Chapter 5
Intestinal Water and Electrolyte Transport

Eugene B. Chang and Po Sing Leung

1 Introduction to Gut Absorption of Fluid and Electrolyte

In addition to *digestion* and *absorption* of nutrients, the **intestinal tract** has several essential functions, including a *barrier* to the outside environment, *synthesis* of secreted proteins, such as those required for fat absorption and immunoglobulin secretion, and elimination of waste products, as well as *transport* of salt and water. Failure to efficiently absorbing water and electrolyte, it will lead to *dehydration* and *electrolyte imbalance*. Most of these processes are dependent on the specialized mucosal functions and structural requirements discussed in this chapter. Particular emphasis will be placed on aspects of intestinal epithelial biology and the transport of fluid and electrolytes. The discussion of other mucosal functions such as digestion and absorption of nutrients will be covered in subsequent chapters in Part Two of this book.

The ***cells relevant to intestinal water and electrolyte transport*** can be roughly divided into **two major groups:** those involved in **electrolyte transport** and those having predominantly a **regulatory role,** i.e. integrating the functional responses of the first group. This organization of the intestinal mucosa is extremely important considering the type of work it must perform. The absorptive epithelium of the intestine receives a luminal load averaging 9 L/day (Fig. 5.1). Approximately 2 L come from oral ingestion and 7 L from endogenous secretions from a variety of

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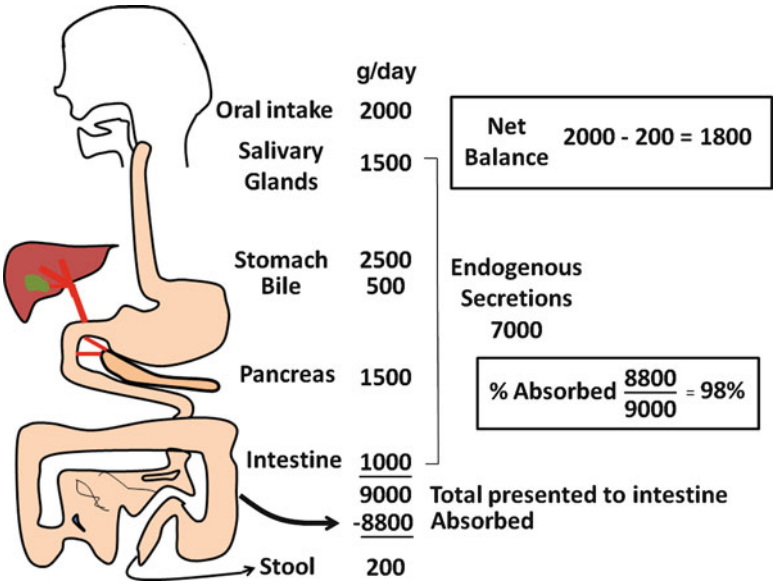

Fig. 5.1 Daily volumes of fluid entering and being absorbed by the gastrointestinal system, and excreted into feces. Fully 98 % of the fluid load is absorbed in the intestine, with only 200 g/day or less excreted via the stool. Compromise of absorption efficiency results in diarrhea (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

sources including the salivary glands, gastric juices, bile, pancreas, and enteric secretions. The endogenous secretions provide the necessary conditions, such as *pH*, *aqueous medium, salts,* and *osmolality,* for rapid and efficient digestion and absorption of nutrients and electrolytes. Of the 9 L presented to the intestinal mucosa each day, approximately 8.8 L or more are absorbed, resulting in less than 200 g/day of stool output (assuming the subject is eating a typical Western, low-roughage diet). Therefore, the gut is capable of absorbing greater than 98 % of the fluid load it is presented, making it a highly efficient organ for absorption of water and electrolytes. However, the gut also has the ability to adjust to large variations in luminal composition and volumes, especially increases. Diarrhea, which results when the absorptive capacity of the gut is exceeded, infrequently occurs under physiological circumstances. This can be attributed to the gut's ability to fine tune its absorptive and secretory processes, achieved through its intricate and often redundant regulatory mechanisms and by input from extra-intestinal sources. If any aberrations occur in the homeostatic regulation of ion-transport functions, stool output could exceed 200 g/day and diarrhea would result.

2 Organization of the Intestinal Mucosa

2.1 Intestinal Cells and Factors Involved in Water and Electrolyte Transport

The transport of water and electrolytes by the intestinal mucosa involves several types of cells and structural relationships. Important components of this process are discussed below.

Epithelial Cells

Epithelial cells represent the largest population of cells of the intestinal mucosa, of which there are **four major types: (1)** columnar, polarized epithelial cells, capable of vectorial transport of nutrients and electrolytes; **(2)** mucosal endocrine cells; **(3)** mucus producing and secreting goblet cells; and **(4)** defense-producing Paneth cells located at the base of intestinal crypts (Fig. 5.2). The latter two cell types will not be discussed, as their role in intestinal water and electrolyte transport is questionable or unknown. Gut epithelial cells emanate from a stable stem-cell population located near the base of the crypt and, with the exception of Paneth cells, differentiating as they migrate up the crypt-villus axis. As the cells reach the villus tip, they undergo **apoptosis** (physiologically programmed cell death) and are sloughed off into the lumen, with the entire sojourn taking 3–5 days. As cells undergo crypt-to-villus differentiation, significant ***changes in cellular morphology*** are evident (Fig. 5.3a), characterized by increasing polarity of the cells, differences in cellular organelle components, development of the microvillus membrane and terminal web, and alterations in other cytoskeletal and tight-junctional structural features. The latter are accompanied by decreases in junctional permeability, a property that may arise out of necessity to achieve efficient absorption of nutrients and electrolytes with a minimum of back flux. The regional differences in tight-junction permeability are reflected by the number of intercellular strands that make up the tight junctional complex. The number of strands in this anastomosing network in villus cells is much greater than in the crypt cells, making the villus regions more impervious to passive diffusion of water and electrolytes.

Alterations in functional characteristics along the crypt-villus axis also occur (Fig. 5.3b). Absorption and secretion of water and electrolytes are two distinct processes in the gut that take place in the villus and crypt cells, respectively. **Cystic fibrosis transmembrane regulator (CFTR),** a cyclic adenosine monophosphate (cAMP) regulated Cl^- channel involved in anion secretion, is predominantly found in **crypt cells**, consistent with a secretory role. As these cells become **villus cells**, the protein synthetic and secretory capabilities increase, reflected by increased development of the Golgi-endoplasmic reticulum complex and numbers of secondary endosomal vesicles. Properties of nutrient absorption and digestion appear, exemplified by increases in brush-border hydrolase activities, glucose

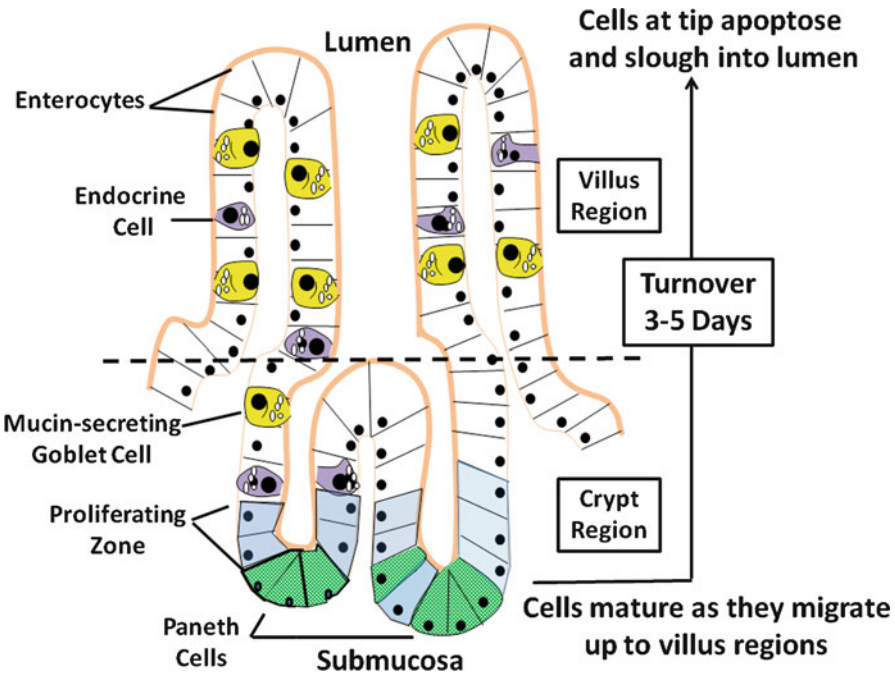

Fig. 5.2 Absorptive and secretory flows that determine the next fluid movement of the intestinal epithelial cells. There are four major types of epithelial cells making up the intestinal mucosa: enterocytes, endocrine cells, goblet cells, and Paneths cell. With the exception of Paneths cells, cells originating from the proliferative zone migrate up the villus axis and mature during the process, which eventually have a turnover rate of 3–5 days

transport and increased surface area of the apical membrane. Thus, the observed morphological, phenotypical and functional changes assumed by differentiating villus cells are consistent with their enhanced capacity for absorption of nutrients and electrolytes.

Blood Capillaries and Lymphatics

Blood capillaries and lymphatics have a major role in **intestinal water** and **electrolyte transport**. During absorption, for instance, they rapidly remove absorbed nutrients, water and electrolytes from the interstitium, thereby allowing vectorial transport to proceed. Similarly, active secretion of water and electrolytes is accompanied by increased mucosal blood flow and capillary filtration and by decreased villus lymph pressure and total lymphatic flow. In each case, in order for efficient absorption and secretion to occur, the events of mucosal transport, capillary flow, and lymphatic function must be coordinated. **Neural and hormonal** agents play a major role in the integration of these events. During secretion, for example, the net

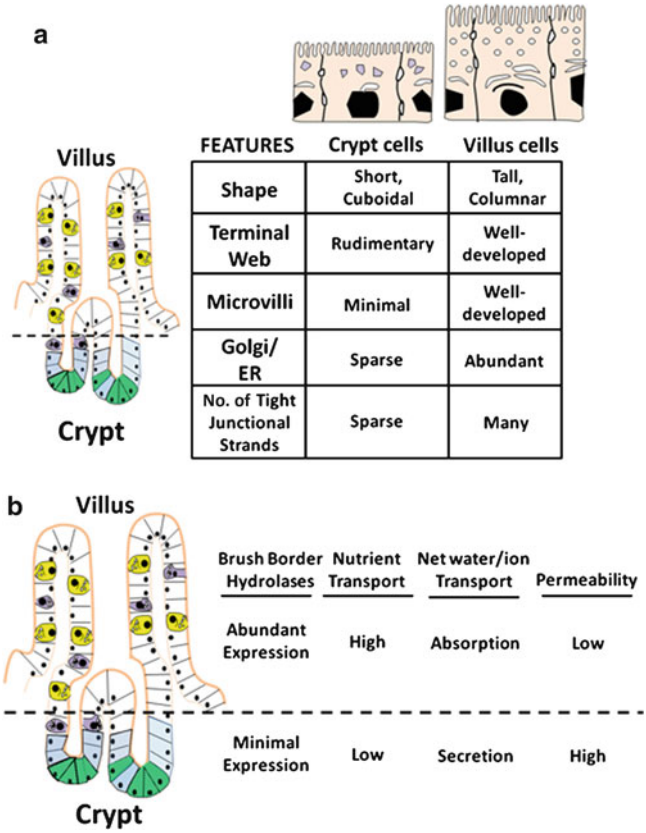

Fig. 5.3 Changes in structures and functions of villus cells and crypt cells. (**a**) As cells undergo crypt-to-villus differentiation, significant changes in cellular morphology become evident. (**b**) Alterations of functional characteristics of enterocytes occur along the crypts-villus axis (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

effect of these agents is to increase delivery of plasma fluid and electrolytes to match the demands of active intestinal secretion. Another purpose of increased blood flow during active secretion is to increase tissue delivery of oxygen to meet metabolic demands.

Intestinal Motility

The relationship between intestinal motility and mucosal water and electrolyte transport is extremely complex and incompletely understood. Although the functional properties of motility and ion transport can be readily studied independently, their physiological roles in intestinal water nutrient and electrolyte transport in vivo are

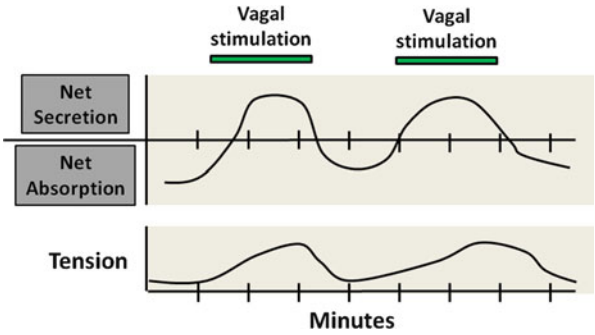

Fig. 5.4 Neural integration of intestinal motility and secretion. Coordination of water and electrolyte transport with intestinal motor function. Enteric reflexes coordinate intestinal water and electrolyte secretion with smooth muscle contractions

very much interdependent. This was recognized as early as 1912 by Babkin and Ishikawi, who noted that the periodicity of intestinal secretion coincided with that of intestinal motor activity. Consistent with this notion, there is ample evidence that **enteric reflexes** coordinate intestinal water and electrolyte secretion with smooth muscle contractions (Fig. 5.4). The integration of these responses serves several important purposes. First, it provides an immediate response to begin the process of digestion and absorption of luminal contents. Increased net secretion is essential for providing the aqueous milieu to reach isotonicity and for digestive enzymes to function properly. Coordinated patterns of intestinal motility ensure that mixing and propulsive activity of luminal contents proceed appropriately. This mechanical activity can significantly enhance the absorption of nutrients, electrolytes, and water through several potential mechanisms. Segmentation of the gut helps mix luminal contents with secretions and digestive juices and increases contact time between the luminal phase and the absorptive mucosal surface. **Increased intestinal motor contractility** is believed to alter the unstirred water layer, present as the result of the overlying layer of mucus gel. This facilitates diffusion of nutrients and electrolytes to the transporters of the brush-border membranes.

Decreased propulsive motor activity may enhance contact time between the absorptive surface area and luminal contents and is probably the major mechanism of action of commonly used antidiarrheal agents. In clinical studies of *loperamide, codeine,* and the α_2-receptor agonist *clonidine*, the predominant proabsorptive effect of these agents appeared to be due to their ability to increase the "enteropooling" capacity of the gut. The net effect of this action is to increase contact time between luminal fluid and the absorptive surface area.

2.2 Mucosal Cells Involved in the Regulation of Gut Water and Electrolyte Transport

Mucosal Endocrine Cells

Endocrine cells are widely distributed in the intestinal mucosa and represent a ***major source*** of **active amines** and **polypeptide hormones** important in the

Regulatory Agents of Intestinal Water and Electrolyte Transport

Source	Stimulate Net Secretion	Stimulate Net Absorption
Mucosal Epithelial Cells	Serotonin Gastrin/CCK Neurotensin Guanylin	Somatostatin
Lamina Propria Cells	Arachidonate metabolites Active Oxidants Nitric Oxide Some cytokines Bradykinin	?
Enteric Neurons	Acetylcholine Serotonin VIP Substance P Purinergic Agonists	Norepinephrine Neuropeptide Y
Blood	VIP Calcitonin Prostaglandins Atrial Natriuretic Peptides	Epinephrine Corticosteroids Mineralocorticoids Angiotensins

Fig. 5.5 Common regulators for the control of gut water and electrolyte transport. There are peptides, active amines, and other agents from different gut layers that can modulate intestinal fluid and electrolyte transport

regulation of fluid and electrolyte transport. Although many of the contents of their secretory granules are also found in nerve cells of the enteric nervous system, it is likely these cells have unique and independent role in modulating various mucosal functions. Like their transporting epithelial counterparts, mucosal endocrine cells are **polarized**. Their ***apical or luminal pole*** is characterized by tufts of microvilli and coated vesicles, whereas their ***secretory granules and nuclei*** are located at the basal domain of the cell. These structural characteristics most likely represent the functional requirements of the cell to sense alterations in luminal content such as pH, osmolality, and chemical content and initiate an integrated mucosal response through the release of secretory-granule contents at the basal surface of the cells. Several peptides, active amines, and other agents appear to modulate intestinal fluid and electrolyte transport (Fig. 5.5). The regional distribution of these agents throughout the gastrointestinal (GI) tract differs markedly. For example, cells containing *gastrin, cholecystokinin (CCK)*, and *secretin* are more prominently found

in the **stomach** and **proximal small intestine,** whereas *neurotensin-containing cells* are largely restricted to the **ileum**. *Serotonin-containing enterochromaffin cells* are found throughout the mucosa but predominantly in the **crypt regions**, where they may project basal processes that run subjacent to neighboring epithelial cells and nerves containing other peptides. Recently, ***guanylin*****,** the natural endogenous peptide agonist of the *E. coli* heat-stable enterotoxin (ST_a) receptor, has been localized to epithelial (nonclassic endocrine) cells of the colonic mucosa (and possibly Paneth cells of the human small intestine). Guanylin is released into the crypt lumen and stimulates luminal receptors on intestinal epithelial cells by a paracrine action to stimulate net secretion.

Mucosal endocrine cells most likely regulate intestinal ion-transport functions through a paracrine action. They can be activated by a variety of luminal and serosal stimuli. Thus, mucosal endocrine cells probably serve **two important functions** relevant to the control of intestinal water electrolyte transport. First, they provide a means for the mucosa to sense and rapidly respond to alterations in luminal content and milieu. The stimulated release of hormonal peptides and active amines causes appropriate changes in ion-transport functions, blood and lymphatic flow, and intestinal motility. Secondly, they may function as a fine tuning mechanism or amplifier for modulatory signals received from neural sources.

Enteric Neurons

The GI tract is one of the most richly innervated organs of the body and has **two major categories of nerves:** the ***intrinsic or enteric nervous system*** and the ***extrinsic autonomic nervous system*** consisting of parasympathetic and sympathetic nerve pathways. Although most **postganglionic sympathetic fibers** terminate in enteric ganglia, a few have been reported in close proximity to intestinal epithelial cells, where they may form actual synapses. Release of norepinephrine from these neurons stimulates α_2-adrenergic receptors on the basolateral membranes of enterocytes, causing increased electroneutral absorption of sodium chloride and inhibition of anion secretion. **Parasympathetic neurons** are also believed to be important in the regulation of intestinal salt and water transport. However, the nature of vagal postganglionic fibers to the intestine is less well understood. Some fibers make up interneurons that modulate enteric system tone or responses.

The **enteric nervous system** is a dense plexus of efferent, afferent, and interneurons, exceeding in number the neurons of the spinal cord. It is composed of ***cholinergic*** and ***non-cholinergic*** neurons that regulate numerous mucosal and motor functions. The number of neurotransmitters found in these nerves is quite large and includes ***active amines*** (such as *serotonin* and *acetylcholine*), ***neuropeptides*** (such as *substance P, neurotensin, CCK, neuropeptide Y, somatostatin, calcitonin gene-related peptide, vasoactive intestinal peptide* and *galanin*), and ***purinergic neurotransmitters*** (such as *adenosine* and *adenosine triphosphate, ATP*). This tremendous diversity of neurotransmitters is probably required to regulate and

coordinate the numerous mucosal and motor functions involved in salt and water transport. Many of the enteric nervous system neurons are part of programmed reflexive circuits that can immediately respond to various stimuli. Mucosal sensory fibers respond to a number of stimuli, including mechanical factor (touch, pressure, and tension), changes in luminal content and composition (pH, osmolality, and amino acids), temperature, and pain. These sensory signals are then relayed to interneurons that rapidly process and sort the signals so that efferent (motor) neurons (regulating smooth muscle, blood vessel, absorptive and secretory cells, and other cells of the lamina propria) can produce patterned and coordinated responses for efficient transport of water and electrolytes**.** The enteric nervous system plays a major role in regulating intestinal water and electrolyte transport, as evidenced by the fact that mucosal and motor functions can proceed independently of extrinsic neural input.

Mesenchymal Cells of the Lamina Propria

Mesenchymal cells of the lamina propria and submucosa play a **juxtacrine** role and modulate intestinal mucosal transport, blood flow, and motor functions. They include many cell types such as sub-epithelial fibroblasts, endothelial cells, mast cells, neutrophils, macrophages, and eosinophils. Their numbers within the mucosa vary considerably depending on the species, the region of the intestine, and the prevailing physiological or pathophysiological circumstances. Although their relative roles in the physiological regulation of intestinal water and electrolyte transport have not been established, it is likely that many of these cells play a major role in causing net secretion, altered motor function, and changes in blood flow under pathophysiological situations such as *mucosal inflammation*.

Many of these cells appear to have important **interactions with neural and epithelial elements** within the intestinal mucosa (Fig. 5.6). For example, *mast cells*, found throughout the intestinal mucosa and often in close proximity or juxtaposed to enteric nerve fibers, activate enteric neurons. This serves to amplify and extend the effects of mast-cell mediators such as *histamine*. These cells have an important immunoregulatory role and are involved in the allergic and anaphylactic reactions to food antigens and helminth parasites, as well as in diseases such as ***systemic mastocytosis***. The number of inflammatory mediators released by the mast cell is large and includes agent such as *histamine, adenosine, platelet-activating factor (PAF), serotonin,* and *arachidonic acid metabolites*. Agents such as *prostaglandin E_2 (PGE_2), adenosine*, and *serotonin* stimulate net intestinal secretion in part by directly activating epithelial receptors, causing decreased absorption of Na^+ and Cl^- and activate secretion of anions. However, these agents and others such as *histamine* and PGD_2 also stimulate net secretion by promoting the release of various neurotransmitters, thus amplifying or augmenting the overall secretory response.

Resident tissue macrophages are also prevalent in the **intestinal mucosa**, constituting 10–20 % of the total cell number in the lamina propria. This makes

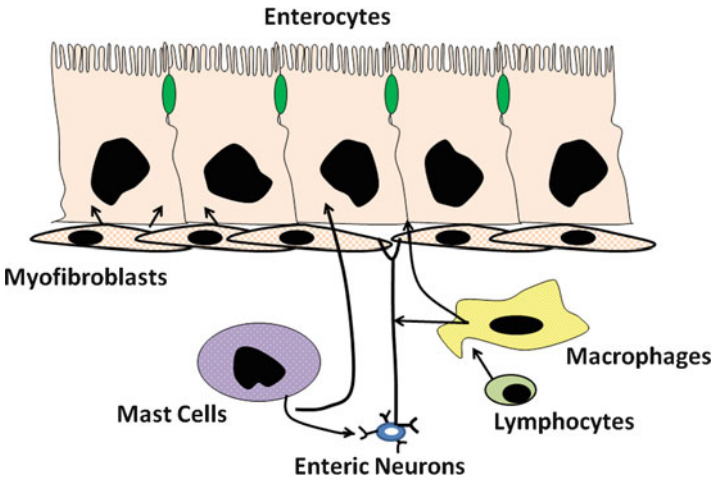

Fig. 5.6 Interaction of enteric cells and other mucoal cells for intestinal water and electrolyte transport. Mesenchymal cells of the lamina propria play an important role in regulating intestinal water and electrolyte transport (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

the small and large intestine one of the largest repositories of macrophages in the body. Under steady-state and physiological conditions, there appears to be a constant turnover of macrophages (on the order of days to weeks), mostly from the replacement of existing tissue macrophages with incoming monocytes. In the intestine, the macrophages may be conditioned by tissue-specific influences, such as *bacterial products from the lumen* (including endotoxin), *extracellular matrix,* and *cytokines.* The continuous exposure to foreign antigens and pathogens, particularly in the colon, may be important in sensitizing macrophages, allowing them to rapidly react to various stimuli. Thus, macrophages function as a ***first-line defense*** against pathogens and antigens and are capable of orchestrating and amplifying an appropriate immune and inflammatory response. The intestinal macrophages are veritable factories for synthesis and release of numerous immune and inflammatory mediators. They are a major source of **carbon monoxide** and **5-lipoxygenase (5-LO) metabolites** and may mediate the secretory effects of many of the secretagogues that are known to activate the arachidonic acid cascade. In response to numerous immune and inflammatory stimuli, they also elaborate **cytokines** such as *interleukin-1 (IL-1), IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF),* and other inflammatory mediators such as *purinergic agents.* Most of these products have now been shown to affect intestinal water and electrolyte transport and have potent effects on modifying intestinal motor functions and capillary blood flow and permeability. Like mast cell products, they have numerous sites and mechanisms of actions that affect ion transport. These will be discussed later in the chapter.

3 Mucosal Electrolyte Transport Processes

3.1 Absorptive Pathways for Water and Electrolytes

Water transport by the intestine is closely coupled with solute movement and is passive. In theory, water flow could occur by transcellular and paracellular routes, but the prevailing evidence indicates that water transport by the intestine occurs through the **paracellular pathway.** Like other tissues that transport electrolytes, the intestine has a variety of **specialized transport proteins**, which can be divided into **three major types** (Fig. 5.7).

Pumps such as sodium pump (Na^+/K^+-ATPase) and the proton pump (H^+/K^+-ATPase) are energy-driven and capable of transporting ions against large electrochemical gradients. In intestinal epithelium, for example, the sodium pump is essential for establishing and maintaining electrochemical gradients (low intracellular Na^+ and electronegative membrane potential) that are required for other types of passive and facilitated transport processes.

Channel proteins are selective membrane "pores" for ions such as Na^+ and Cl^-. Channel transport is dependent on favorable electrochemical gradients, is often membrane-potential sensitive, and is generally electrogenic, i.e. causing a potential difference across the epithelial layer that promotes passive diffusion of a counter ion. For example, electrogenic Cl^- secretion in the gut causes a potential difference (serosa is positive relative to lumen) across the mucosa that promotes passive transport of Na^+, resulting in net sodium chloride secretion.

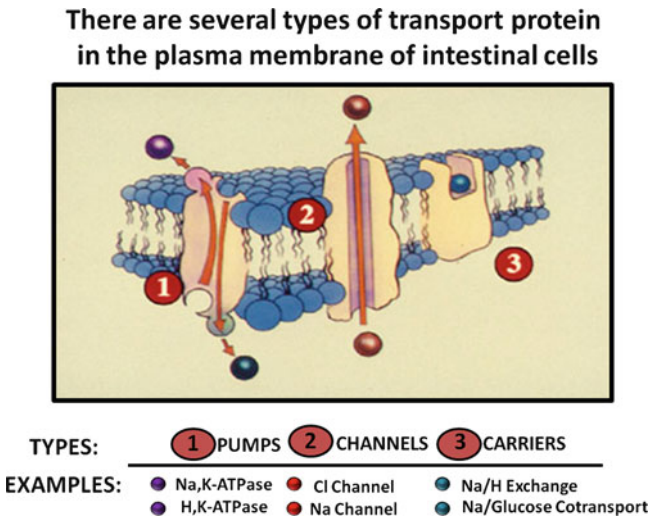

Fig. 5.7 Intestinal transport proteins. There are three types of transport proteins that are found in the plasma membranes of intestinal cells: pumps, channels and carriers (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

Carrier transport proteins facilitate transport of ions and nutrients across the cell membrane, and their transport activity is dependent on existing electrochemical gradients. ***Several types of carrier proteins*** exist in gut epithelium. **Uniport** carrier proteins, such as the *facilitated glucose transporter GLUT2*, mediate the transport of a single ion or nutrient molecule; **symport** carrier proteins, such as *sodium/glucose cotransport-1 (SGLT-1) protein*, are carriers that simultaneously transport two or more molecules, often taking advantage of favorable electrochemical gradients for one molecule to actively transport others. Transport by these carriers occurs only if all solutes are present. In addition, glucose transport will not occur if an inwardly directed Na^+ gradient is absent; **antiport** carriers, such as the Cl^-/HCO_3^- and Na^+/H^+ *exchangers,* exchange one molecule for another.

Absorptive Pathways for Electrolytes

Na^+ and Cl^- are avidly absorbed by the intestinal mucosa, albeit differing in amount and by region-specific transport mechanisms of the gut. Several of these pathways and their relative distribution along the horizontal axis of the intestine are illustrated in Fig. 5.8.

In the **small intestine**, for example, Na^+ is in part absorbed by **solute-dependent Na^+-cotransport processes** that are quantitatively greater in the proximal than in the distal small bowel. In addition, the luminal bioavailability of nutrients and digestive enzymes is also largest in the proximal small intestine. **Non-nutrient dependent Na^+ absorption** in humans occurs predominantly via luminal membrane-located, amiloride-sensitive Na^+/H^+ exchangers that are not coupled to Cl^-/HCO_3^- exchangers in the jejunum, as is the case in the more distal regions of the bowel (Fig. 5.9). Consequently, Na^+ absorption is accompanied by an apparent HCO_3^- absorption, resulting from extrusion of protons, carbon dioxide formation, and increased cellular HCO_3^- secondary to diffusion of carbon dioxide. Cl^- absorption in this region is passive, dependent on transmural potential differences and concentration gradients.

In the **distal small intestine** and **proximal colon**, Na^+ and Cl^- absorption are coupled and electroneutral. Although a furosemide-sensitive Na^+-Cl^- cotransport protein has been proposed, it is likely that most coupled Na^+-Cl^- transport is carried out by the **two distinct proteins**, ***Na^+/H^+ exchanger*** and ***Cl^-/HCO_3^- exchanger,*** which are coupled by the formation of intracellular HCO_3^- and protons from carbonic acid (Fig. 5.10). The presence of these carrier proteins has been confirmed by numerous studies of brush-border membrane vesicles and is further supported by the findings in patients with **familial chloridorrhea**, a rare inborn error of transport manufactured by an ***absence of Cl^-/HCO_3^- exchanger activity***. These patients develop *moderate diarrhea* and may have *metabolic alkalosis* and *stool pH in the acidic range*. Luminal perfusion studies demonstrate abnormality in the ileum and colon, where HCO_3^- secretion appears to be replaced by H^+ secretion. In the ileum and colon, **Cl^-** is also absorbed by a ***HCO_3^--dependent pathways***, probably involving a luminal membrane Cl^-/HCO_3^- exchanger not coupled to Na^+/H^+ exchanger, as well as by **potential difference-dependent diffusion**.

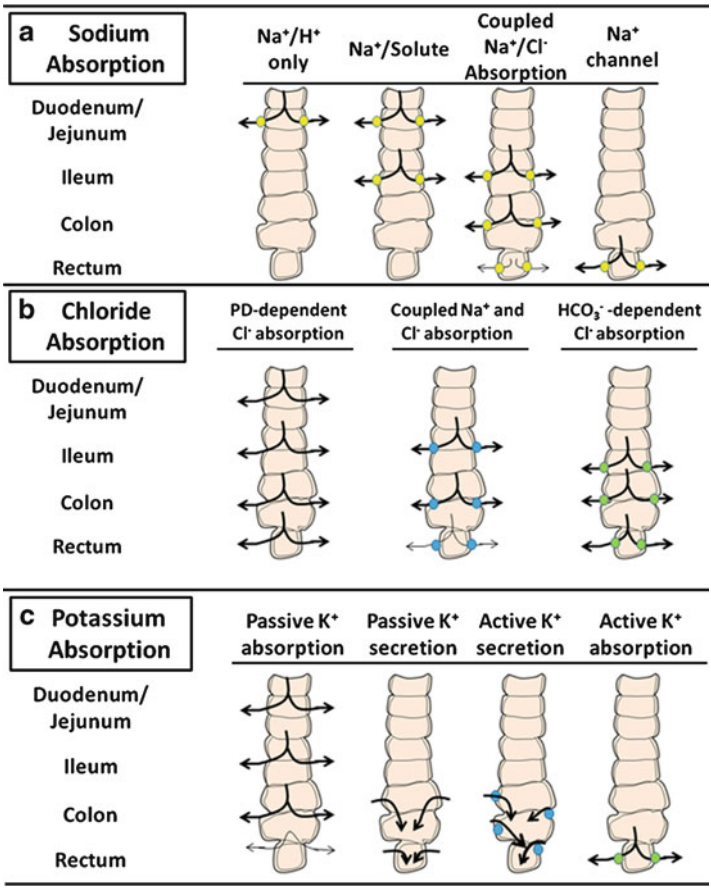

Fig. 5.8 Intestinal transport pathways for absorption. There are three types: sodium absorption (**a**), chloride absorption (**b**), and potassium absorption (**c**). These transporters are distributed along the length of the gut (*arrows*) (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

In the **distal colon**, active Na^+ absorption must occur against very large electrochemical gradients. To accomplish this, the rectum absorbs Na^+ by an electrogenic, amiloride-sensitive ***Na^+ channel*** present in the luminal membrane (Fig. 5.11). Because this region of the gut has the least paracellular permeability, back diffusion of ions is minimal, and large potential differences can be maintained. The latter is necessary for passive absorption of the counter ion Cl^-/K^+ absorption in the colon, in contrast to its exclusively passive transport in the small intestine, is actively absorbed predominantly in the recto-sigmoid area. This is probably mediated by ***K^+/H^+ exchanger*** of a luminal membrane H^+/K^+-ATPase, which has recently been cloned (Fig. 5.12). This protein has 63 % amino acid homology

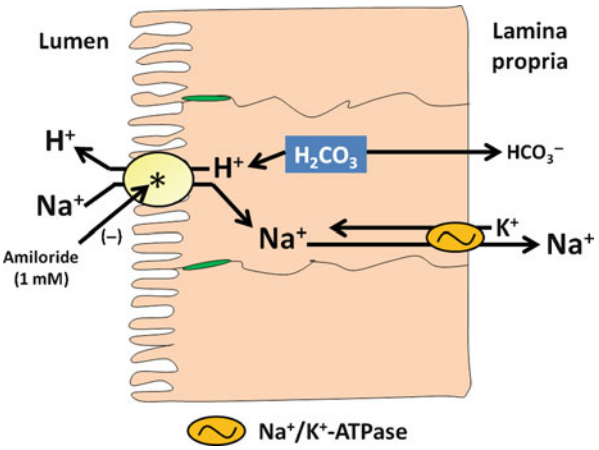

Fig. 5.9 Nonnutrient-dependent sodium absorption in proximal small intestine mediated by Na^+/H^+ exchange (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

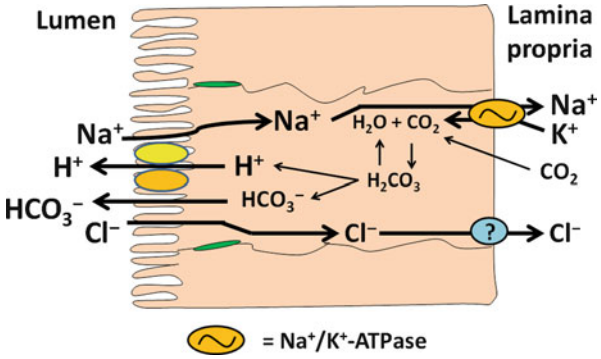

Fig. 5.10 Coupled Na^+-Cl^- transport in ileum and colon. The transport is achieved via the mediation of two distinct brush-border ion exchangers: Na^+/H^+ exchange and Cl^-/HCO_3^- exchange. This process is electroneutral (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

with the gastric H^+/K^+-ATPase-α subunit and is most abundantly expressed in the distal colon.

Finally, the **colon** is also the major site for the generation and absorption of **short-chain fatty acids (SCFA).** SCFA are products of bacterial metabolism of undigested complex carbohydrates derived from dietary sources such as *fruits* and *vegetables.* They are produced in large quantities by colonic bacterial flora and in fact represent the major luminal anions of the region. Although SCFA are believed to have many important trophic effects on colonic mucosa, they also appear to promote Na^+ absorption by the colonic mucosa. Unfortunately, the exact mechanism for Na^+-SCFA absorption remains controversial. Nevertheless, luminal SCFA may play an extremely important role in aiding colonic water and electrolyte absorption.

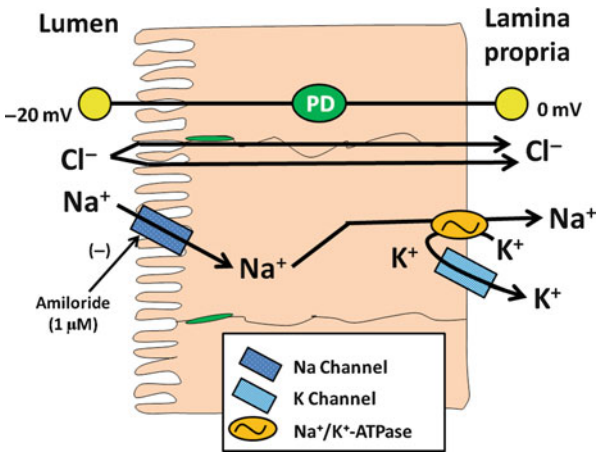

Fig. 5.11 Electrogenic Na^+ absorption in distal colon. The process involves an amiloride-sensitive Na^+ channel in the luminal membrane (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

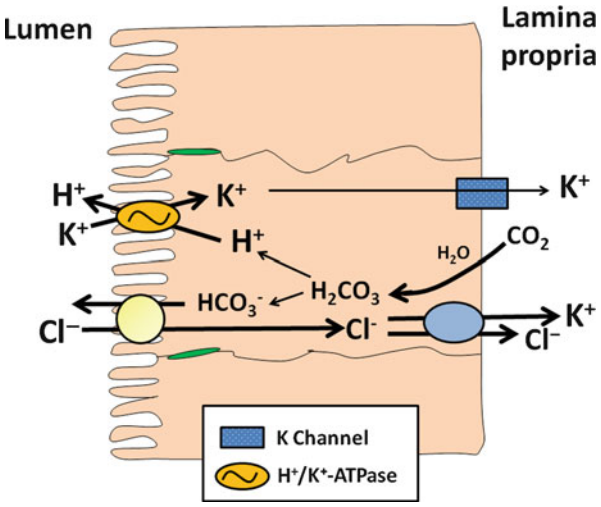

Fig. 5.12 K^+ absorption in the recto-sigmoid area. This electroneutral process is probably mediated by K^+/H^+ exchange by the K^+/H^+-ATPase in the luminal membrane (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

3.2 Secretory Pathways for Water and Electrolyte

Active water and electrolyte secretion serve several important purposes. Its major physiological role is to provide the aqueous medium for proper digestion and absorption of luminal nutrients. Intestinal secretion is largely driven by active secretion of Cl^- or HCO_3^-.

Secretion of Cl^-

The secretion of Cl^-, in particular, has been well characterized and appears to involve the coordinated actions of **four membrane proteins: (1)** a

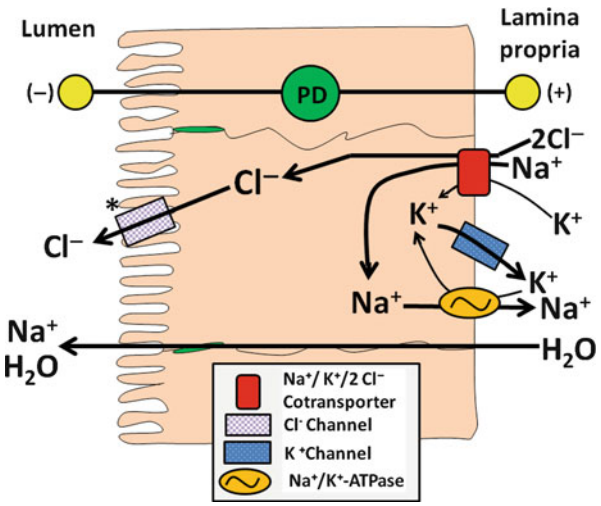

Fig. 5.13 Electrogenic Cl^- secretion. Cl^- enters the cells by the $Na^+/K^+/2Cl^-$ cotransporter and exits into the lumen via Cl^--sensitive channels (*). PD = potential difference (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

luminal-membrane **Cl^- selective channel**, **(2)** the basolaterally located **$Na^+/K^+/2Cl^-$ co-transporter**, **(3) K^+-selective channels**, and **(4)** the **Na^+/K^+-ATPase**, or **sodium pump** (Fig. 5.13). Briefly, Cl^- enters the cells by the $Na^+/K^+/2Cl^-$ co-transporters and exits into the lumen via Cl^--selective channels (one of which may be cystic fibrosis transmembrane regulator channel, CFTR), with the openings of the channels being modulated by various protein kinases. K^+ and Cl^-, which accompany Cl^- entry into the cell, are recycled across the basolateral membrane by K^+-selective channels and the Na^+/K^+-ATPase, respectively. Na^+ secretion that accompanies active Cl^- secretion is a passive process, driven by the trans-epithelial potential difference resulting from Cl^- secretion. Cl^- secretions can be regulated by numerous neurotransmitters and gut peptides (discussed below).

Secretion of HCO_3^-

In contrast to Cl^- secretion, much less is known about HCO_3^- secretion. In rabbit ileum, HCO_3^- secretion appears to be electrogenic and vectorially transported across the epithelium, rather than generated by the production of HCO_3^- from the action of carbonic anhydrase. Furthermore, HCO_3^- secretion appears to be dependent on the presence of serosal Na^+ and is postulated to involve at least **three different transporters: (1)** an apical membrane **anion-selective** (HCO_3^- and possibly Cl^-) **channel**; **(2)** a coupled, electrogenic **Na^+/HCO_3^- cotransporter** in the basolateral membrane; and **(3)** a **Cl^-/HCO_3^- exchanger** in the apical membrane. In the **distal colon**, HCO_3^- secretion appears to be electroneutral and may involve a Na^+-independent Cl^-/HCO_3^- exchanger located in the apical membrane. Along with HCO_3^- secretion, it is important for providing the aqueous phase for luminal digestion and nutrient absorption.

Secretion of K^+

Active K^+ secretion is also found throughout the **colon**, apparently mediated by a barium-sensitive K^+ conductance in the apical membrane. K^+ enters the basolateral membrane of the colonocyte via the Na^+/K^+-ATPase pump, and possibly by the $Na^+/K^+/2Cl^-$ co-transporter. This is a process that can be stimulated by increases in cellular cAMP and Ca^{2+}.

4 Physiological Regulation of Gut Water and Electrolyte Transport

The intestines contribute 12–14 % of the secretions needed to maintain the chyme in a fluid state. In addition to allowing for efficient digestion and absorption of the complex components of mammalian meals, the secretions serve as a conduit for the luminal delivery of secretory **immunoglobulin A (IgA) glycoproteins** and for flushing out infectious agents and noxious stimuli. The regulation of intestinal secretion is multifactorial, involving *luminal* and *systemic* influences. It has long been recognized that simple **mechanical stimulation** of the gut lumen can increase secretion. Similarly, **chemical stimuli**, no matter in the form of the normal breakdown products of dietary intake, toxigenic elaborations of the microflora, or noxious chemicals and antigens, elicit secretions. **Systemic metabolic changes**, including *volume overload, dehydration,* and *acidosis* or *alkalosis*, also influence secretion. Finally, in addition to local regulation of neurohumoral factors, there is increasing evidence that *higher centers of the brain* have modulatory effect on intestinal secretion. All these stimuli act on an intricate complex of neural, hormonal and autocrine modulators in the mucosa and gut wall that govern both basal and stimulated states of secretion. As described above, these agents act on specific receptors on the target cells, which can be on either the enterocytes or underlying neural, vascular, or immune elements.

4.1 Neurohormonal Agents That Cause Net Intestinal Secretion or Increase Net Absorption

Factors that regulate intestinal epithelial ion-transport properties can be broadly classified into **two groups:** the **secretagogues** and the **pro-absorptive agents**. As their names imply, secretagogues cause net accumulation of fluid in the intestinal lumen by either stimulating active secretory processes and/or inhibiting absorption; pro-absorptive agents promote absorption by having the opposite effect. The major secretagogues and pro-absorptive agents known to act on enterocytes are listed in Fig. 5.5. The source of regulatory agents varies. Some, such as *neurotransmitters*

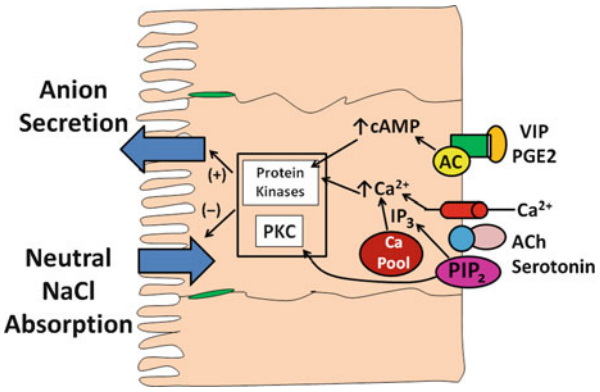

Fig. 5.14 Intracellular processes mediating agonist-stimulated net secretion

and *paracrine hormones*, are released locally near the basolateral membrane of the enterocyte. Other substances, such as *guanylin*, are released into the lumen, and substances such as *adrenalocorticoids* reach the enterocyte via the systemic circulation. Enterocytes have receptors on both apical and basolateral membranes and, in the case of the steroids, intracellular receptors as well. In addition to **species and regional differences** in receptor distribution, **multiple receptor isotypes** for each neurotransmitter/hormone appear to exist. Likewise, several ***histamine-, muscarinic-,*** and ***adrenergic-receptor subtypes*** have been identified in different regions of the gut. The type of ligand-receptor interaction is a major determining factor of the duration of the response. Thus, the effects of a number of **calcium-dependent secretagogues** and **prostaglandins** are *short-lived,* and some of these are due to **receptor-associated tachyphylaxis**. These short-lived responses are probably crucial for dealing with the minute-by-minute challenges in the gut milieu. In contrast, the **steroid-mediated responses** are much *longer lived*. For example, in the distal colon, they act through specific intracellular receptors in the enterocytes initially to increase the recruitment of transporters to the epithelium by promoting the synthesis of various proteins needed for transport; they include apical membrane Na^+ channels Na^+/H^+ exchange, as well as increasing the number of Na^+, K^+-ATPase pumps in the basolateral membrane to provide the necessary driving force for transport. Long-term changes are more beneficial in an adaptation-type of response, as seen in exposure to a low-sodium diet or dehydration.

Mechanisms of Regulation of Ion Transport

As with many types of cells, a number of signal transduction pathways are involved in the regulation of ion transport. **Secretagogues** act mainly by stimulating one of the classic signal transduction cascades; the pathways dependent on *cAMP, cyclic guanosine monophosphate (cGMP), Ca^{2+},* or *phosphatidylinositol (PI)* (Fig. 5.14). These second messengers activate their respective protein kinases that phosphorylate proteins directly involved in ion transport or critical in regulating

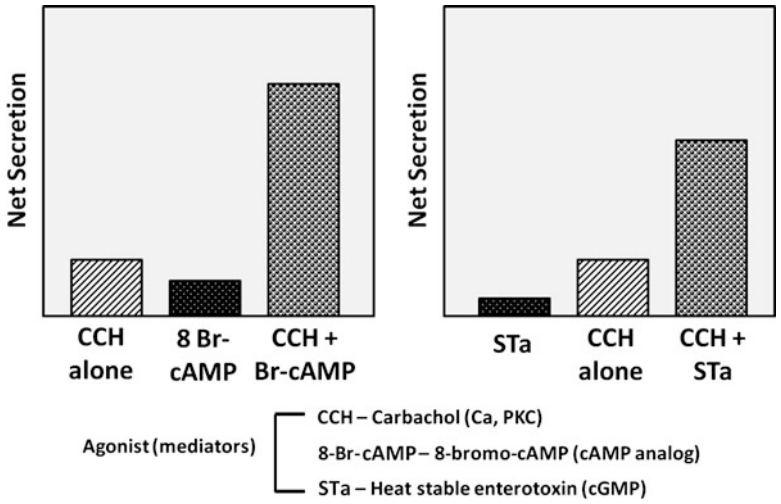

Fig. 5.15 Synergistic effect of intracellular mediators that regulate intestinal electrolyte transport

transport activities. The mechanisms of action of the **pro-absorptive agents** vary and include an *activation of the inhibitory G protein (G_i) cascade,* the *inhibitory arm of the adenylate cyclase cascade*, and the *PI cycle*. The mechanism of activation of these second messengers could also influence the duration and type of the biological response. This is best exemplified by comparing the effects of cholera toxin, vasoactive intestinal peptide (VIP), and prostaglandins, all three of which stimulate secretion via the cAMP cascade. The activation of secretion by *cholera toxin* involves an essentially irreversible covalent modification of the stimulatory G protein (G_s)-type of guanosine triphosphate (GTP)-binding proteins. Activated Cl^- secretion is only "shut off" when the enterocyte is sloughed off at the end of its normal life span. Secretagogues such as *VIP* can cause sustained stimulation of secretion in vitro; secretion returns to baseline as the hormone/neurotransmitter is degraded. The effects of prostaglandins are limited by receptor tachyphylaxis. The general dogma is that second messengers activate specific protein kinases to cause a biological effect and that endogenous phosphoprotein phosphatases reverse this effect to return the system to the basal state. There is considerable evidence to indicate a role for protein phosphorylation in regulating intestinal ion transport, but recent evidence suggests that there may be direct, non-kinase activation of Cl^- channels by cyclic nucleotides as well. Although a regulatory role for protein phosphatases in signal transduction gains acceptance, to our knowledge, a role for them as a primary trigger of intestinal ion transport has not yet been demonstrated.

Considerable cross-talk also exists among the different signaling mechanisms and among different steps of the same signaling pathway. Two examples are provided here and illustrated in Fig. 5.15. Synergistic actions between *cAMP and Ca^{2+}-mediated secretion*, as well as *cGMP (ST_a) and Ca^{2+}-mediated secretion,* have been demonstrated. In both cases, the effects of the combined additions are

greater than the effects of each agent added alone. In contrast, *phorbol esters*, activators of protein kinase C, do not have any effect when added alone but attenuate cAMP-mediated Cl^- secretion.

Regulation of ion transport by intestinal epithelial cells must involve the **coordination of transport processes** at the ***apical*** and ***basolateral*** membranes. For example, it is known that *Na^+/H^+ exchangers* are present in both membrane domains. Simultaneous activation of these transporters would result in counterproductive actions and ineffective absorption of Na^+. This does not occur because different Na^+/H^+ exchanger isoforms are present in each domain that respond differently to intracellular signals. For example, stimulated increases in cytosolic Ca^{2+} and activation of protein kinase C appear to inhibit luminal *Na^+/H^+ exchangers*, whereas they may activate basolateral isoforms. Another example of coordinated regulation of cellular transport processes is the stimulation of active Cl^- secretion. Here, the opening of the *Cl^- channel* is accompanied by activation of the *$Na^+/K^+/2\ Cl^-$ co-transporter*, the latter event required for bringing in additional Cl^- ions for sustained secretion. Again, this coordination of cellular processes requires the actions of intracellular second messengers and protein kinases that simultaneously activate co-dependent transport pathways.

Finally, the regulation of intestinal transport processes may in part involve **modulation of paracellular permeability**. For instance, the activation of protein kinase C by various agonists or by the **zonula occludens toxin (ZOT)** of *Vibrio cholera* may cause cytoskeletal alterations that affect the peri-junctional actin ring, a major component of the tight-junction apparatus. Alterations in paracellular permeability markedly affect both absorptive and secretory processes.

5 Abnormality in Water and Electrolyte Transport

Alterations in intestinal transport function in response to a variety of pathophysiological processes can be mediated by many different mechanisms. In some instances, the responses are appropriate, i.e. as part of defensive or healing mechanisms or in response to increased metabolic and nutritive demands caused by disease. In other instances, however, the response is an aberration or manifestation of the disease and serves no clear physiological role. This section will briefly discuss a few illustrative examples of mechanisms by which disease processes affect intestinal water and electrolyte transport.

5.1 Adaptive Transport Mechanism in Diabetes

Diabetes has significant and complex effects on nutrient and electrolyte transport functions of the intestinal mucosa, some of which have now been well characterized. An uncommon but debilitating complication of chronic diabetes is the development

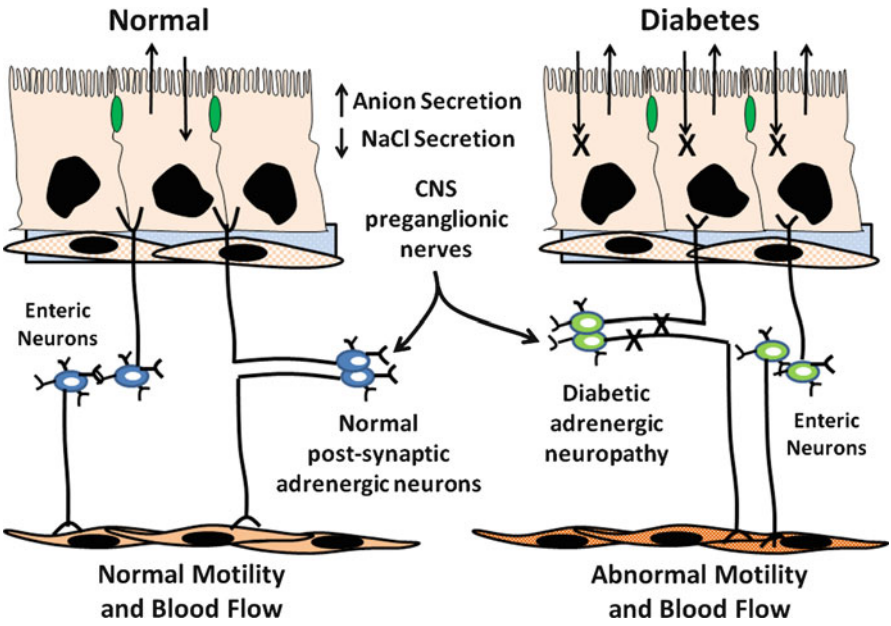

Fig. 5.16 Cell mechanisms of diabetic diarrhea. Autonomic and possibly enteric neuropathy in diabetes leads to impaired homeostatic regulation of intestinal fluid and electrolyte transport, abnormal motility, and alterations in capillary blood flow (*right side*), compared with normal condition (*left side*) (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

of ***diabetic diarrhea***. This condition is invariability associated with ***autonomic neuropathy*** and arises from an aberrant neural regulation of salt and water transport, as well as abnormal motility. In streptozotocin-treated diabetic rats, for instance, a selective impairment of adrenergic innervation of the mucosa results in an imbalance in factors that regulate absorptive and secretory processes, favoring the latter (Fig. 5.16). Thus, the development of autonomic and possibly enteric neuropathy in diabetes causes *impaired homeostatic regulation of intestinal fluid and electrolyte transport, abnormal motility*, and *alterations in capillary flow.*

5.2 Transport of Inflamed Mucosa

In mucosal inflammation, the interactions and effects of the factors and cellular components that normally regulate ion transport functions are dramatically altered or diminished as a result of the large number of infiltrating inflammatory cells. These cells secrete large amounts of immune and inflammatory mediators and cause net intestinal secretion; they can also adversely affect mucosal integrity and function

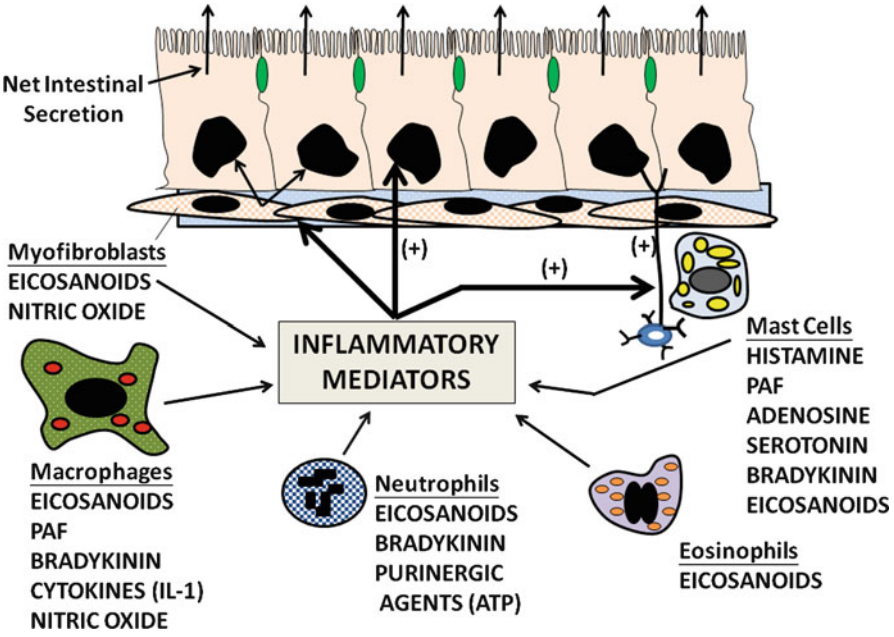

Fig. 5.17 Effects of inflammatory mediators on ion transport. These cells from several sources cause direct and indirect stimulation of intestinal secretion (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

(Fig. 5.17). While net secretion serves to purge the gut of noxious agents and pathogens, it may also cause severe fluid losses and metabolic imbalances. **Arachidonic acid metabolites** from ***neutrophils, fibroblasts*** and ***activated macrophages*** play a major role in stimulating net secretion. While many prostaglandins such as PGE_2 appear to activate specific epithelial cell receptors to stimulate anion secretion and inhibit Na^+ and Cl^- absorption, agents such as PGD_2, PGI_2, and the *peptido-leukotriene* LTC_4 activate secretomotor neurons. Similarly, other inflammatory products such as *radical oxygen metabolites, serotonin, histamine,* and *platelet-activating factor* that are made and secreted by activated phagocytic and inflammatory cells have multiple sites of action. Many of these agents cause immediate changes in motility and in blood capillary and lymphatic flow conducive to net secretion.

Some immune and inflammatory mediators appear to stimulate changes in electrolyte transport via stimulation of intestinal arachidonate metabolism. For example, *interleukin-1* has been shown to stimulate anion secretion by activating arachidonic acid metabolism of submucosal cells. The nonapeptide bradykinin is liberated from the precursor kininogen by the enzyme **kallikrein**, found either in plasma or tissue. **Bradykinin** is a potent secretagogue, stimulating large increases in prostaglandin production from the intestine; however, it may also have a direct effect on intestinal epithelial transport. **Nitric oxide**, a non-adrenergic and non-cholinergic

(NANC) neurotransmitter and product of endothelial cells, also has many unique actions that may play a role in inflammation-induced secretion. It is produced by activated phagocytic cells such as neutrophils and macrophages and is probably produced in large amounts in inflamed tissue. Nitric oxide activates the iron- and sulfur-containing soluble form of guanylate cyclase, which, in intestinal mucosa, is predominantly found in lamina propria cells. However, it is not clear whether this effect mediates the secretory actions of nitric oxide. On the other hand, nitric oxide does appear to stimulate arachidonate metabolism and enteric secretomotor neurons, which mediate the secretory action of this agent. Purinergic agonists such as *adenosine* and *ATP* are also major products of inflammatory cells and stimulate net intestinal secretion. They may be important mediators stimulating secretion after their release from neutrophils in crypt abscesses, as their secretory effects are most pronounced on the luminal side. Adenosine may act through stimulation of adenosine type 2 receptors, increasing cAMP but at low concentrations; its secretory effects may be mediated by other mechanisms.

A common denominator of the actions of many inflammatory mediators is their ability to activate the secretomotor neurons of the enteric nervous system. Enteric nerves may therefore be important in amplifying the actions of numerous immune and inflammatory mediators, either by potentiating their actions at target tissues through the release of neurotransmitters or by enlarging the domain of action and affecting numerous target tissues simultaneously. Stimulated secretomotor neurons would affect smooth muscle function and the flow and permeability of blood capillaries and lymphatic in a manner that would help sustain or enhance the secretory effects.

5.3 *Effects of Other Conditions and Disease Processes on Transport*

Infectious Pathogens

Diarrhea, a common sequela of infections by enteric pathogens, arises from numerous mechanisms (Fig. 5.18). Enterotoxigenic organisms cause net secretion by stimulating intestinal anion secretion and inhibiting Na^+ and Cl^- absorption. *Cholera toxin*, for example, specifically binds to the GM_1-ganglioside receptor of the enterocyte luminal membrane and activates epithelial adenylate cyclase following ADP-ribosylation of G_s the GTP-binding regulatory protein (Fig. 5.19). In contrast, *E. coli* heat-stable enterotoxin (ST_a) binds to the putative guanylin receptor and activates guanylate cyclase to increase cellular cGMP.

Many cytotoxic bacterial toxins such as those from *Salmonella* and *Shigella* and viral pathogens obviously cause **mucosal destruction** and loss of absorptive surface area, leading to luminal accumulation of fluid and loss of plasma proteins.

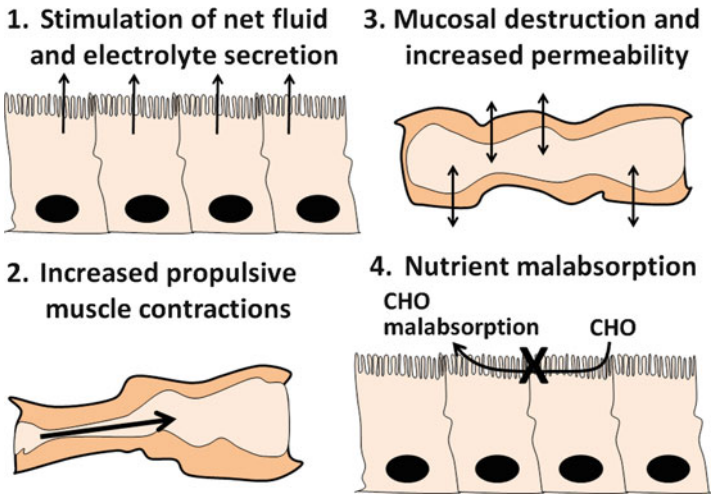

Fig. 5.18 Cellular mechanisms of action by which enteric pathogens cause diarrhea (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

The induced inflammatory response plays a key role in stimulating net intestinal secretion, propulsive motor contractions, and alterations in blood flow. Others, such as **toxin A** of *Clostridium difficile*, cause net secretion by directly stimulating epithelial anion secretion and by increasing paracellular permeability. Toxin A also appears to have chemo-attractant properties and is capable of stimulating immune and inflammatory cells by a Ca^{2+}-mediated mechanism. Finally, several **non-invasive enteric pathogens**, such as entero-adherent *E. coli*, *Giardia lamblia*, and *Cryptosporidium*, may cause diarrhea by affecting luminal membrane function. These organisms adhere to the brush-border membrane and can cause subtle structural alterations, best appreciated at the ultrastructural level. Often there is an effacement of microvilli and disruption of the microvillus and terminal-web cytoskeleton. These abnormalities may cause or contribute to defective ion transport and maintenance of tight-junction integrity. In *Giardia* infections, other mucosal alterations may be present; they include a significant decrease in crypt depth, decreased villus height in the duodenum, increased villus height in the ileum, and a generalized shortening of microvillus height.

Adaptation Following Extensive Small Bowel Resection

Following extensive resection of the small bowel, several morphologic and functional alterations of the intestinal mucosa occur and thus increase the absorptive capacity of the remaining gut. There is a significant (about 30 %) increase in villus size caused by **mucosal hyperplasia**. The net effect of these structural changes

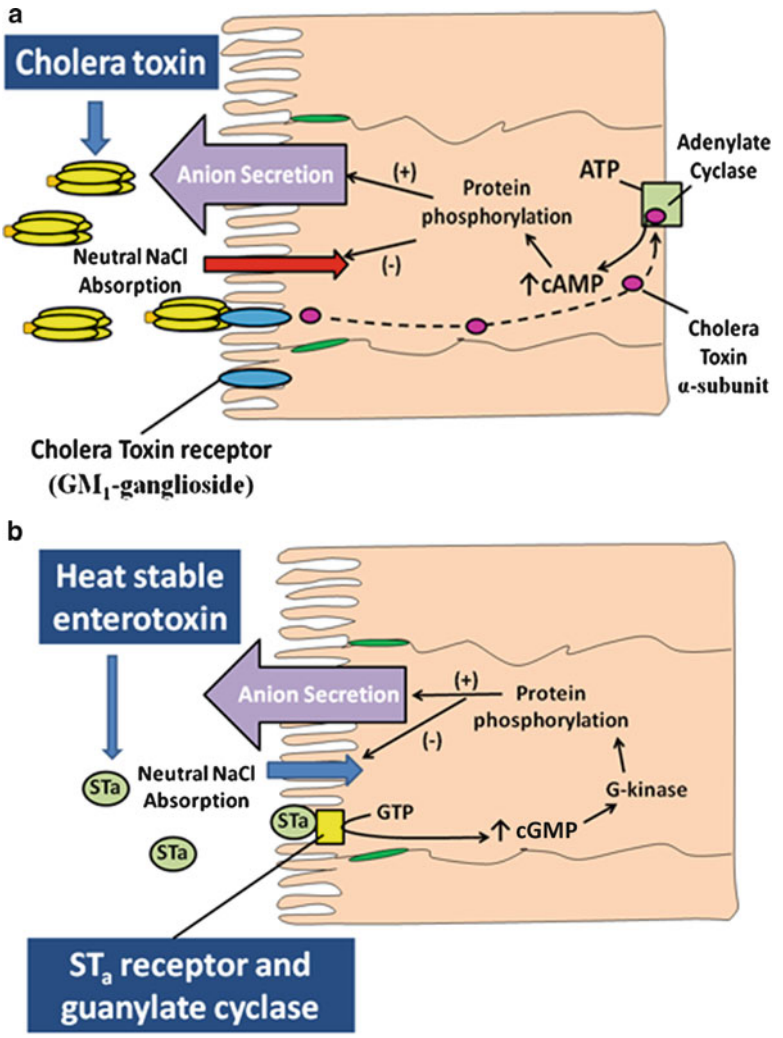

Fig. 5.19 Cellular mechanisms of action by which bacterial enterotoxins causes diarrhea. (**a**) Cholera toxin binds to a specific membrane receptor, enters the cell, and activates adenylate cyclase. (**b**) *E. coli* heat-stable enterotoxin causes diarrhea by stimulating guanylate cyclase and increasing cyclic GMP (Adapted from American Gastroenterological Association Teaching Slide Collection 25 ©, Bethesda, Maryland; Used with permission)

is to increase the surface area and the absorptive and digestive capacities of the remaining mucosa. The mechanisms underlying these adaptive changes are not fully elucidated, but they are believed to involve stimulation by luminal factors such as *dietary nutrients, pancreatic and biliary secretions,* and *intestinal growth and trophic factors*.

Clinical Correlations

Case Study 1

While on vacation in Mexico, a medical student develops severe watery diarrhea without blood, abdominal pain, and nausea. He becomes increasingly dehydrated and weak. Immediately after returning to Hong Kong, he seeks medical attention. Stool examination is negative for fecal leukocytes, fat, or blood, and sigmoidoscopy reveals normal mucosa.

Questions

1. **How would you explain the pathogenesis of watery diarrhea in this patient?**
   Answer 1: This patient has an infectious diarrheal illness frequently experienced by travelers visiting places where *sanitation and water supply may be sub-optimal*. Because of the absence of blood and fecal leukocyte and the normal appearance of gut mucosa, the most likely pathogen in this instance is an **enterotoxigenic *E. coli*** that elaborates a **heat-stable enterotoxin (ST_a).** STa mainly binds to luminal receptors for guanylin in the colon. This receptor is a guanylate cyclase and converts GTP to cGMP. Increases in cellular cGMP activate cGMP-dependent protein kinase, which phosphorylates a number of target substrate proteins that mediate ion transport. Thus, ST_a stimulates net secretion of water and electrolytes by stimulating active secretion and inhibition of sodium absorption. Mucosal histology and endoscopic appearances are intact, as this organism is not invasive and does not induce an inflammatory reaction.
2. **How would you treat his condition?**
   Answer 2: The treatment is symptomatic. Most patients have a self-limiting diarrheal illness, and by the time they seek medical attention, they are usually feeling better. If dehydration or metabolic abnormalities are severe, **intravenous replacement of fluid and electrolytes** may be indicated. Otherwise, **oral rehydration** is sufficiently enough (see oral rehydration therapy below). Antibiotics are *not* usually required, as the diarrhea is purgative and the organisms are cleared within a few days.

Case Study 2

While in rural Bangladesh, you witness an outbreak of cholera during flooding which is caused by the rainy season. One of the major clinical manifestations of the affected people they experience is profuse watery diarrhea that can cause dehydration and electrolyte imbalance, thus death ensues. Because of the limited health resources in your area, you must treat patients with whatever is available to you.

Questions

1. **What is the underlying mechanism of cholera that causes watery diarrhea?**
   Answer: Cholera is a major cause of morbidity and mortality in the world which is caused by ***Vibrio cholerae*****,** a bacterial organism that contaminates water

and food supplies and it is acquired by **fecal-oral transmission.** *V. cholerae* elaborates a heat-labile toxin called ***cholera toxin***, which is one of the most potent secretagogue substances known. The toxin causes a functional derangement of sodium and water transport. After the toxin binds GM_1-ganglioside receptors of the luminal membrane of enterocytes, the alpha subunit is inserted into the cell. The subunit catalyzes the ADP-ribosylation of the alpha subunit of stimulatory G protein (G_s), irreversibly activating it and adenylate cyclase activity. Resultant increases in cAMP activate cAMP-dependent protein kinase and phosphorylation of proteins involved in mediating active anion secretion or neutral sodium chloride absorption. The effects of the toxin are only diminished after the enterocyte population turns over (several days). During this time, no mucosal lesions are seen, but patients experience profuse watery diarrhea of such severity that many die of *dehydration* and *metabolic disturbances*.

2. **What is the most effective treatment option that you recommend for this condition?**
   Answer: Oral replacement with water and sodium is *not* effective because cholera toxin inhibits absorption by the gut, probably by inhibiting luminal Na^+/H^+ exchangers. However, by taking advantage of other Na^+-transport pathways not affected by increases in cellular cAMP, oral replenishment of lost fluid and electrolytes is possible. Thus, by **adding sugar (e.g. *glucose*) to oral salt replacement fluids**, one can dramatically increase intestinal absorption of salt and water. Since the function of the luminal carrier protein, called **sodium-dependent glucose co-transporter 1 (SGLT1),** is intact and unaffected by cholera toxin, hexoses such as glucose will promote the absorption of sodium and water. With this type of oral formulation, millions of lives each year are saved.

   In this instance, where glucose may not be readily available, one could try the **traditional remedy of rice water supplemented with salt,** which contains starch or complex carbohydrates. Starch is made up of glucose polymers assembled by 1,4- and 1,6-glycosidic linkages. Starch is rapidly hydrolyzed by pancreatic and intestinal membrane-bound enzymes or disaccharidases (which are intact in cholera) to form glucose. Luminal glucose (as described above) is co-transported with Na^+.

Case Study 3

A newborn infant develops abdominal distention and vomiting within 48 hours of birth. Physical examination of the abdomen is consistent with intestinal obstruction. Barium enema shows a microcolon and meconium, normally excreted after birth, in the distal ileum, suggesting a diagnosis of meconium ileus.

Questions

1. **What might this child have and how does it predispose to meconium ileus?**
   Answer: This child has **cystic fibrosis (CF),** which was later confirmed by an ***abnormal sweat test***. The defects in CF involve mutations of the cystic fibrosis transmembrane regulator (CFTR) gene, resulting in the failure of CF-protein

insertion into the cell membrane and activation by cAMP-dependent protein kinase. In the intestinal mucosa, CFTR is a cAMP-regulated Cl^- channel of the luminal membrane that mediates active water and electrolyte secretion. Its defect in CF results in inadequate luminal hydration of intestinal contents, especially in utero. As a consequence, meconium (consisting of ingested contents of amniotic fluid, secretions that collect in the intestinal lumen, and mucosal, pancreatic, and other enteric proteins) become inspissated and extremely viscous. This can eventually result in obstruction and failure of luminal contents to enter the colon (hence a **microcolon**). This patient may require **surgical intervention or medical treatment** aimed at ***reducing meconium viscosity*** (e.g. acetylcysteine) or ***increasing its hydration and breakup*** (Gastrografin).

2. **Would a patient with CF be susceptible to cholera?**
   Answer: Probably not. In fact, it has been hypothesized that the development of CF-genetic lesions arose from a selection process that favored resistance to cholera toxin. Since these patients have **defective regulation of $C1^-$ secretion by cAMP**, they are virtually immune to the actions of cholera toxin.

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