Chapter 1
Regulation of Gastrointestinal Functions

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1 Introduction of the Gastrointestinal System

The **Gastro-Intestinal (GI) system** is divided into **two parts:** the **luminal GI** and **hepato-biliary-pancreatic GI.**

The **luminal (or tubular) GI** consists of the alimentary (digestive) canal or GI tract, which extends from the mouth to the anus (Fig. 1.1)**.** The GI tract includes the **pharynx, esophagus, stomach, small intestine** (*duodenum, jejunum and ileum*) and **large intestine** (*colon, cecum and rectum*), as well as the **anus.** The GI tract is a muscular tube of about *5 m* long when one is alive; however, after a person dies and during autopsy or postmortem examination, the length of the tract can be doubled to *10 m.* This is due to the loss of muscle tone. The GI tract can contract and relax with different transit time in each segment of the tract, which, in turn, depends on its own specific function (i.e. **motility** or **secretion**) of each segment. The motor and secretory activities of the GI system are highly controlled and integrated by the **gut endocrine** and **enteric nervous systems** (see Section on "Neural and Hormonal Regulators of Gastrointestinal Function").

The **hepato-biliary-pancreatic GI** consists of the associated glands and organs of the GI system; they include the *salivary glands* (parotid, sublingual and submandibular glands), *pancreas, gallbladder* and *liver* which empty their secretions into the lumen of the GI (e.g. luminal digestive enzymes). The **salivary glands** secrete saliva for digestion and lubrication; the **pancreas** produces hydrolytic enzymes for the digestion of our daily foodstuff and bicarbonate for

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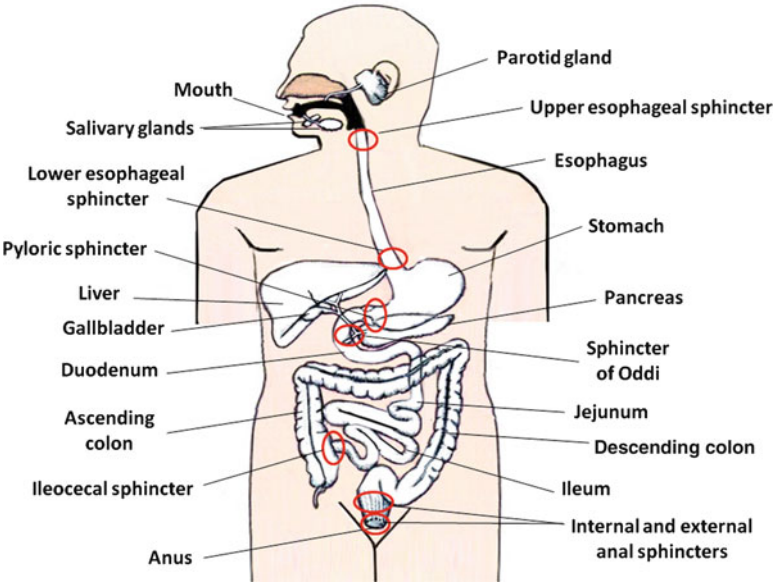

Fig. 1.1 A schematic diagram of the gastrointestinal system showing the digestive tract and the associated organs. The *circled* structures indicate the key locations that separate the digestive tract from each other by the structures called "sphincters"

the neutralization of our gastric contents; the **liver** secretes bile, which is stored temporarily in the gallbladder and subsequently delivered to the duodenum for fat digestion and absorption.

There are key locations that separate the different parts of the GI tract from each other by a structure called ***"sphincter",*** e.g. esophageal (upper and lower), pyloric, sphincter of Oddi, ileocecal, and anal sphincters (Fig. 1.1)**.** Sphincters are made up of **smooth muscle** and they act as the "valve of a reservoir" for holding luminal content adequately before emptying the content into next segment by their highly coordinated activity. **Dysregulation of the activity of sphincters** results in **GI motility disorders** (e.g. *Gastroparesis*/*Dumping Syndrome* and *Achalasia*/*Gastro-Esophageal Reflux Disease (GERD)*). As a basic concept, dysfunction of either GI motility or secretion, or both, can lead to some common GI disorders including, but not limiting to, *GERD*, *Peptic ulcer Disease (PUD),* and *Diarrhea*.

1.1 General Structure of the Gastrointestinal Tract

The structure of the GI tract varies greatly from region to region, but common features exist in the overall organization of the wall of the tract (Fig. 1.2)**. From inside out**, there are four characteristic layers.

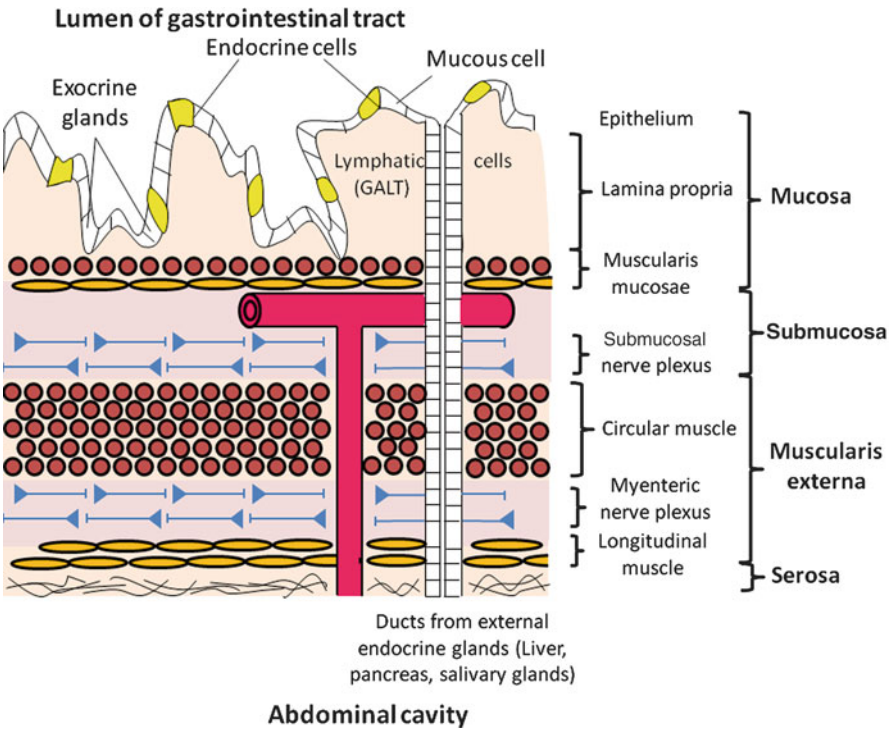

Fig. 1.2 A longitudinal section of the digestive tract wall illustrating the four major gut layers from inside outward, i.e. mucosa, submucosa, muscularis externa and serosa. GALT indicates gut-associated lymphoid tissue (Modified from Widmaier et al. [9])

The **first layer** *mucosa* is the innermost layer, and it consists of an epithelium, the lamina propria, and the muscularis mucosae. In the ***epithelium***, it contains exocrine gland cells and endocrine cells, which secrete mucus and digestive enzymes into the lumen, and release GI hormones into the blood, respectively. The endocrine cells are interspersed among the epithelial lining and they constitute the *gut endocrine system*. In the ***lamina propria***, it contains small blood vessels, nerve fibers, and lymphatic cells/tissues, the latter being called *gut-associated lymphoid tissue,* as introduced in Sect. 1.2. In addition, a thin muscle layer called ***muscularis mucosae*** is also found and the activity of its muscle is responsible for controlling mucosal blood flow and GI secretion.

The **second layer** *submucosa* is a connective tissue with major blood and lymphatic vessels, along with a network of nerve cells, called the **submucosal nerve plexus**, passing through.

The **third layer** *muscularis externa* is a thick muscle and its contraction contributes to major gut motility (segmentation and peristalsis). This muscle layer typically consists of two substantial layers of smooth muscle cells: an **inner circular layer** and an **outer longitudinal layer**. A prominent network of nerve cells, called

the **myenteric nerve plexus**, is also located between the circular and longitudinal smooth muscle layers. The myenteric nerve plexus and the submucosal plexus constitute the ***enteric nervous system (ENS).***

The **fourth layer** *serosa* is the outermost layer, which mainly consists of connective tissues and it connects to the abdominal wall, thus supporting the GI tract in the abdominal cavity.

1.2 Functions of the Gastrointestinal System

The function of the GI system can be described in terms of **four physiological processes: (1) *Digestion*, (2) *Secretion*, (3) *Absorption* and (4) *Motility*,** and the mechanisms by which they are controlled. While digestion, secretion, and absorption are taking place, contractions of smooth muscles in the GI tract wall mix the luminal contents with various secretions and move them through the tract from proximal to distal regions, i.e. from the *mouth* to the *anus*. These contractions are referred to as the **motility of the GI tract.** Physiologically, the motility and secretion are finely tuned in order to achieve optimal digestion and absorption; it in turn facilitates assimilation of nutrients, which is the primary role of our GI system. Put it simply, the overall function of the GI system is to take in nutrients and to eliminate waste. In fact, one can survive without the GI system (yet the liver is still essential for survival) if one is fed parenterally and some vital secretions (such as *digestive enzymes, intrinsic factor* and *insulin*) are replaced.

In general, the cells lining the luminal intestinal organs are exposed to hostile environments, including antigens from food and bacteria, digestive enzymes and various solutions at variable pH levels. In view of this fact, certain ***non-immunologic defense mechanisms*** are present to protect against these potential hazards; they include *gastric acid secretion, intestinal mucin, epithelial cell permeability barrier* and *gut peristalsis*, which are critical for maintaining the ecology of intestinal flora. For example, abnormally high levels of bacteria in an individual with impaired small intestinal peristalsis can lead to diarrhea and/or steatorrhea (fecal fat excretion), a clinical condition being referred to as ***Intestinal Blind Loop Syndrome*.** Of note, the GI tract is also an important part of the immune system of the body. The so-called ***Gut-Associated Lymphoid Tissue* or *GALT*** (Fig. 1.3) consists of both organized aggregates of lymphoid tissue (e.g. *Peyer's patches*) and diffuse (or migrating) populations of immune cells (e.g. *intraepithelial lymphocytes*)**. GALT has two primary functions: (1) protection** against the potential microbial pathogens, and **(2)** permission of **immunologic tolerance** to both the potentially immunologic dietary substances and bacteria that normally reside primarily in the lumen of the GI tract (called the ***intestinal microflora***). The GALT and intestinal microflora play critical roles in regulating GI functions, thus having clinical relevance to gut diseases.

Immunologically, GALT is a part of the ***Mucosa-Associated Lymphoid Tissues* or *MALT*** of the body, which contributes significantly to our gut defense mechanism or GI immune system. Apart from GI tract, MALT can also be found in respiratory

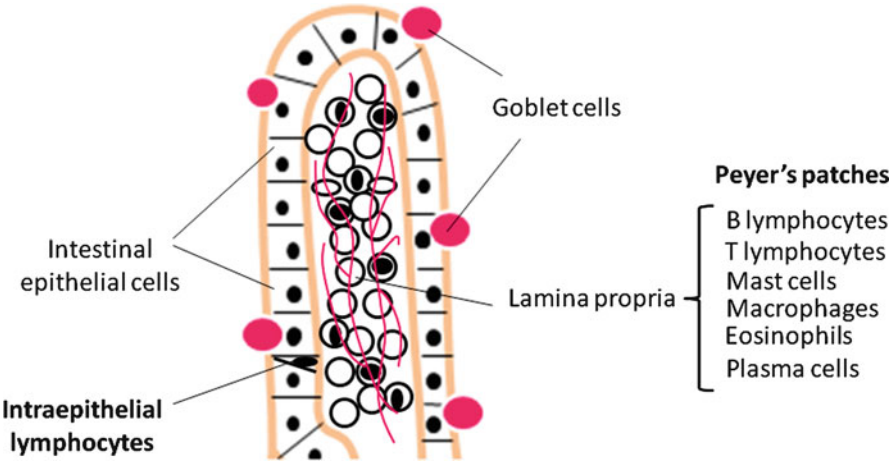

Fig. 1.3 A schematic diagram showing the Peyer's patches (lymphoid nodules) and intraepithelial lymphocytes (migrating immune cells) that constitute the major components of the gut-associated lymphoid tissue (Modified from Berne and Levy's Physiology, 2008)

and urinary systems. Even though GALT has some interactions with the systemic immune system, GALT is functionally and operationally distinct from the systemic system. There is evidence of communication between the GALT and other MALT such as the pulmonary epithelia, as manifested in asthma. The GALT system secretes antibodies in response to specific food or bacterial antigens, and triggers immunological reactions against them, thus finally leading to mucosal inflammation and damage. Activation of this local GI immune system is involved in some of the common GI disorders, including *celiac disease*, and *inflammatory bowel diseases (IBD)* such as *ulcerative colitis* and *Crohn's disease*.

2 Integration of Gastrointestinal System

Upon the ingestion of a food bolus into the GI tract, a sequence of regulatory mechanisms is elicited. This includes complex digestive, secretory, absorptive, and excretory processes. Most of these events occur automatically without conscious effort and, for the most part, they work in an integrated manner. Considering the substantial variations in the content, volume, and timing of our daily oral intake, it is remarkable that the gut is so accommodating and adaptable. Adequate nutrition is finely maintained to meet our metabolic needs so that abdominal symptoms are rarely experienced.

The luxury of taking our digestive system for granted is largely due to complex and seemingly redundant regulatory systems that make it possible to achieve great efficiency in the digestion and absorption of what we ingest. As an example of the highly integrated nature of gut functions, stimulation of the smooth muscles of the

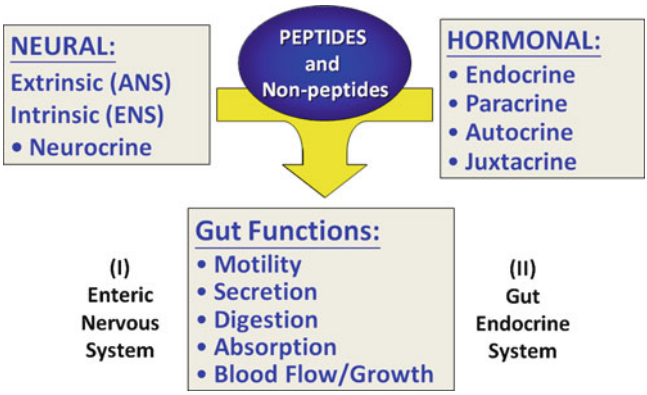

Fig. 1.4 A summary illustrating the basic neuro-hormonal mechanisms by which the gastrointestinal functions are regulated and integrated. There are two major body systems involved in these regulatory pathways, namely the enteric nervous system and the gut endocrine system

esophagus at different levels must be coordinated; this in turn leads to sequential stimulation to produce the unified propulsive contractile wave front **(peristalsis)** that is required for distally directing boluses of food. For food to enter the stomach, the lower esophageal sphincter (LES), which is usually closed to prevent reflux of gastric contents back into the esophagus, must be open at the precise arrival of the peristaltic wave. To achieve this, the gut uses intricate neural and hormonal signals to coordinate esophageal and gastric functions and to prepare the rest of the gut for processing of food. Occasionally, something goes awry and severe GI symptoms can develop. This will be discussed in greater detail in the following chapter.

2.1 Neural and Hormonal Regulators of Gastrointestinal Function

In view of the complex and automatic nature of gut functions, it is not surprising that the GI tract has its own endocrine system, i.e. ***gut endocrine system*** and its local nervous system, i.e. ***enteric (intrinsic) nervous system (ENS)*** of the body. Although its functions can be modulated by the **central nervous system (CNS)** and **autonomous (extrinsic) nervous system (ANS),** the gut can work on its own and independently from the CNS and ANS. This is because numerous regulatory systems are intrinsic and "hard-wired", making it possible for the gut and associated digestive organs to produce reflexive and measured responses to luminal contents and metabolic needs. Figure 1.4 summarizes the regulation and integration of GI physiological processes via neural and hormonal pathways of the GI system. In general, there are **three principal control mechanisms** involved in the regulation of GI function, namely ***endocrine***, ***paracrine***, and ***neurocrine*** pathways, depending on the methods by which the regulators are delivered to their target sites.

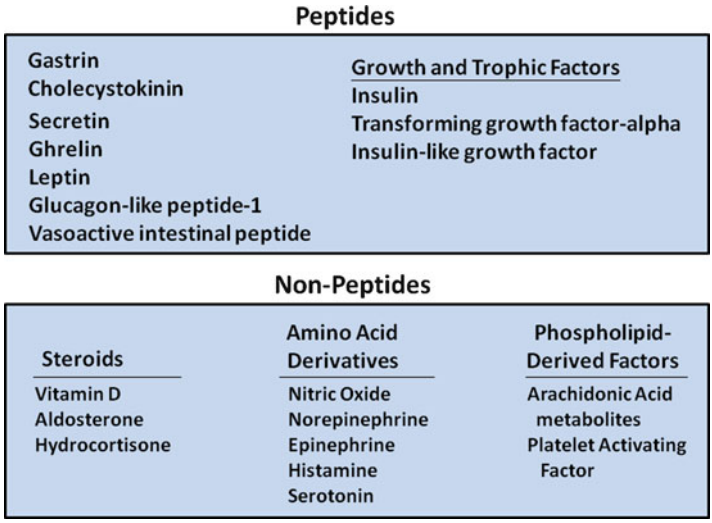

Fig. 1.5 Some typical examples of gut regulators that are grouped into the categories of peptides and non-peptides

2.2 Peptide Hormones

The regulators of the gut is grouped into several different classes of compounds in the form of ***peptides*** and ***non-peptides*** (Fig. 1.5)**.** As shown, peptide hormones such as gastrin, cholecystokinin (CCK), secretin, vasoactive intestinal peptide (VIP), gastric inhibitory peptide/glucose-dependent insulinotropic peptide (GIP), and motilin are recognized as extremely important regulators of the gut function. Many other peptide hormones have recently been identified, which are released by GI endocrine cells and influence gut functions.

Ghrelin is a 28-amino acid peptide, released from the **stomach**, which acts as a regulator of food intake or **appetite enhancer**. Plasma levels of ghrelin increase during fasting and fall during feeding. Interestingly, ghrelin levels are raised in dieters who try to lose weight; this observation may explain why it is difficult for most dieters to maintain their weight loss. In contrast, ***leptin,*** a peptide hormone released from **fat cells** or **GI tract,** acts as a circulating satiety factor or **appetite-suppressant**. Rather than regulating meal-to-meal food consumption as ghrelin, leptin helps maintain the usual level of adiposity (fat storage) of the body. Interestingly, leptin has been shown to affect nutrient absorption via direct inhibition of luminal amino acid uptake by the enterocytes. Similarly, several novel gut peptide candidates have also recently been discovered to control nutrient absorption by the intestine; one of the good examples is *angiotensin II*, which is a physiologically active peptide of the *renin-angiotensin system (RAS).* In this context,

locally generated angiotensin II from the enterocytes is found to inhibit sodium-dependent glucose co-transporter-1 (SGLT-1)-mediated glucose uptake across the small intestinal border membrane and thus it has clinical implications in diabetes.

Glucagon-like peptide-1 (GLP-1) is released from the enteroendocrine **L cells** in the **intestine.** GLP-1 is a 30-amino acid peptide of the secretin family with a 50 % sequence similarity with glucagon. The glucagon gene is composed of six exons that produce **preproglucagon.** In the **pancreatic α-cells,** preproglucagon is processed to ***glucagon*** and ***glucagon-related polypeptide***. In the **intestinal L cells,** preproglucagon is processed to ***GLP-1***, ***GLP-2*** and ***glycentin***. GLP-1 has a short half-life (1–2 min) due to the rapid degradation of its N-terminus by an enzyme, called ***dipeptidyl peptidase IV*** **(DPP-IV).** As such, inhibition of this enzyme by a DPP-IV inhibitor (e.g. *Sitagliptin* or *Januvia*, a Food and Drug Administration (FDA) approved oral hypoglycemic drug from Merck) is beneficial as it can prolong the action of GLP-1 in the blood. Interestingly, a naturally-occurring peptide in the saliva of the Gila monster, called **exendin-4**, shares sequence similarity with GLP-1; however, exendin-4 has a prolonged half-life because it is resistant to DPP-IV degradation. The drug *exenatide (Byetta)* is a synthetic exendin-4, which is the first GLP-1 based drug for the treatment of diabetes approved by the FDA.

The GI tract is a major site for production and release of many of the peptide hormones, some acting exclusively on GI organs while some affecting extra-intestinal tissues, and a few having actions that are still unknown. These regulators can be found not only in endocrine cells throughout the GI tract but also in enteric neurons. Many of these agents are also found in the brain, leading some to believe that the gut has a "*visceral brain*" that regulates intestinal function in response to food or other stimuli. Abnormalities in the regulation by these agents or their overactive responses to external stimuli, such as stress, may contribute to certain diseases, including peptic ulcer disease, motility abnormalities, and irritable bowel syndrome.

Most peptide hormones of the gut are **single peptide chains**, insulin being a notable exception. About half of the bioactive gut peptide hormones are **amidated** (i.e. having an additional terminal amide or NH_2 group) at the carboxyl terminal end, a specific post-translational processing event that appears to be essential for biological activity and stability of the peptide. Based on structural similarities**,** most gut peptides can be grouped into a variety of **peptide families** (Fig. 1.6).

Gastrin-Cholecystokinin Family

In the gastrin-cholecystokinin family, there are various forms of gastrin and cholecystokinin (CCK) arising from post-translational modifications; they share an identical **C-terminal tetra-peptide sequence** (Fig. 1.7a), which is the biologically active domain of both peptides. Not surprisingly, each peptide can bind to the receptors of the other peptides, but with lesser affinity than to its own receptor,

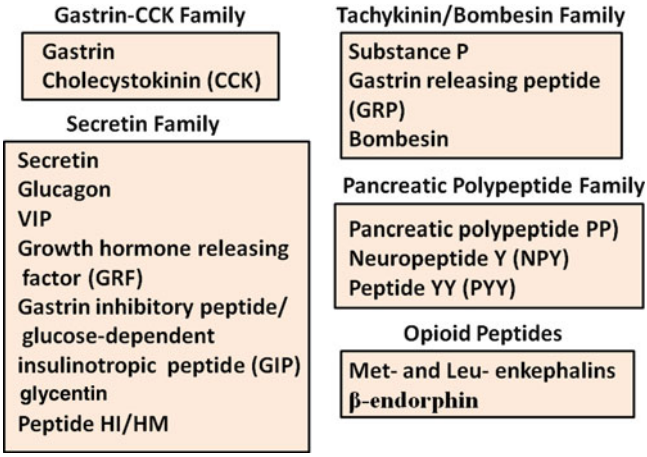

Fig. 1.6 Some representatives of the major gut peptide families including gastrin-cholecystokinin family, secretin family and tachykinin family

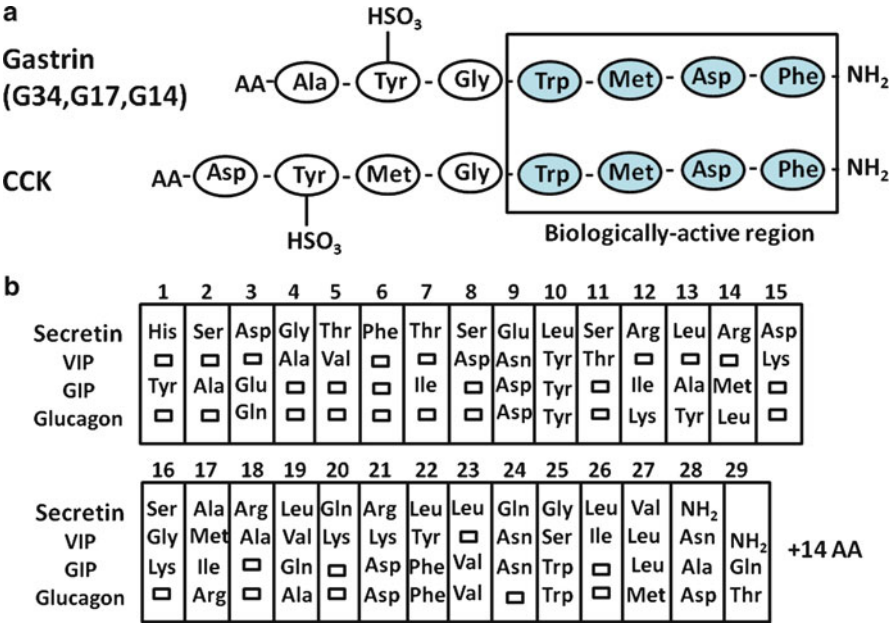

Fig. 1.7 Comparisons of peptide sequences of the (**a**) gastrin-CCK and (**b**) secretin families. In the gastrin family, gastrin and cholecystokinin (CCK) members share identical C-terminal tetrapeptide sequences, which is the biologically active domain of the family. Members of the secretin family have structural similarities, but to a lesser extent than the gastrin family. Boxes within lower panel indicate amino acids that are identical to those in secretin

i.e. CCK_A for CCK and CCK_B for gastrin, thus exhibiting similarities in physiological function; it is called ***"Structural-Activity (Function) Relationship" (SAR).*** Other post-translational modifications, such as the sulfation of the CCK tyrosyl residue in position 7, impart different functional and binding characteristics. For instance, removal of this sulfate group causes the CCK peptide to have properties more similar to gastrin.

Secretin Family

The secretin family merits further discussion here, as several of its members have prominent and well-defined roles in the activation of digestive processes. Members of this family also have structural similarities, but to a lesser extent than members of the gastrin-CCK family (Fig. 1.7b). These members share some structural similarities throughout the amino acid sequence that is critical for the biological activity. As such, they have, not surprisingly, diverse and independent actions. **Gastric inhibitory polypeptide (GIP)** and **vasoactive intestinal polypeptide (VIP)**, for instance, each has nine amino acids that are identical to secretin, albeit in different positions. Consequently, the known physiological actions and target tissues of these peptides can vary significantly. For example, secretin and GIP both inhibit gastric acid secretion and gastric emptying, but, unlike secretin, GIP has little or no effect on pancreatic function. Unlike members of the gastrin-CCK family, most peptides in the secretin family require the entire molecule for biological activity.

Tachykinin Family

The tachykinins are a family of peptides which share a number of biological actions, especially on gut smooth muscle, and have a common C-terminal sequence Phe-X-Gly-Leu-Met-NH_2, where X is a variable amino acid residue. The members of this family include **substance P**, **neurokinin A**, **neurokinin B**, **gastrin releasing peptide (GRP)**, and **bombesin** (Fig. 1.6).

Finally, several other types of the regulatory peptides not typically associated with endocrine or neural tissues are worthwhile mentioning here, particularly those of growth and trophic factors, and cytokines. Many of these agents are synthesized locally by a variety of epithelial and mesenchymal cell types (Fig. 1.5). ***Transforming growth factors-α and β (TGF-α and TGF-β),*** for instance, are made and secreted by epithelial cells of the intestinal mucosa, as well as by cells in the lamina propria. ***Insulin-like growth factor (IGF),*** on the other hand, is largely made by lamina propria cells. Many of these agents have recently been shown to affect mucosal functions, including barrier function, water and electrolyte transport, and cellular growth and differentiation. Although they have prominent roles in mediating tissue responses during injury or inflammation, these peptides probably serve important physiological roles in maintaining mucosal functions as well.

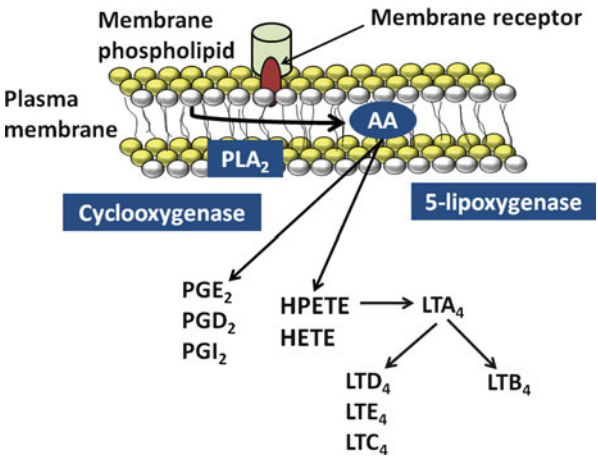

Fig. 1.8 Examples of some arachidonic acid-derived gut regulators. Prostaglandin and leukotriene metabolites of arachidonic acid (AA) metabolism are important regulators of gut function. PLA_2, Phospholipase A_2

2.3 Non-peptide Regulators

In addition to peptide hormones, many non-peptide regulatory agents are involved in the modulation and coordination of gut functions (Fig. 1.5). Factors such as ***glucocorticoids*** (e.g. cortisol) and ***mineralocorticoids*** (e.g. aldosterone), which affect intestinal fluid and electrolyte absorption, are steroids made by the adrenal gland. Vitamin D_3, or 1,25-dihydroxyvitamin D_3, is also a steroid that has significant effects on intestinal Ca^{2+} absorption and possibly growth and differentiation of gut mucosa.

Several non-peptide bioactive amines and neurotransmitters should also be worthwhile mentioning. These include substances derived from single amino acid sources, for example, ***epinephrine*** **(adrenaline),** ***dopamine***, and ***norepinephrine (noradrenaline),*** which are derived from phenylalanine and tyrosine; ***nitric oxide*****,** derived from L-arginine metabolism; and ***histamine*** from the decarboxylation of histidine. The catecholamines within the gut are exclusively made and secreted by enteric neurons, whereas nitric oxide is found in many different cell types, serving as an intracellular mediator as well as a cellular signaling agent. **Epinephrine and norepinephrine**, secreted by the adrenal glands and sympathetic nerves, have numerous effects on intestinal blood flow, water and electrolyte transport, and motility. **Nitric oxide** is believed to be a major ***non-adrenergic and non-cholinergic (NANC)*** neurotransmitter important for the regulation of intestinal motor functions and mesenteric blood flow. **Histamine**, which is secreted by the gut *enterochromaffin-like (ECL)* cells, is a major regulator of gastric acid secretion.

Several regulatory substances of gut functions originate from membrane-derived fatty acids, such as the synthesis of **platelet activating factor (PAF)**, as illustrated in Fig. 1.8, showing metabolites of arachidonic acid. These agents are made by

virtually all cell types and have been recognized as being important intracellular mediators. However, they are made and secreted in large quantities by some cells and appear to have effects on numerous target tissues. Although they have been more thoroughly investigated in the context of intestinal inflammation, they also have important physiological roles in regulating gut functions such as gastric acid secretion, mesenteric blood flow, and intestinal motility.

3 Cellular Mechanisms of Gut Regulators

Gut hormones and neurotransmitters stimulate intracellular processes through a variety of mechanisms (Fig. 1.9). **Hydrophobic substances** such as corticosteroids and nitric oxide rapidly permeate the plasma membrane to stimulate intracellular receptors or targets. On the other hand, **hydrophilic mediators** such as peptide hormones, purinergic agonists, bioactive amines, and acetylcholine bind to and stimulate specific surface membrane receptors, which in turn initiate a number of intracellular signal transduction pathways so as to mediate alterations in cell functions or behaviors.

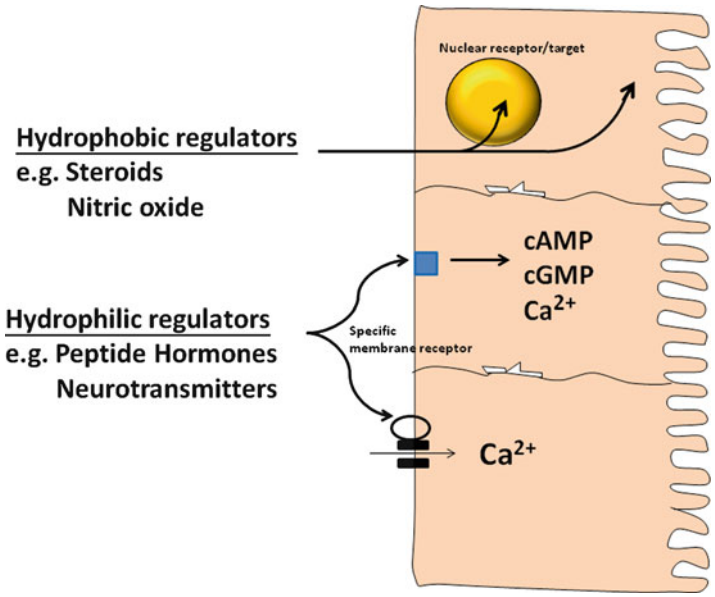

Fig. 1.9 Cellular sites of action for regulatory agents of the gut. Hydrophobic regulators permeate the plasma membrane to stimulate intracellular receptor or targets. Hydrophilic mediators generally bind to and stimulate specific surface-membrane receptors, initiating intracellular events that mediate alterations in cell functions or behaviors

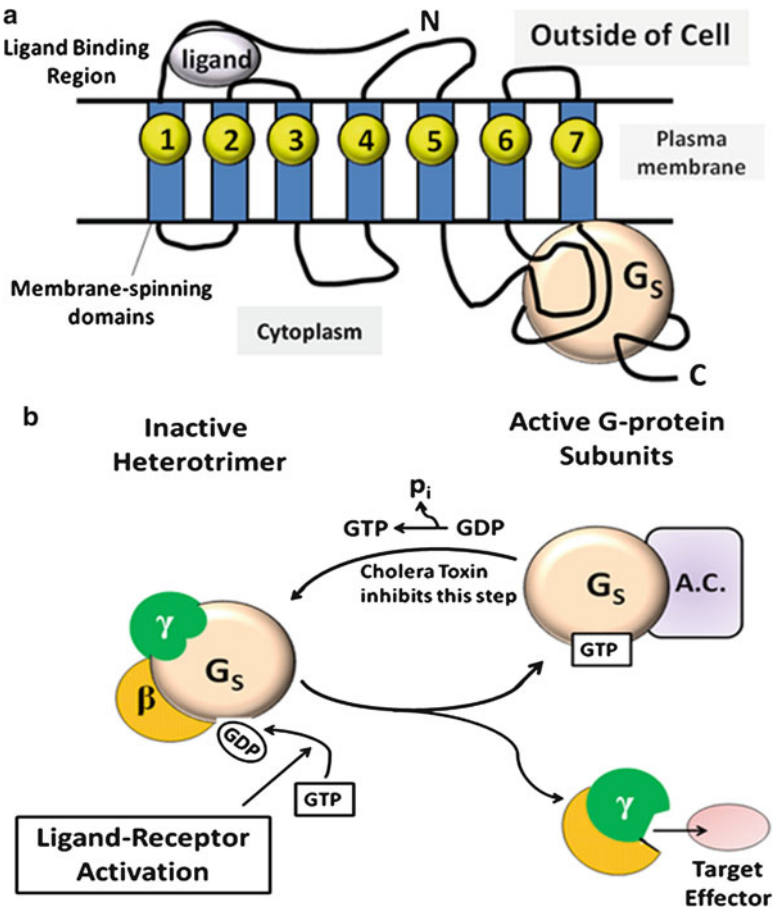

Fig. 1.10 G protein-mediated receptor action. (**a**) G proteins have structural and functional similarities, characterized by seven helical hydrophobic membrane-spanning domains and a cytoplasmic binding site for certain G proteins. (**b**) When a ligand binds to the G-protein receptor, GDP (normally occupying the guanine nucleotide binding site) rapidly exchanges for GTP, resulting in physiochemical alterations in G-protein structure and function

3.1 Types of Membrane Receptors

Several types of membrane receptors are now well characterized. Among these, the family of receptors associated with **guanosine triphosphate (GTP)-binding regulatory proteins or G proteins,** is perhaps the most numerous. These receptors share structural and functional similarities, typified by **seven hydrophobic, helical, membrane-spanning domains** (Fig. 1.10a)**,** and a cytoplasmic binding site for certain G proteins. G proteins are heterotrimeric complexes formed from **α, β**

and γ subunits. Because the β and γ subunits are shared among G proteins, it is the α subunit that confers functional and binding specificity to the various types of G proteins. Each α subunit has an intrinsic GTPase activity at the guanine nucleotide binding site and separates specific binding sites for the receptor and effector proteins, such as adenylate cyclase and other hydrolases.

When a ligand binds to the receptor (Fig. 1.10b)**,** guanosine diphosphate (GDP), normally occupying the guanine nucleotide binding site, rapidly exchanges for GTP. This results in a series of rapid physiochemical alterations in G-protein structure and function. The G protein immediately dissociates from the receptor and α subunit from the β and γ subunits. The α subunit and β-γ complex appear to activate other effector proteins of various biochemical pathways. Additionally, some G proteins appear to directly regulate ion channels such as *voltage-sensitive* Ca^{2+} *channels* and *inwardly rectified* K^{+} *channels*. When GTP is hydrolyzed by the intrinsic GTPase activity of the α subunit, the G protein heterotrimeric complex reforms, and becomes ready to be activated again if further receptor ligand signals are still present. As will be discussed below and in subsequent chapters, the cycling of certain G proteins can be biochemically altered by bacterial toxins such as *cholera* and *pertussis toxins*.

Several **non-G protein-coupled receptors** have also been characterized. One group includes receptors for growth factors such as *epidermal growth factor (EGF), insulin,* and *platelet-derived growth factor (PDGF)*, which have only one membrane-spanning domain but possess **ligand-activated protein kinase activity**. For most growth and trophic factors of the gut, activated receptors have tyrosine kinase activity, which can stimulate several other signal transduction pathways, including phosphatidylinositol metabolism, the arachidonic acid cascade, and mitogen-activated protein (MAP) kinase. Another class of receptors includes those with **endogenous guanylate cyclase activity**, best characterized by the receptors for *atrial natriuretic factor (ANF)* and *guanylin.*

Guanylin is a recently identified gut peptide that stimulates secretion of water and electrolytes by gut epithelial cells, particularly **crypt cells** in which guanylin receptors are most highly expressed. This receptor is also the target of the heat-stable enterotoxin of **enterotoxigenic *Escherichia coli***, which stimulates increases in mucosal **cyclic guanosine monophosphate (cGMP)** levels and causes profuse watery diarrhea. Finally, some receptors appear to be ion channels, including the nicotinic acetylcholine receptor and the serotonin receptor subtype 5-HT_3. Most of these receptors, when activated, undergo conformational changes resulting in the formation of membrane "pores" that allow the entry of different ions.

3.2 Intracellular Effector Pathways

Several intracellular effector pathways mediate the actions of gut hormones and neurotransmitters. None is specific to a particular receptor. In some instances, such as activation of growth factor receptors, several pathways may be simultaneously

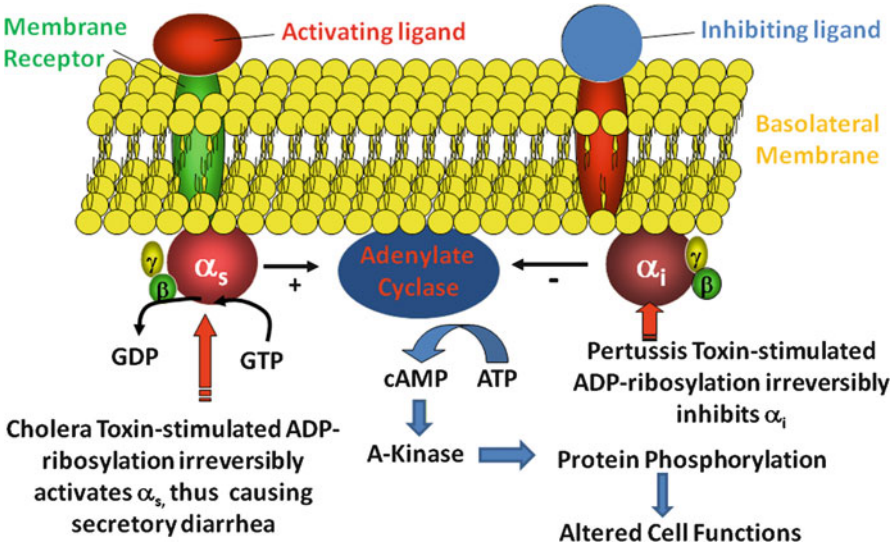

Fig. 1.11 Regulation of cellular cAMP levels. Adenylate cyclase activity is regulated by the α subunit of two G proteins, i.e. G_s and G_i. The ADP-ribosylation of the G_s–α, stimulated by cholera toxin, prevents the re-association of the inactive heterotrimeric G_s protein. This results in irreversible activation of G_s–α and adenylate cyclase activity. In contrast, ADP-ribosylation of G_i–α, stimulated by pertussis toxin, results in inactivation of the counter-regulatory pathway of adenylate cyclase and shifting the balance in favor of stimulation and increased cellular cAMP

stimulated. This may occur when different G proteins are coupled to a common receptor or when the activated pathway initiates other effector mechanisms essential for activating or amplifying requisite events of the cellular response.

Adenylate Cyclase

Adenylate cyclase is a membrane-bound enzyme with several isotypes. As illustrated in Fig. 1.11, the activity of adenylate cyclase I is regulated by the α subunits of two G proteins, **G_s and G_i**. On receptor-ligand binding, G_s-α dissociates from the β-γ subunits and activates adenylate cyclase, which catalyzes the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). **Counter-regulatory hormones**, such as somatostatin and α_2-noradrenergic agonists, stimulate the dissociation of G_i-α from the G_i-protein complex, which inhibits adenylate cyclase activity. Thus the balance of these regulatory mechanisms of adenylate cyclase is an important determinant of steady-state levels of cellular cAMP. ***Cholera toxin*** stimulates the ADP-ribosylation of G_s-α, which prevents the re-association of the inactive heterotrimeric G_s protein. This causes irreversible activation of G_s-α and adenylate cyclase activity and is the mechanism by which cholera toxin causes profuse *watery diarrhea* in the absence of tissue injury.

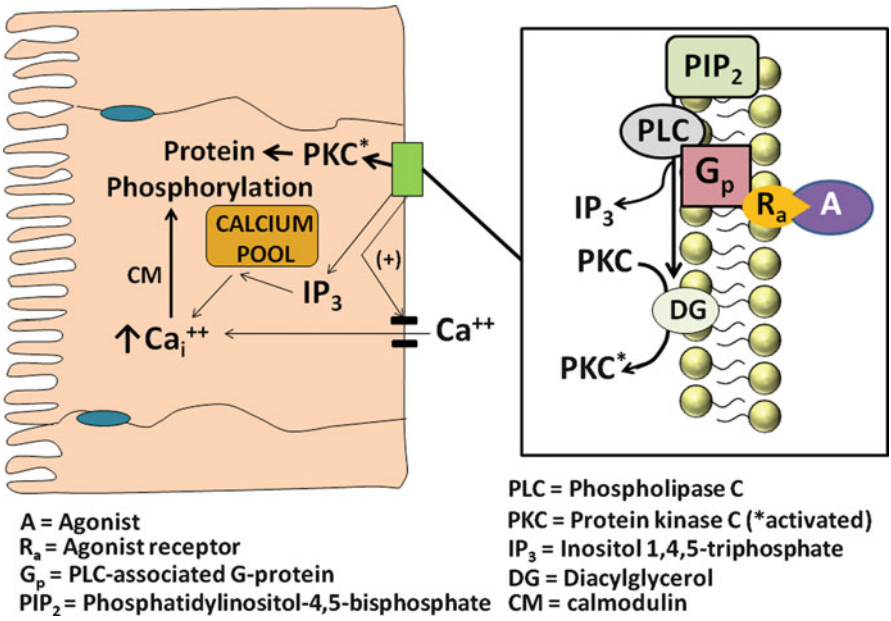

Fig. 1.12 The phosphatidylinositol pathway. This is a major pathway by which hormones and neurotransmitters lead to increases in cytosolic Ca^{2+} and activation of protein kinase C

Pertussis toxin, on the other hand, stimulates ADP-ribosylation of G_i-α, uncoupling the G_i protein from its receptor. This results in inactivation of the counter-regulatory pathway of adenylate cyclase, shifting the balance in favor of stimulation and increased cellular cAMP.

An **increase in cAMP** activates cAMP-dependent protein kinases (protein kinase A or A-kinase), which have numerous intracellular phospho-protein targets. The phosphorylation of these proteins initiates a series of events that ultimately leads to alterations in cellular function or behavior, such as stimulated ion secretion, altered motility, and changes in capillary and absorptive functions. These events will be discussed at greater length in subsequent chapters.

Phosphatidylinositol (PI) Pathway

Phosphatidylinositol 4, 5-bisphosphate (PIP_2) is a membrane phospholipid that serves as an important substrate for **phospholipase C**, a membrane-associated enzyme, when activated by receptor-associated G proteins. The hydrolysis of PIP_2 results in the formation of two products, **inositol 1,4,5-triphosphate (IP_3)** and **1,2-diacylglycerol (DAG)** (Fig. 1.12). IP_3 is a water-soluble product that freely

diffuses into the cytosol and stimulates the increase of cytosolic Ca^{2+} by releasing it from intracellular calcium stores. This action is mediated by a specific receptor for IP_3, which regulates a membrane calcium channel for intracellular calcium stores.

Characteristically, a rapid, **initial-phase increase** in cytosolic Ca^{2+} is observed, which is believed to serve as a triggering event for the second and more sustained phase of increased Ca^{2+}. In most cells, the **second plateau phase** is dependent on the influx of extracellular Ca^{2+} through Ca^{2+}-activated calcium channels in the plasma membrane. Increases in cytosolic Ca^{2+} have numerous effects on cell function depending on the cell type. In many cells, the increase activates a multifunctional **calcium-calmodulin-dependent protein kinase, CaMK II kinase. Calmodulin** is a small, calcium-dependent regulatory protein that mediates many of the actions of increased cellular Ca^{2+}, including phosphorylation and activation of myosin light chain kinase (an important step in smooth muscle contraction), the stimulation of Ca^{2+}-dependent ATPase (important for restoration of resting Ca^{2+} levels), and the regulation of adenylate cyclase activity.

In contrast to IP_3, DAG is lipophilic and remains associated with the plasma membrane. It is a specific activator of **protein kinase C (PKC)**, which is cytosolically located but translocated to and activated at the plasma membrane by DAG. Although PKC activity is Ca^{2+}-dependent, DAG stimulation causes a shift in the calcium requirement such that PKC is fully active at resting cytosolic Ca^{2+} concentrations. PKC stimulates cell-specific serine and threonine phosphorylation of many protein substrates, which can cause alterations in cell functions, growth, and differentiation.

Guanylate Cyclases

There are at least **two classes of guanylate cyclase**: one is an integral part of the plasma membrane, and the other is soluble and located within the cytosol (Fig. 1.13). The latter is activated by a number of non-receptor-associated systems including nitric oxide, which stimulate rapid increases in cGMP from GTP in many cells. As will be discussed in subsequent chapters, increases in cGMP in smooth muscle cells cause muscle relaxation. By contrast, **membrane guanylate cyclases** are ligand-activated, and in most cases function as receptors themselves. G-protein coupling with guanylate cyclase receptors is not likely. Ligand-receptor interaction activates the guanylate cyclase activity of a family of guanylate cyclase receptors, which includes those for *atrial natriuretic factor (ANF),* and the gut peptide *guanylin* or heat-stable enterotoxin of *E. coil* (ST_a). Among them, *guanylin* is a recently discovered peptide produced by the ileum and colon, and its name is derived from its ability to activate the enzyme guanylate cyclase. These agonists result in increases in cGMP, smooth muscle relaxation, and stimulation of water and electrolyte secretion in epithelial cells. These actions are mediated by cGMP-dependent protein kinases, which phosphorylate critical membrane proteins involved in these processes.

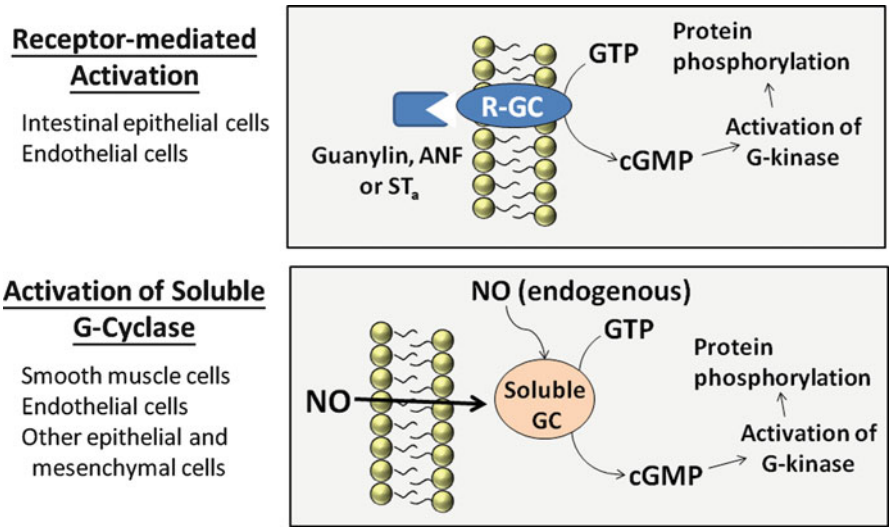

Fig. 1.13 Regulation of cellular cGMP. There are two types of guanylate cyclases that are found in intestinal cells, one integral with the plasma membrane and the other in the cytosol. A receptor-mediated mechanism activates the membrane-bound guanylate cyclase (*upper panel*), whereas the cytosolic guanylate cyclase, which is soluble, is stimulated by endogenous agents. e.g. nitric oxide which is able to permeate the plasma membrane (*lower panel*)

Tyrosine Kinases

The actions of many intestinal growth factors such as *EGF, PDGF* and *IGF* are mediated by the activation of cellular tyrosine kinase receptors. Tyrosine kinase receptors are trans-membrane proteins that can be single polypeptides or heterodimers. They have extracellular domains for specific ligand binding and cytoplasmic domains that possess intrinsic tyrosine kinase activity. The activation of the receptor often induces auto-phosphorylation of the receptor, which may negatively feedback on its activity. There may be considerable amplification of the initial signal by the integration of this system with other signal transduction pathways (Fig. 1.14). Several substrates appear to be the **targets of tyrosine kinase receptors**, including important regulatory proteins of other biochemical pathways such as phospholipase C-γ and phospholipase A_2. Additionally, **auto-phosphorylation of the receptor** appears to be an important event since it provides recognition and binding sites for SH2 (src homology) domain of the adaptor protein Grb2. This in turn causes the binding of another protein, SOS, at the SH3 domain of Grb2, required for activation of ras proto-oncogene. The latter initiates a cascade of events that activate Raf-1 and MAP kinases, involved in regulating numerous cellular and transcriptional processes. Details of this pathway are beyond the scope of this discussion.

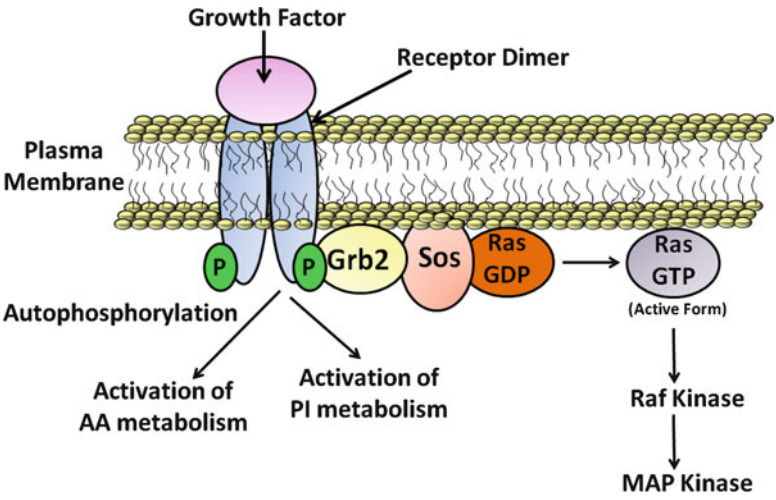

Fig. 1.14 Cellular activation by growth factors. The action of many intestinal growth factors such as EGF, PDGF, and IGF are mediated by the activation of cellular tyrosine kinase receptors

4 Gut Regulatory Pathways

4.1 Neural Hormonal Mechanisms

The regulation and integration of gut functions are mediated by a variety of pathways, each having unique characteristics suited for specialized tasks (Fig. 1.15). These pathways are present throughout most of the gut, although they assume more importance in certain regions relative to others. Likewise, the regulatory agents mediating the actions of each pathway can substantially differ. On the other hand, it is also clear that some regulatory agents are common to several pathways, albeit affecting different target tissues.

Endocrine Pathway

This represents the traditional concept of regulatory hormones **secreted into the blood stream** and delivered to distant target tissues. This system has the advantage of simultaneously affecting large numbers and regions of target tissues. *Insulin secretion from pancreatic beta cells* stimulated by increased blood glucose concentration is an example of this classic endocrine pathway. Insulin has a large systemic action, including effects on GI and hepatic metabolism, and functions. Another example is the *release of gastrin into the blood* stimulated by gastric

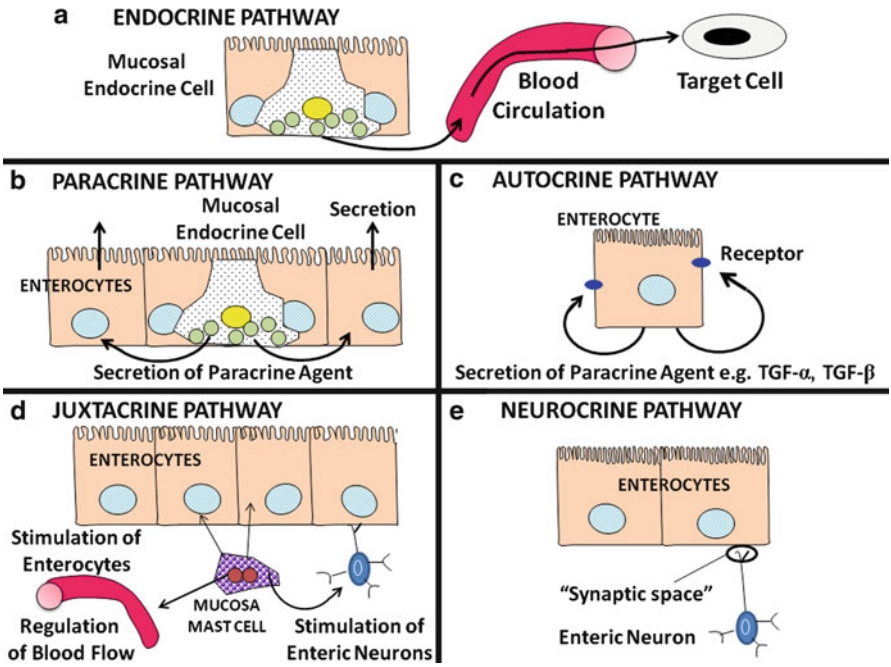

Fig. 1.15 Gut neural and hormonal mechanisms. The regulation and integration of gut functions are mediated by a variety of pathways, which are unique for specialized tasks. (**a**) Endocrine, (**b**) Paracrine, (**c**) Autocrine, (**d**) Juxtacrine, and (**e**) Neurocrine pathways

contents and increased intraluminal pressure. Gastrin stimulates gastric acid and pepsin secretion and activates gastric motility important for grinding up food and emptying gastric chyme into the duodenum. Gastrin also promotes increased tone of the lower esophageal sphincter to prevent reflux of gastric contents. Thus gastrin affects several target tissues simultaneously, which function coordinately to start the initial phase of digestion.

Paracrine Pathway

This represents the mode of action of numerous endocrine cells interspersed among epithelial cells of the intestinal and gastric mucosa. These cells are morphologically distinct, characterized by **epithelial polarity**, and have well-defined **microvillous membranes** at the luminal surface, **whereas nuclei and dense secretory granules** are located at the base of the cells. These cells are capable of sensing changes in the chemical and osmotic conditions of the intestinal lumen, which trigger the release of their regulatory substances stored in the basally located granules at the

contra-luminal membrane. Additionally, neural structures and products of other endocrine cells may regulate the release of paracrine factors by stimulating specific receptors on the baso-lateral surfaces of these cells. The released paracrine agents traverse the interstitial space to adjacent target cells, altering their functions or cellular behaviors. This mechanism of action is particularly suitable for the intestine, as the effect is a localized, immediate, and measured response to changes in an ambient environment. Potential systemic effects of these agents are thus avoided and adjacent areas of the gut that may have other important and separately-regulated functions are not affected.

Autocrine Pathway

This pathway is closely related to paracrine action, except that the stimulated release of a hormone message serves to **auto-regulate** the functional or biological behaviors of the cell itself. In some instances, this appears to serve as a **negative feedback mechanism** to auto-regulate the hormonal secretory process. However, these autocrine signals may also serve to auto-regulate cellular functions under special circumstances or at certain stages of development, such as growth and differentiation. For example, TGF-α and TGF-β, which are made and secreted by intestinal epithelial cells at critical points in cellular development, may be involved in the differentiation process of immature crypt cells to more mature villus cells.

Juxtacrine Pathway

This pathway is a newly-described mechanism of action of several regulatory agents that are secreted by **cells in close proximity to their target tissues** within the intestinal mucosa. This includes cells of the **lamina propria**, which are now believed to be important in regulating mucosal functions such as epithelial fluid and electrolyte transport, capillary blood flow, enteric neural stimulation, and motility. For example, a layer of myofibroblasts underlies the intestinal epithelium. These cells elaborate arachidonic acid metabolites, platelet activating factor (PAF), purinergic agonists (adenosine, ATP), and other bioactive substances that modulate the electrolyte transport function of the overlying epithelial cells. It is also believed that these cells secrete **trophic/growth factors** that nurture the epithelial cells and play a role in their development to mature epithelial cells. Cells using this pathway are distinct from paracrine cells in that they are not typical endocrine cells, can exhibit **considerable motility** (e.g. immune cells of the lamina propria), and can **affect numerous target tissues**. Apart from playing a role in regulating physiological processes of the guts, many of these cells also have a prominent role in the intestinal responses to injury and inflammation (e.g. against pathogen invasion of the intestinal mucosa).

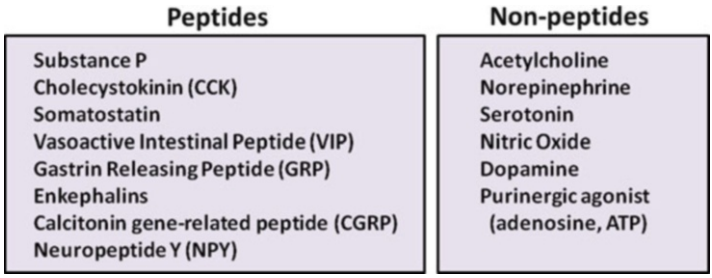

Fig. 1.16 Some typical examples of neuroregulators of the gut. These regulators are divided into peptides and bioactive non-peptide substances

Neurocrine Pathway

This pathway is involved in regulatory agents that are made and released from enteric neurons and function as **typical neurotransmitters**; that is, after release from terminal axons they traverse a narrow "synaptic space" and stimulate specific receptors of the target tissue. This form of regulation is quite ***specific*** in that the delivery of the neurotransmitters precisely and rapidly affects a designated target cell. On the other hand, the neural regulation of intestinal function can be quite ***extensive***, as neurons are organized into intricate complexes capable of producing rapid and faithful patterns of stimulation that simultaneously affect numerous structures to coordinately regulate their functions. These patterns are *hard-wired*, reflexive responses involved in physiological functions such as swallowing, gastric emptying, and defecation, as well as coordination of secretory, motor, and capillary functions. Integrated neural responses to physiological stimuli will occur repetitively and proportionately to the intensity of the afferent stimulus. A variety of target cells of motor neurons is known, including *epithelial*, *muscle*, *endothelial*, and other *mesenchymal cells*.

4.2 Organization of Enteric Neurons

Neurotransmitters Involved

The neurotransmitters involved in neurocrine regulation of the gut can be divided into **peptides** and bioactive **non-peptide substances** (Fig. 1.16). Non-peptide agents include serotonin (5-hydroxytryptamine, 5-HT), nitric oxide, purinergic agonists, acetylcholine, and norepinephrine; whereas for gut neuropeptides, numerous have now been identified. In fact, many were originally identified as neurotransmitters of the brain, but some, such as cholecystokinin (CCK) and somatostatin, are also found in endocrine cells of the gut. Neuropeptides are largely concentrated in the intrinsic nerves of the gut.

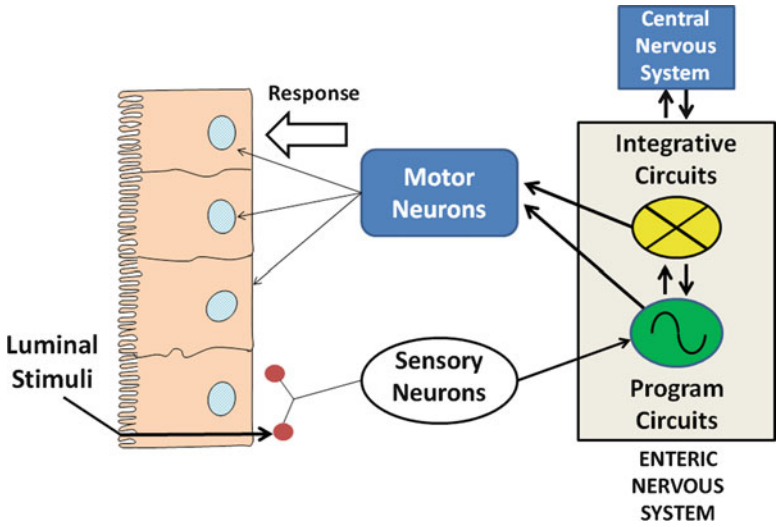

Fig. 1.17 Organization of the enteric nervous system. Enteric neurons have their own sensory neurons, interneurons and motor neurons which are capable of producing motor and secretory responses upon luminal stimuli. These responses can be modified by input from autonomic nerves from the central nervous system. (Modified from Chang EB, Binder HJ. Diarrheal diseases. American Gastroenterological Association Teaching Slide Collection 25 © slide 36, Bethesda, Maryland. Used with permission)

Enteric Nervous System

The intrinsic or enteric nervous system is composed of **afferent (sensory) neurons**, **interneurons**, and **efferent (motor) neurons**, whose cell bodies are located within the bowel wall. Enteric neurons are quite numerous and well organized. As shown in Fig. 1.17, enteric nerves are organized into hard-wired circuits that produce characteristic and rapid patterns of response. Interneurons, nerves that connect and integrate afferent signals to efferent motor neurons, play an important role in integrating the neural response, receiving inputs from sensory neurons and activating several neural targets of intestinal plexuses. Their functions can be modified by inputs from autonomic nerves from the central nervous system. But still, the interneurons are also quite capable of functioning independently despite loss of autonomic neural input.

Sympathetic Innervation

The gut receives extensive innervation by sympathetic and parasympathetic neurons. Most sympathetic fibers of the gut are **postganglionic**. Efferent sympathetic fibers to the ***stomach*** originate from the celiac plexus, whereas those to the ***small intestine*** originate from the celiac and the superior mesenteric plexuses.

Fibers to the ***cecum***, ***appendix***, ***ascending colon,*** and ***transverse colon*** arise from the superior mesenteric plexus. The ***remaining portion*** of the colon receives sympathetic fibers from the superior and inferior hypogastric plexuses. Sympathetic neurons to the gut have a variety of functions. Some regulate inter-glandular tissues or closely approximate intestinal mucosa by regulating transport functions of these cells. Sympathetic neurons also innervate smooth muscle cells of blood vessels, thereby regulating blood flow to the intestine, and neuronal cells of the intramural plexus, specifically inhibitory receptors of presynaptic regions of enteric neurons. Stimulation of α_2-noradrenergic presynaptic receptors inhibits the release of acetylcholine and serotonin, representing one mechanism by which sympathetic fibers are counter-regulatory to parasympathetic and serotoninergic stimulation. In other regions of the gut, sympathetic fibers play a role in regulating sphincter function, such as the lower esophageal and anal sphincters where sympathetic stimulation appears to be excitatory.

Parasympathetic Innervation

Parasympathetic innervation to the ***stomach, small intestine,*** and ***proximal colon*** arises from the **vagus nerve**, with its fibers running along blood vessels and ending in the myenteric plexus. ***The rest of the colon*** receives parasympathetic innervation from the pelvic nerves of the **hypogastric plexus**, which also end in the myenteric plexus. All parasympathetic fibers are **preganglionic** and most are **cholinergic and excitatory**. However, other neurotransmitters, such as *substance P, vasoactive intestinal peptide (VIP), and enkephalin-like compounds,* are also made and released by parasympathetic neurons. For example, VIP released from parasympathetic nerve endings causes relaxation of the lower esophageal, pyloric, and internal anal sphincters.

The **efferent response of vagal fibers** requires a continuous exchange of information between the gut and brain. This is mediated by afferent vagal fibers that connect with neurons of the **hypothalamus**, **globus pallidus**, and the **limbic systems**. In this way, regulation of intestinal functions can be modulated by inputs from the central nervous system. For example, signals from stretch receptors and chemoreceptors of the stomach and alterations in metabolic conditions, such as *glucosideapenia* (low glucose content inside cells), when perceived by the brain, prompt an immediate efferent response to stimulate gastric acid secretion and motility.

4.3 Determinants for the Integration of Gut Functions

You may wonder: why does the gut have such intricate and seemingly redundant regulation systems? Given the complexity and the number of regional and temporal

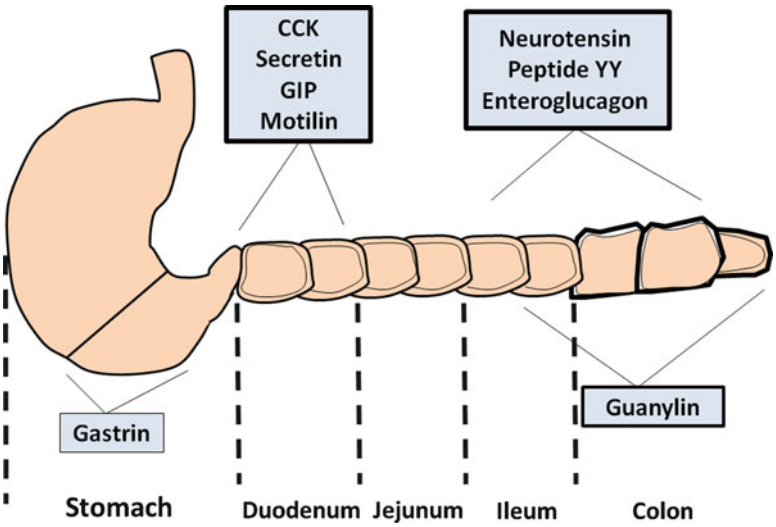

Fig. 1.18 Region-specific distribution of mucosal endocrine cells. The gut endocrine cells are not randomly but regionally specific distributed in the gut

events that must be coordinated for digestive and absorptive functions to proceed autonomously and efficiently, such regulation systems are necessary. Different levels of organization are utilized, as indicated in the examples that follow.

4.4 Regional Distribution of Mucosal Endocrine Cells

Most mucosal endocrine cells are distributed in a **region-specific** way (Fig. 1.18). This actually makes teleological sense, as the physiological roles of many gut peptides depend on their regional presence, either to produce a rapid, appropriate, and measured stimulation of their release or to regulate regional tissue responses. This basic principle can be illustrated by the predominant expression of the peptides *gastrin, CCK, GIP,* and *secretin* in the stomach and upper intestinal tract (Fig. 1.19). The entry of a food bolus into the ***stomach*** stimulates gastrin release from the antral G cells (mucosal endocrine cells located in the distal one-third of the stomach) into the blood. Through a classical endocrine effect, gastrin initiates gastric motility, increases the tone of the lower esophageal sphincter, and stimulates gastric acid secretion. As the gastric chyme enters the ***duodenum***, mucosal endocrine cells are stimulated to release GIP, CCK, and secretin, which activate enteric neural pathways and/or stimulate via an endocrine mechanism. Pancreatic and biliary secretions begin the next phase of food digestion. In addition, these hormones provide feedback inhibition of gastric motility and acid secretion. As will be

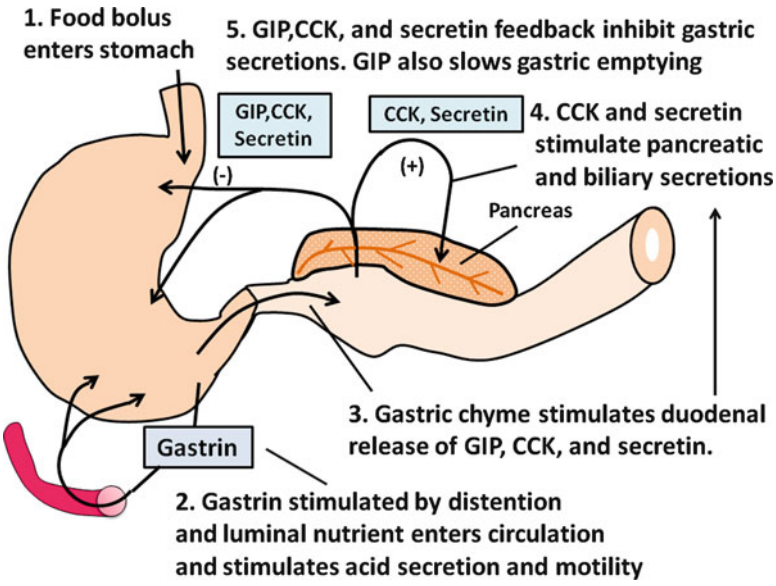

Fig. 1.19 Physiological roles of gut peptide hormones during digestion. The hormones are released in a sequential manner in the regulation of intestinal functions in response to a meal

discussed in the subsequent chapters, precise regulation of the timing of these events and the degree of tissue response are critical for preventing maldigestion of food and development of abnormal symptoms.

4.5 Systemic Integration of Associated Gut Functions

Upon the reception of physiological stimuli, the response of tissues and organs to the stimuli is regulated by the regulatory systems of the gut. This is achieved through the simultaneous and coordinated activation of several key co-dependent processes. As an example, neural regulation of any regions of the gut integrates the processes of intestinal water and electrolyte transport, motility, and blood flow. **Neurocrine regulation of the small intestine** is initiated by chemoreceptors and mechanical stretch receptors (Fig. 1.20). **Afferent neurons** stimulate *interneurons of intestinal neural plexuses* to activate several efferent motor pathways. Some neurons *directly* stimulate *intestinal epithelial cells* to secrete water and electrolytes into the lumen, necessary for providing the aqueous phase and proper chemical composition for luminal digestion and absorption. Concomitantly, *motor neurons* are activated to stimulate segmental contractions of the small intestine, for mixing intestinal contents with digestive juices. Finally, **motor neurons** stimulate *alterations in mesenteric and splanchnic blood flow* necessary for absorption of nutrients and their delivery to the liver.

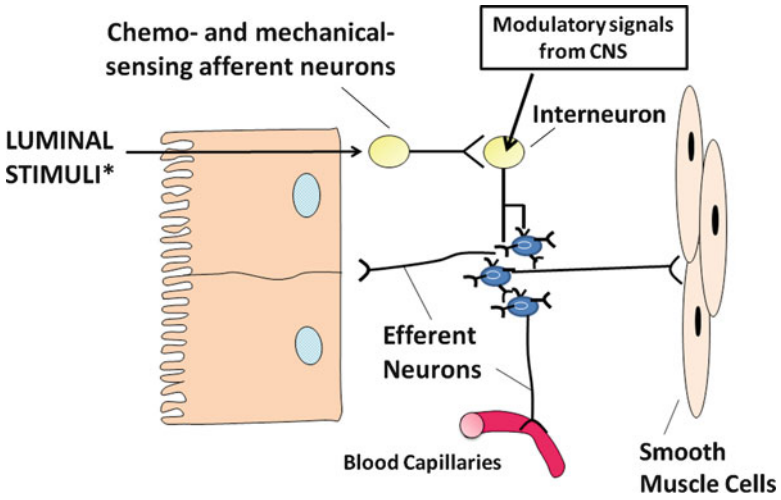

Fig. 1.20 Enteric regulation of gut functions. Neuroregulation of the gut integrates the processes of intestinal water and electrolyte transport, motility and blood flow in response to food stimuli. Luminal pressure and chemical signals activate chemo- and mechano-receptors of the sensing afferent enteric neurons and thus stimulate a response such as simultaneous alterations in motor, capillary and mucosal functions

4.6 Integration of Regulatory Systems of the Gut

Considerable "cross-talk" is essential between regulatory systems of the gut to prevent counterproductive and inefficient actions. An example of this is the relationship between *juxtacrine* and *neurocrine* cells of the intestinal mucosa (Fig. 1.21). Under physiological and pathophysiological situations, juxtacrine cells of the lamina propria (e.g. sub-epithelial myofibroblasts and other mesenchymal cells) are stimulated to secrete a variety of bioactive substances, including arachidonic acid metabolites. These agents can directly stimulate intestinal epithelial, endothelial, and smooth muscle cells. However, their effects are further amplified by activation of secreto-motor enteric neurons, which potentiate the actions of the mediators at the target tissues. Thus, the intensity and regional effects of juxtacrine agents can be significantly enhanced.

Summary

- The **gastrointestinal (GI) system** is massive in size compared to all other organ systems; it consists of ***esophagus***, ***stomach***, ***small intestine***, ***large intestine***, ***gallbladder***, ***liver,*** and ***pancreas***. In view of this, complex control mechanisms are needed to integrate these seven organs together into a functional correlate.
- The **major functions of the GI system** are ***secretion***, ***motility***, ***digestion***, ***absorption***, ***metabolism***, and ***defense mechanisms,*** as well as serving ***immunity***.

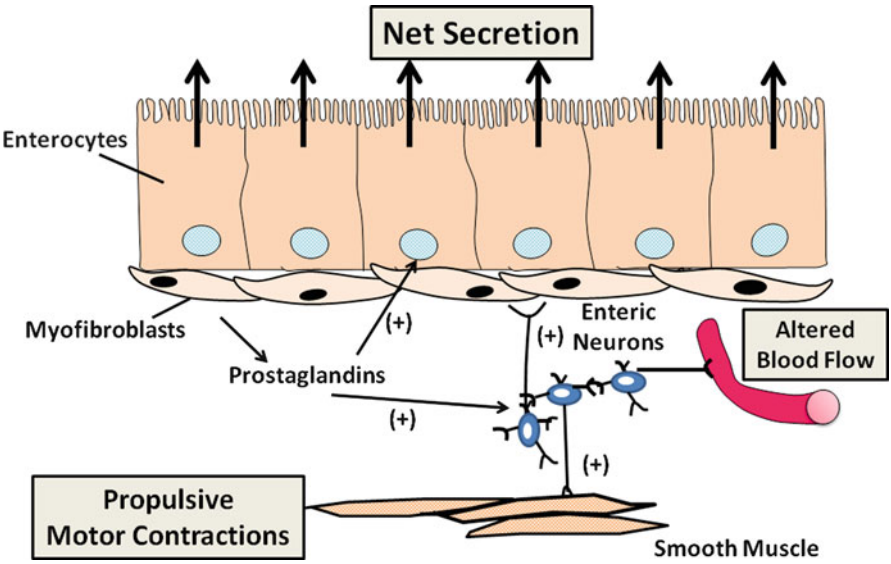

Fig. 1.21 Cross-talk between gut regulatory systems. Such an interaction is exemplified by the effects of prostaglandins on secretory function that can be amplified by secretomotor enteric neurons

- The **GI function is regulated** by the *extrinsic, intrinsic*, and *hormonal* mechanisms via ***endocrine***, ***paracrine*** and ***neurocrine*** pathways. Each regulatory mechanism does not occur as an isolated event but are all **integrated into one control mechanism**. For example, extrinsic nerves alter hormone release, which are in turn affected by paracrine agents. One representative example is typified by the *control of gastric acid secretion*, where extrinsic nerves, local enteric reflexes, paracrines, and hormones act in a highly integrated manner.

Clinical Correlations

Case Study 1

A 50-year-old man presents with a 6-month history of severe watery diarrhea and dehydration. The diarrhea is characterized by intermittent loose stools or watery diarrhea and occasional flushing. As his symptoms become worse, his family doctor prescribes him with antibiotics and several antidiarrheal medications, but to no avail.

He is admitted to the hospital when found to be orthostatic by blood pressure and pulse (i.e. blood pressure falls and pulse increases, indicative of severe dehydration), hypokalemic (low serum K^+), and hypochloremic (low serum Cl^-). His serum electrolyte abnormalities are corrected by intravenous replacement, but his diarrhea persists in spite of fasting for 48 h. Stool output over a 24-h period averages 1–1.5 L. Stool examination reveals no blood, pathogens, leukocytes, or fat. Diagnostic studies, including endoscopy and barium studies of the bowel, are unrevealing.

A computerized axial tomography (CAT) scan of the abdomen, however, shows a pancreatic mass and numerous lesions in the liver, consistent with tumor metastases. Plasma VIP levels are markedly elevated.

Questions:

1. **What does this patient have?**
   Answer: This patient has a rare endocrine tumor originating from the pancreas called a **VIPoma**. It is a functional endocrine tumor that makes and secretes large amounts of gut peptides; they include **VIP (vasoactive intestinal polypeptide), motilin,** and **neurotensin**. Because these tumors are generally slow growing, patients can tolerate them for years before they become clinically manifested.
2. **What is the pathophysiological basis of the clinical symptoms?**
   Answer: VIP is an important gut peptide typically found in neuroendocrine cells (but also expressed in some enteric neurons) that regulates numerous intestinal functions including motility, intestinal water and electrolyte transport, and blood flow. Because this tumor produces abnormal blood hormone levels, agents like VIP, in particular, can have significant systemic effects. VIP causes vasodilation that is manifested by facial flushing and sometimes hypotension. It is also one of the most potent secretagogues (i.e. stimulants that cause net secretion of water and electrolytes) of the gut; this action is mediated by stimulation of adenylate cyclase and increased cAMP. ***VIP-induced diarrhea*** persists despite fasting, a clinical feature of secretory (opposed to "osmotic") diarrheal diseases. ***Hypokalemia*** occurs because of stool losses and the chronic effects of aldosterone, a mineralocorticoid that is secreted by the adrenal gland in response to hypovolemia (decreased blood volume). Aldosterone increases renal reabsorption of Na^+ at the expense of increased excretion of K^+. ***Hypochloremia*** may be a consequence of increased stool Cl^- losses.
3. **How would you treat this patient's diarrhea?**
   Answer: Because this tumor has already spread, surgical intervention is not feasible. However, treating the patient with the long-acting somatostatin analog, ***Octreotide***, can inhibit the effects of the tumor. Octreotide has minor direct effects on intestinal mucosa cells that promote net absorption, probably mediated by activation of the inhibitory G-protein, G_i (thereby inhibiting VIP-stimulated adenylate cyclase activity). Octreotide's major effect appears to be the inhibition of hormone release (and possibly synthesis) by tumor cells. This is evidenced by plasma levels of the peptides, VIP and neurotensin, returning to normal following the administration of Octreotide, which is accompanied by a marked and rapid reduction of daily stool output to normal (<200 gm/day).

Case Study 2

A 30-year-old woman has increasing symptoms of abdominal bloating, weight loss, and diarrhea. The latter is characterized as foul smelling and bulky (typical of fat in the stool, or steatorrhea). Although the pancreas appears to be anatomically normal, exocrine pancreatic functions are abnormal, i.e. decreased secretion of pancreatic

enzymes and bicarbonate. Her gallbladder also empties poorly after meals. Fecal fat levels are very high, consistent with fat maldigestion and malabsorption. A small bowel biopsy shows villus atrophy, inflammation, and crypt cell hypertrophy.

Questions:

1. **What does this patient have?**
   Answer: This patient has **Celiac disease (Celiac sprue)**, an inflammatory condition (enteropathy) of the small intestinal mucosa triggered by dietary exposure to gluten. **Gluten** is a water-insoluble protein moiety of cereal grains (primarily wheat) that stimulates an inflammatory or immune response in individuals who are genetically susceptible. The condition is characterized by the development of small intestinal mucosal inflammation, most severe in the duodenum and proximal jejunum. The histology shown above is typical of Celiac disease, showing *villus atrophy* (shortening or absence of villi), *crypt hypertrophy*, and a *lamina propria packed with immune and inflammatory cells*. As an aside, Celiac disease is a common disorder that likely has a genetic basis, but is often clinically silent. It is a relatively "new" disease, as humans only started eating wheat about 10,000 years ago.
2. **What is the pathophysiological basis of the patient's symptoms and abnormal gut functions?**
   Answer: As mentioned above, the duodenum is severely affected by Celiac disease. Many of the mucosal endocrine cells that regulate the early digestive phases of intestinal function are located in this region, including those that secrete CCK, GIP, and secretin. **Compromised secretion of these gut peptides**, after gastric chyme enters the duodenum, impairs pancreatic function because CCK and secretin are required for activating pancreatic enzyme and bicarbonate secretion, respectively. Similarly, gallbladder contraction is dependent on the release of CCK. **Compromised pancreatic and biliary secretions** prevent proper digestion of food. **Injured and inflamed small bowel mucosa** impairs proper absorption of nutrients, water, and electrolytes. Net secretion of water and electrolytes occurs because inflammation stimulates active mucosal secretion and crypts cells are hypertrophied (crypt cells are secretory cells). As a result, the patient develops ***maldigestion***, ***malabsorption***, ***steatorrhea***, ***weight loss***, and ***abdominal bloating***.
3. **How would you treat this patient?**
   Answer: By going on a **gluten-free diet** (e.g. no more wheat-based bread or pasta), the patient should experience gradual improvement and weight gain. Pancreatic and digestive functions should also return to normal. **Glucocorticoid treatment** is recommended if deemed to do so; glucocorticoid is a potent drug with anti-inflammation and immunosuppression.

Case Study 3

A medical student traveling through South America develops acute, severe watery diarrhea without fever or chills. Stool examination shows no blood, leukocytes, or fat. However, stool cultures are positive for the pathogenic bacteria, enterotoxigenic *E. coli*.

Questions:

1. **How does this bacteria cause diarrhea in the student?**
   Answer: This strain of enterotoxigenic *E. coli* makes an enterotoxin called **heat-stable enterotoxin (ST_a)** that binds to the guanylin receptor on the luminal surface of intestinal epithelial cells. **Guanylin** is a gut peptide made by gut mucosal endocrine cells that stimulates net water and electrolyte secretion by a paracrine pathway. The guanylin receptor is a membrane guanylate cyclase that is also activated by binding with ST_a. Resulting increases in cellular cGMP stimulate cGMP-dependent protein kinases, setting off a cascade of biochemical events that ultimately leads to increased mucosal secretion while inhibiting absorption. Also compare with the mechanism of cholera-induced diarrhea (Chap. 5).
2. **What do you expect from an intestinal mucosal biopsy of this student?**
   Answer: It would be entirely normal (i.e. intact villus architecture). *E. coli* ST_a causes a functional impairment; however, the organism is not invasive and does not cause an inflammatory reaction.
3. **How would you treat this student?**
   Answer: You do not need any specific treatment and **oral rehydration solution** is sufficiently enough in most cases, as the disease is self-limiting in this sort of patients. However, **antibiotics** taken immediately after the development of symptoms can shorten the duration of illness. In the chapter on "Intestinal Physiology", you will learn why cholera is more severe and how oral rehydration solutions work.

Further Reading

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