub- stance P in biopsies from these areas. However, there is a relative increase in neurons that express VIP within the myenteric plexus, and this may be essential in allowing Chagas' patients to survive for many years, as VIP is essential for the maintenance of mucosal integrity. Diarrhoea In infants with acute gastroenteritis, there is an increase in enteroglucagon, glucagon, PYY, and motilin levels, while galanin-1 is responsible for increased colonic secretion in rodent models of rotavirus, Salmonella typhimurium, shigella, and Escherichia coli in- fections. In patients with functional diarrhoea, pancreatic polypep- tide levels are increased. Obesity Many of the gut hormones have effects on food intake and energy expenditure—PYY, PP, GLP-1, oxyntomodulin, and CCK—are anorexigenic, while ghrelin is orexigenic. These act via the 'gut–brain axis', transmitting signals from the gastrointestinal tract to the hypo- thalamus and brainstem directly, and indirectly via the vagus nerve. These should work to keep weight stable, with energy intake and expenditure equal, but given the increasing prevalence of obesity it is clear that this system is not flawless. In obesity, the hormonal milieu changes to be orexigenic and less satiating, with lower fasting levels of PYY3–36, PP, and CCK, lower postprandial rises in PYY and GLP-1, while there is a higher proportion in ghrelin in the active,

acylated state, and ghrelin levels fail to fall after eating. Moreover, these changes are exacerbated in dieting: fasting ghrelin and NPY increase, while GIP, PP, and amylin all fall. The reduced levels of satiety hormones may contribute to the rebound in body weight commonly seen when people stop dieting. After gastrointestinal surgery The changes seen postoperatively depend on the type and extent of surgery. After subtotal gastrectomy for early gastric cancer, there is a rapid change in the levels of gut hormones ghrelin, obestatin, and PYY, but these normalize in 3 days, suggesting that there are com- pensatory mechanisms. After total gastrectomy, PYY levels tend to increase overall, possibly to compensate for the rapid gastric transit. In short bowel syndrome, levels of PYY, enteroglucagon, and VIP have been reported to change, but increments or decrements depend on the extent of the resection. Bariatric surgery Bariatric surgery is at present the most effective and long-lasting treatment for obesity. This is in part through alterations in gut hor- mones to produce a more anorexigenic environment (Table 15.9.1.1). After Roux-en-Y bypass, GLP-1, PPY, oxyntomodulin, glucagon, and CCK levels are all increased, while ghrelin levels fall. There is some evidence that gastrin levels fall as nutrients have less contact with G cells, but most patients are commenced on proton pump in- hibitor therapy which subsequently elevates gastrin. The increase in GLP-1 may cause the early resolution of diabetes seen after gastric bypass, before there is any change in body weight. FURTHER READING Afroze S, et al. (2013). The physiological roles of secretin and its re- ceptor. Ann Transl Med, 1, 29. Besterman H, et al. (1983). Gut hormones in inflammatory bowel dis- ease. Scand J Gastroenterol, 18, 845–52. Bloom S, Long R (eds) (1982). Radioimmunoassay of gut regulatory peptides. Saunders, London. Cegla J, Bloom S (2014). Gastrointestinal tract and appetite control. In: Lomer M (ed) Advanced nutrition and dietetics in gastroenter- ology, pp. 48–54. Wiley-Blackwell, Chichester. Ceranowicz P, Warzecha Z, Dembinski A (2015). Peptidyl hormones of endocrine cells origin in the gut—their discovery and physiological relevance. J Physiol Pharmacol, 66, 11–27. Chandra R, Liddle R (2007). Cholecystokinin. Curr Opin Endocrin Diabetes Obes, 14, 63–7. Dacha S, et al. (2015). Hypergastrinemia. Gastroenterol Rep (Oxf), 3, 201–8. Dimaline R, Varro A (2014). Novel roles of gastrin. J Physiol, 592, 2951–8. Gribble F, Reimann F (2015). Enteroendocrine cells: chemosensors in the intestinal epithelium. Annu Rev Physiol, 78, 277–99. Harrison E, Lal S, McLaughlin J (2013). Enteroendocrine cells in gastrointestinal pathophysiology. Curr Opin Pharmacol, 13, 941–5. Hay D, et al. (2015). Amylin: pharmacology, physiology and clinical potential. Pharmacol Rev, 67, 564–600. Holzer P (2009). Opioid receptors in the gastrointestinal tract. Regul Pept, 155, 11–17. Kirchgessner A (2002). Orexins in the brain-gut axis. Endocr Rev, 23, 1–15. Larsson L (1994). Hirschsprung's disease—immunohistochemical findings. Histol Histopathol, 9, 615–29. Loh K, Herzog H, Shi Y (2015). Regulation of energy homeostasis by the NPY system. Trends Endocrinol Metab, 26, 125–35. Mustain W, Rychahou P, Evers B (2011). The role of neurotensin in physiologic and pathologic processes. Curr Opin Endocrinol Diabetes Obes, 18, 75–82. Rai U, et al. (2015). Therapeutic uses of somatostatin and its ana- logues: current view and potential applications. Pharmacol Ther, 152, 98–110. Table 15.9.1.1 Gut hormones levels in obesity and after Roux-en-y gastric bypass. In obesity, the satiety signals are reduced, including PYY, PP, GLP-1, and CCK; this may lead to further food intake. After Roux-en-Y bypass, many of these responses are restored, which will aid weight loss. The enhanced GLP-1 release after bypass contributes to the improvement in glucose tolerance seen after bariatric surgery. Hormone Obesity Roux-en-Y surgery PYY ↓ postprandial rise ↑ postprandial response PP ↓ ↓ GLP-1 ↓ postprandial rise ↑ postprandial response Oxyntomodulin ↑ postprandial response CCK ↓ ↑ postprandial response Ghrelin ↓ but fails to fall postprandially ↓ GIP ↔ ↓ Gastrin ↔ ↓ but elevated by proton pump inhibitor treatment

Revision #1
Created 2026-01-22 16:39:03 UTC by Omar Ayman
Updated 2026-01-22 16:39:03 UTC by Omar Ayman