MINIREVIEW

Immune System Control of Intestinal Ion Transport (43252)

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In the past several years it has become evident that there are three major systems that control water and electrolyte transport by the intestinal epithelium (1, 2). The *enteric nervous system* is the best studied of the controlling systems. Through its different components—extrensic sympathetic and parasympathetic nerves, enteroendocrine cells, and, most importantly, the submucosal and myenteric plexuses—it constitutes the "little brain" that controls most gastrointestinal functions. Although hormones of the *endocrine system*, for example, gastrin and secretin, are highly important in regulating pancreatic and gastric secretion, a classic example of endocrine control of intestinal electrolyte transport is the renin-aldosterone axis, which serves to increase sodium and water absorption by the large intestine. The newest regulatory system, which has come to the fore only in the past few years, is the *immune system*. It is now clear that this system is capable of complex regulatory control of transport through the secretion of various soluble mediators that both directly and indirectly (via the enteric nervous system) alter ion and water movement. Furthermore, it seems likely that there is a complex interaction among these three controlling systems such that they can be up-regulated or down-regulated through various paracrine, autocrine, and endocrine mechanisms.

This minireview will: describe the various effector cells responsible for immune-mediated electrolyte transport; discuss the important soluble mediators which serve as the messengers between the various components of this system; describe the final pathways for mediating electrolyte transport in response to activation of the immune system; touch briefly on the elements that both up-regulate and down-regulate the entire system.

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Effector Cells and Functional Morphology

The effector cells responsible for immune-mediated intestinal secretion can be divided into three groups (2, 3). (i) Lamina propria immune cells, which modulate ion transport via paracrine action, include mast cells, macrophages, and polymorphonuclear granulocytes such as the neutrophils and eosinophils. (ii) There is emerging evidence of a paracrine role for subepithelial mesenchymal elements, such as the fibroblast and myofibroblast, the endothelial cells, and perhaps the vascular smooth muscle. (iii) Hypothetical candidates for an effector role, for which there is no definite evidence of a paracrine action aside from their spatial anatomical relationships with the epithelium, include the leukocytes found *within* the epithelium, such as intraepithelial lymphocytes and intraepithelial neutrophils.

The immune cells in the lamina propria change quantitatively and qualitatively with various enteric infections or, in susceptible individuals, with exposure to foreign proteins. Both may lead to proliferation of mast cells. In the rat, the number of mast cells per villus-crypt unit may increase 2- to 4-fold following nematode infection with *Trichinella spiralis* or *Nippostrongylus brasiliensis* (4). Similarly, the number of phagocytic cells increases with parasitic, bacterial, or viral infections. For example, with cryptosporidiosis the ratio of lamina propria inflammatory cells to enterocytes changes from 1:10 in the control state to approximately 1:1 at the height of disease (5). In other bacterial (e.g., salmonellosis) or idiopathic intestinal inflammatory states (ulcerative colitis), the ratio of polymorphonuclear leukocytes to enterocytes may reverse (6).

Lamina Propria Effector Cells. *Mast cells.* The gastrointestinal mucosa contains a large number of mast cells which differ from the classical connective tissue mast cell in morphological, histochemical, and

functional characteristics (Table I). These mucosal mast cells derive from a pluripotential hemopoietic stem cell in response to a series of soluble growth factors such as IL-3 and granulocyte colony-stimulating factor (7). These mast cells reside mainly in the lamina propria, often reaching concentrations of 20×10^3 mast cells/mm^3 of intestinal tissue (8). Within the lamina propria, there is a close functional and morphological relationship between mast cells and nerve fibers (see below).

After exposure to antigens, immunoglobulin (Ig) E is produced by stimulated B cells, and this immunoglobulin comes to occupy surface receptors on the mast cell. If antigen is then reintroduced, the IgE-occupied receptors are cross-linked and the mast cell undergoes activation and degranulation. This degranulation process is initiated by a brief increase in intracellular cAMP, but changes in intracellular calcium and phosphoinositol metabolites and activation of protein kinase C appear to be the more important intracellular mechanisms for mast cell degranulation (9, 10). Mucosal mast cells can also be made to degranulate in response to calcium ionophores such as A23187, to adenosine, and to complement fragments such as C5a and C3a (11).

One of the important concepts now well appreciated in mast cell biology is the heterogeneity of the mast cell types (6–8). This heterogeneity can be seen in the mast cell response to various inhibitors. For example, mucosal mast cell degranulation is not inhibited by cromoglycate, or theophylline, but, like the connective tissue mast cell, can be inhibited by cAMP, corticosteroids, or sulfasalazine. Among the many secretory products of degranulating mast cells are proteoglycans of uncertain function such as chondroitin sulfate, which is released by the mucosal mast cell, and heparin, which is released by the connective tissue mast cell. Proteases can also be released by mast cells and these enzymes may actually damage the epithelial cells or the basement membrane (11). Kallikrein is a specific protease released by the mast cell which can led to kinin formation through cleavage of kininogen (12). The mast cell also releases two different classes of soluble mediators: (i) amines, such as histamine, serotonin, and adenosine; and (ii) various bioactive lipids, such as prostaglandins (PG), hydroxy and hydroperoxy fatty acids, leukotrienes (LT), and platelet-activating factor (PAF). These soluble mediators and kinins formed from kallikrein action are capable of potent stimulation of intestinal secretion (2, 3, 8, 12).

Macrophages. Intestinal macrophages originate from blood monocytes and are present in the noninflamed intestine in numbers of 14×10^6/g wet weight of tissue (13). They play an important role in phagocytizing and killing microorganisms, but also initiate the immune response and regulate the fibroblast and matrix formation. The activated macrophage is capable of producing a large number of biologically active molecules, such as proteases, phospholipases, interleukins (and other cytokines), and growth factors (Table II). These cells also simultaneously produce protease inhibitors, phospholipase inhibitors, and interleukin inhibitors (14, 15). Like the mast cell, they secrete bioactive lipids including PG, hydroxy and hydroperoxy fatty acids, LT, and PAF (16). Unique products of phagocyte activation are reactive oxygen species such as superoxide anion, hydrogen peroxide, hydroxyl ion, hypochlorous acid, and *N*-chloramine (17, 18). Activation of macrophages occurs as they phagocytize opsonized (IgG-coated) microorganisms, particles, cell debris, or sterile bacterial cell wall components (peptidoglycan). Macrophages can also be activated by lipopolysaccharide, complement fragments, interferon (IFN)-γ, and, in an autocrine fashion by interleukin (IL)-1, tumor

Table I. Mast Cell Heterogeneity: Properties of the Connective Tissue and Mucosal Mast Cells[a]

Property	Connective tissue mast cells	Mucosal mast cells
Morphology[b]	Many large red-blue granules, uniform size 9–10 μm	Smaller blue granules, uniform size
T cell-dependent proliferation (IL-3)	–[c]	+
Fibroblast-dependent proliferation	+	–
Locomotion	Fixed	Migratory
Life-span/half-life	Long/>6 months	Short/<40 days
Proteoglycan	Heparin	Chondroitin sulfates
Protease	RMCP I (chymase, carboxypeptidase)[d]	RMCP II (?collagenase)
Secretagogues		
Adenosine	+	+
Serotonin	+	+
Histamine	10–30 pg/cell	<2 pg/cell
Arachidonic acid metabolites	$PGD_3 > LTC_4$ and B_4	LTC_4, $LB_4 > PGD_2$

[a] Modified from refs. 2 and 7.
[b] Alcian blue (Safranin strain).
[c] RCMP, rat mast cell protease.

Table II. Secretagogues Released by Phagocytes[a]

Cytokines	Bioactive lipids
IL-1	PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2[b]
IFN	HPETE and HETE
IL-6	LTB_4, C_4, D_4, E_4
IFN-α and -β	PAF
gro	
Enzymes	**Reactive oxygen species**
Proteases	O_2^-
Phospholipases	H_2O_2
Lysosomal hydrolyses	$OH^{\cdot}$
	HOCl
Hormones	**Inhibitors**
β-Endorphins	Protease inhibitor
ACTH	Phospholipase inhibitor
Vitamin D_3	IL-1 inhibitor

[a] Modified from refs. 2 and 14.
[b] TXA_{12}, thromboxane A_2; HPETE, hydroperoxy fatty acids; HETE, hydroxy fatty acids, *gro*, growth factors; ACTH, adrenocorticotrophic hormone.

necrosis factor (TNF) and transforming growth factor (TGF)-β. The various monokines secreted by the macrophages, such as IL-1, IL-6, and TNF, activate the T cell system with subsequent IL-2 production and clonal proliferation of various T subsets. Furthermore, these monokines may up-regulate mesenchymal elements such as fibroblasts and epithelial cells to make them more sensitive to other inflammatory mediators (see below). Macrophages are down-regulated by prostaglandins of the E and I subclasses, by glucocorticosteroids, and by α-melanocyte-stimulating hormone.

Polymorphonuclear granulocytes. Eosinophils (EOS) and neutrophils (PMN) are derived from bone marrow stem cells and circulated in blood, ready to take up residence in target tissues in response to a form of directed motility called chemotaxis (19). Resident EOS and PMN normally present in noninflamed gut may have different properties than their blood-circulating sibling. The EOS is the predominant resident phagocyte in the intestine, where it is present in numbers of 1.9×10^6 cell/g wet weight of tissue, approximately 1 log greater than the normal PMN content (13). With infection, ischemia, or trauma, chemotaxis can be induced by chemotactic peptides such as the *N*-formylated peptides (*N*-formyl-methionyl-leucyl-phenylalanine) produced by gut bacteria and, most importantly, by PAF or lipoxygenase products (LTB_4) of arachidonic acid metabolism released from mast cells and phagocytes (20). The act of phagocytosis or the occupation of surface receptors by chemotactic agents will cause PMN or EOS degranulation. Many of the products released by PMN and EOS are the same products released by macrophages. However, even higher concentrations of reactive oxygen metabolites, prostaglandins E_2 and I_2, thromboxane A_2 and the products of the lipoxygenase pathway, particularly lipoxins, LTB_4, and the peptidoleukotriens (LTC_4 and LTD_4) are secreted (16, 21). All of these agents are capable of influencing intestinal water and electrolyte transport. Recently, it has been found that *Clostridium difficile* toxin A activates granulocytes as well and this may play an important role in the pathogenesis and diarrhea of pseudomembranous enterocolitis.

Subepithelial Mesenchymal Elements. *Fibroblasts and myofibroblasts.* Myofibroblasts form a self-renewing population of mesenchymal cells in a subepithelial and pericryptal, three-dimensional network or sheath just below the basal lamina of the small intestine and colon (22). In the region of the crypts, the fibroblastic sheath is several layers thick. Toward the mouth of the crypts and in the villi, the layer becomes fenestrated. In the small intestine, the myofibroblasts are joined by cell junctions and are capable of contracting in response to injury (23). The sheath has an important role in collagen synthesis, and in certain diseases, such as collagenous colitis, there may be a proliferation of collagen which forms a layer between the fibroblasts and the epithelial cells.

During inflammation, the fibroblasts are stimulated by mediators, such as histamine, bradykinin, interleukins, or cytokines, which influence growth, collagen synthesis, and release of prostaglandins (24, 25). These cells are also the site of growth factor production (for example, insulin-like growth factor 1) (26). These growth factors and other unknown fibroblast messengers sustain both epithelial and immune cell growth and survival (27).

Endothelial cells and other capillary elements. Capillaries are made up of endothelial cells, smooth muscle cells, and pericytes. In the intestine, endothelial cells are fenestrated. Furthermore, the venules of the intercryptal regions are specialized in a fashion similar to that of the high endothelial venules of the lymphatic tissue and thus are able to regulate vessel permeability to other immune cells and molecules (28). During inflammatory reactions, the endothelial cells undergo functional and morphological alterations in response to cytokines such as IL-1 and to bioactive lipids such as PAF (29, 30). These agents act on endothelial cells to increase leukocyte adhesion and also to release several inflammatory mediators, particularly prostacyclin. Because these capillaries are very close to the epithelium, it is likely that they also play an intermediate and augmenting role in inflammation-induced electrolyte secretion by release of prostaglandins and other soluble mediators.

Intraepithelial Immune Cells. *Intraepithelial lymphocytes.* Intraepithelial lymphocytes are part of the gut-associated lymphoid system. Although rare in the newborn and germ-free state, they are common in the gut of mature mammals, attaining numbers of 20 per 100 epithelial cells in the adult human jejunum to 5

per 100 in the colon (3). In the rat and human, most of these cells are T cells of the suppressor/cytotoxic type. They are present in increased numbers in several gastrointestinal diseases, including celiac sprue, inflammatory bowel disease, and protozoan parasitic infections. Their function is not known, but by virtue of their close anatomic relationship with the columnar epithelium of the intestine, it is quite possible that they could act as paracrine regulators of epithelial function.

Intraepithelial granulocytes. Both PMN and EOS can also be found in intraepithelial locations. These cells may normally egress from the vascular compartment, move across the epithelium into the bowel lumen, and then back again. In severe acute colonic inflammation, they accumulate in the crypts of the colon where they form a histologic hallmark known as the crypt abscess (31). Very recently, monolayers of T-84 colon carcinoma cells grown on permeable supports have served as a model for the transmigration of granulocytes across the intestinal epithelium (6). Using this model, it has been shown that PMN secrete a novel and still unidentified soluble factor that acts on the apical membrane receptor of the epithelial cells to initiate intestinal secretion (32).

Immune Cell Secretagogues and Final Common Pathways

Models of Immune-Mediated Intestinal Secretion. Two general types of immune system-mediated alterations in intestinal ion transport have been identified: (i) those mediated by degranulation of mast cells, and (ii) those initiated by phagocytes (Fig. 1). It is likely that there are also transport alterations initiated by T lymphocytes, but experimental and natural models (for example, possibly graft-versus-host disease) remain to be clearly identified and systematically studied.

An important and useful way to define the action of immune cell mediators is to add these substances directly to the serosal bath of Ussing-chambered mammalial intestine or to transporting cell culture monolayers, which mimic intestinal crypt secretory cells such as T-84 colon carcinoma cells (33). Contrasting the effects of these agonists in native intestine with those in the T-84 cell system allows definition of whether these mediators act on the epithelial cells, on the enteric nerves, or on both. Furthermore, these T-84 cells can be co-cultured or juxtaposed acutely with mesenchymal cell lines such as fibroblasts to investigate the role that these mesenchymal elements may play in the secretion brought about by inflammatory mediators. In these systems, specific antagonists of the mediators can be examined (e.g., PAF antagonists), as can blockers of synthesis of substances that might be released by the mediators (e.g., cyclooxygenase inhibitors). In addition, tetrodotoxin (TTX) or neurotransmitter antagonists such as hexamethonium (HEX) or atropine (ATR) can be utilized to determine the role of the enteric nervous system in the immune-mediated secretory response.

Models of mast cell-initiated intestinal secretion can be created through the addition of anti-IgE immunoglobulin (that is, immunoglobulins of the IgG class raised in one species, such as sheep, against the IgE of another species, such as rat) to the serosal solution of Ussing-chambered rat colon (34). Anti-IgE will cross-link IgE-occupied receptors on resident mast cells and initiate degranulation. Similarly, the addition of specific antigens, such as pulverized *T. spiralis* or *N. brasiliensis*, ovalbumin, or β-lactoglobulin, to the Ussing-chambered intestine of animals previously sensitized to these foreign antigens are also useful models of intestinal anaphylaxis (35–37). In the anaphylaxis models, the addition of antigen to immunologically naive intestine elicits no response, whereas the addition of the antigens to previously sensitized intestine causes mast cell degranulation, resulting in a significant increase in short circuit current (Isc). This change in Isc is often biphasic in nature and of considerable duration, reflecting changes in ion transport. Isotopic flux measurements show that these Isc changes reflect inhibition of neutral NaCl absorption and stimulation of electrogenic Cl^- secretion. By pretreating the tissue with specific antagonists (e.g., antihistamines) or mediator synthesis inhibitors (e.g., cycloxygenase blockers) in the Ussing chamber prior to stimulation, or by the addition of neurotransmitter inhibitors (e.g., TTX, HEX, or ATR), the various roles of the different classes of inflammatory mediators or of the enteric nervous system can be dissected.

Phagocyte-mediated intestinal secretion can be studied by the addition of agents which specifically stimulate phagocytes, e.g., the chemotactic peptide formyl-methionyl-leucyl-phenylalanine (38, 39), or through study of natural models of intestine, such as experimental salmonellosis (40) or cryptosporidiosis (41). As is the case with the mast cell models, the addition of specific secretagogue synthesis inhibitors, mediator receptor antagonists, or neurotransmitter antagonists allows definition of phagocyte-mediated changes in intestinal ion transport.

Specific Mast Cell Secretagogues. *Histamine.* In both Ussing-chambered mammalian intestine and in T-84 cells, histamine elicits Cl^- secretion through activation of H_1 receptors which increase enterocyte calcium levels, initiating phosphoinositol and protein kinase C activity (42). Histamine also stimulates prostaglandin release from cells in the lamina propria and, in some species and intestinal segments, as much as 80% of histamine's effect can be blocked by indomethacin pretreatment (43).

In the antigen-intestinal anaphylaxis models, the addition of anti-IgE to intestine activates resident mast cells, whereas the addition of specific antigen to previ-

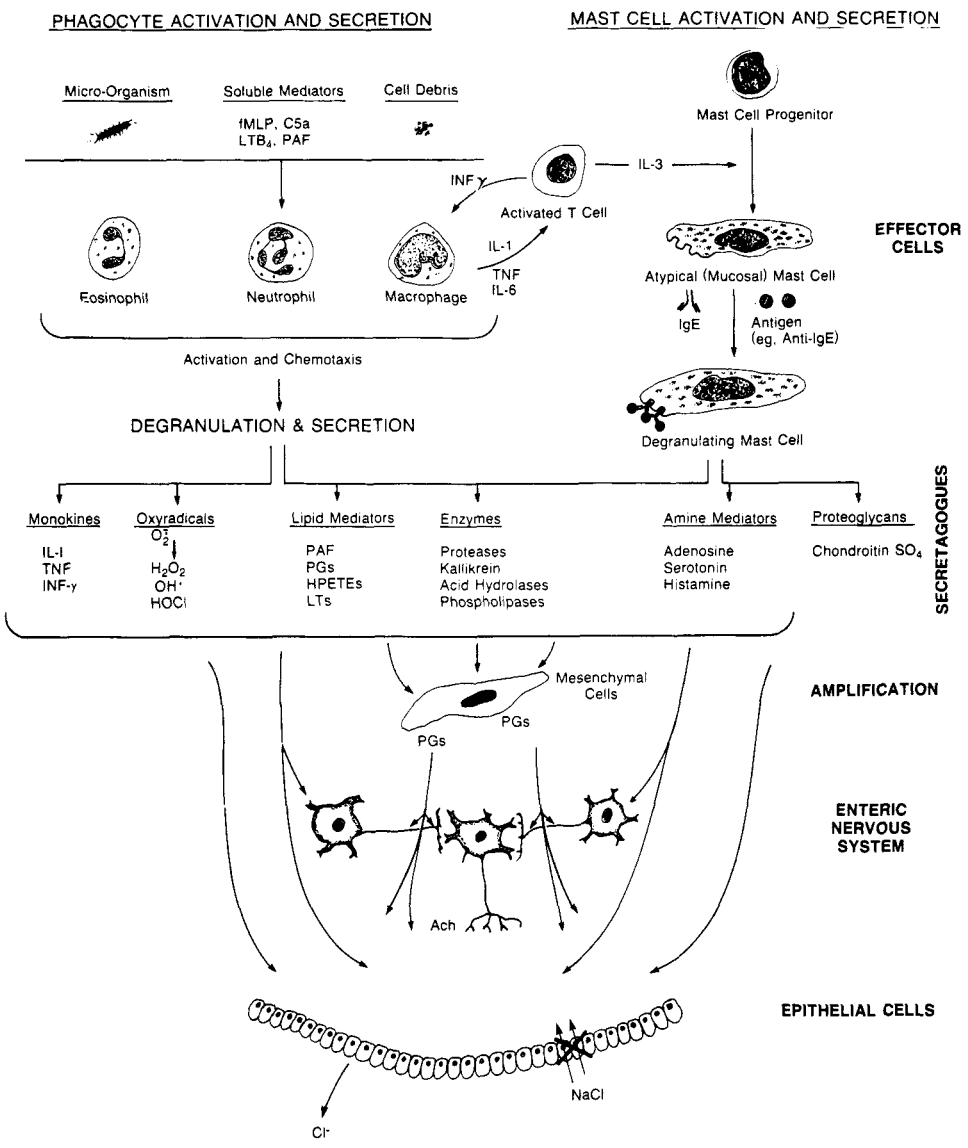

Figure 1. Scheme for immune system control of intestinal electrolyte transport. Three levels of contributing elements are proposed: (i) the effector level—activation of phagocytes and mucosal mast cells, secretion of preformed products and newly synthesized inflammatory mediators; (ii) the amplification level—mesenchymal cells such as endothelium and fibroblasts respond to mediators released by white blood cells and then act as paracrine cells by releasing prostaglandins. In addition, the enteric nervous system responds to the inflammatory mediators and prostaglandins by releasing neurotransmitters. Furthermore, the inflammatory mediators may act on these intermediate targets, or may act directly on the epithelium. Thus, the inflammatory signal may be amplified; (iii) the final target: epithelial cells respond with increased Cl^- secretion and decreased NaCl absorption. Modified from Ref. 2.

ously sensitized intestine degranulates recruited mast cells. When only a few mast cells are degranulated, e.g., the anti-IgE model, the Isc response is short-lived and monophasic (34). In the anaphylaxis models, a sustained biphasic response can be seen (44, 45). In these models, H_1 antagonists such as diphenhydramine or pyrilamine inhibit at least one phase of the response by as much as 40–90%.

Serotonin (5-HT). 5-HT is present in mucosal enterochromaffin cells, in a subset of myenteric neurons, and in mast cells. 5-HT stimulates a calcium-dependent change in Isc which, on flux measurements, proves to be inhibition of neutral NaCl absorption and electrogenic Cl^- secretion (46). In guinea pigs but not in rats, the 5-HT response is partially blocked by TTX and ATR, suggesting a neural site of action (47). Recently, there has been evidence for involvement of 5-HT in the intestinal secretion induced by cholera toxin. In that model, 5-HT_3 receptor antagonists such as ICS 205930 are able to inhibit secretion. It has been suggested that H_3 receptors are located on the enteric nerves (48). In the intestinal anaphylaxis models, 5-HT_2 receptor antagonists such as ketanserin partially block secretion, indicating a role for 5-HT in anaphylaxis (49). The 5-HT_2 receptor is thought to be located on the epithelial cells.

Adenosine. Adenosine is also released by stimulated mast cells and, in various tissues, adenosine can activate responses through A_1 (calcium-mediated) receptors, A_2 (cAMP-mediated) receptors, or through a third (R) type receptor. In the T-84 system, adenosine analogues have been found to stimulate Cl^- secretion through both mucosal and serosal receptors (50). Neither cyclic guanosine 5′-monophosphate nor intracellular calcium were elevated by adenosine in the T-84 model. Presumably, A_2 receptors are involved in the intestinal response, although there was a poor correlation between the dose response for Cl^- secretion and the increase in cAMP. Specific antagonists of adenosine receptors have not been well studied in the various mast cell models, therefore a role of this mediator in intestinal anaphylaxis-induced secretion remains to be determined.

Phagocyte Secretagogues. *Reactive oxygen metabolites.* Reactive oxygen metabolites such as superoxide anion, hydroxyl radical, and hydrogen peroxide are products of the respiratory burst of phagocytic cells (51). Myeloperoxidase simultaneously secreted by the phagocytes promotes the local conversion of hydrogen peroxide to hypochlorous acid, which can then react with amino acids to form very reactive oxidants called chlorinated amines (RNHCl). It was previously thought that these oxygen-centered free radicals and oxidants were primarily toxic agents, and indeed the oxygen radicals, especially hydroxyl radical, certainly are. However, in concentrations obtainable in normal tissue, e.g., 500 μM or less, hydrogen peroxide seems to be nontoxic. Furthermore, it has a small direct secretory effect on the epithelial cell, and a more profound stimulatory effect via the release of prostaglandins from the lamina propria (52).

Cytokines. Recently purified IL-1 and IL-3 have been shown to cause Cl^- secretion in Ussing-chambered chicken ileum predominantly by releasing prostaglandins (53). Furthermore, IFN-γ appears to affect intestinal tight junctions (54), thus potentially altering passive electrolyte transport. However, it is more likely that these cytokines serve as messengers which up- and down-regulate the leukocytes and mesenchymal cells that are involved in the immune response rather than act as acute modulators of electrolyte transport. This immune regulatory action is discussed in more detail below.

Secretagogues Common to both Mast Cells and Phagocytes. *Bradykinin (BK).* Both tissue-derived and plasma kallikrein synthesize vasoactive kinins such as BK and kallidin (lys-BK) from plasma α-globulin precursors produced in the liver and circulated in the plasma (12). Proteases of the kallikrein type have been localized with immunofluorescent studies to both goblet cells and mast cells of the large and small intestine (55). Although the mechanism of activation of kallikrein is unclear, such activation occurs in both phagocyte- and mast cell-mediated inflammation. The nonapeptide BK and the decapeptide lys-B both stimulate Cl^- secretion (56), probably through calcium-mediated pathways. Furthermore, BK receptors have been found on the mammalian epithelium through autoradiographic localization studies (54). This suggests that there is a direct effect of BK on mammalian epithelial cells (57). However, in mammalian intestine, a considerable portion of the BK effect is derived by release of prostaglandins from subepithelial elements (58). BK and lys-BK increase both PGE_2 and PGI_2 synthesis 2-fold in the intestinal subepithelium, but not in the epithelial cells per se (59).

Platelet-activating factor. PAF, or acetyl glyceryl ether phosphorylcholine, is the name of a group of biologically active phosphoglycerides with potent vasoactive properties (60). Primary sources in the gut are phagocytes, platelets, mast cells, and vascular endothelium. Like the eicosanoids, PAF is not stored in a preformed intracellular pool, but is synthesized from membrane phospholipids following phospholipase A_2 liberation of arachidonic acid from the *sn*-2 position. Thus, PAF shares the same substrate and initial stimulation pathways as the eicosanoids. After synthesis, PAF is secreted, although some remains intracellularly, where it has an unknown function. Like the leukotrienes, PAF is a potent chemoattractant and it also synergizes with the leukotrienes in a number of inflammatory reactions (61).

In both the small intestine and the colon, PAF causes a biphasic Isc response and, as determined in the T-84 cell system, it has some direct secretory action on epithelial cells (62, 63). However, in the intact mammalial colon, most of its effect is blocked by indomethacin, indicating that its predominant electrolyte transport action is via release of prostaglandins. Recent studies in our laboratory have suggested that there may be an endogenous inhibitor present in rat colon; i.e., the sensitivity of this tissue to exogenous PAF can be increased severalfold by washing the tissue with saline solutions containing delipidated albumin (64). Furthermore, preliminary studies with PAF antagonists suggest that PAF has a role in the prostaglandin production and Cl^- secretion initiated by anti-IgE (mast cell degranulation) and by H_2O_2 (a model of phagocyte-mediated secretion).

Prostaglandins. Of all of the inflammatory mediators released by mast cells, phagocytes, and mesenchymal cells, the prostaglandins come the closest to being the universal final common mediator. Prostaglandins are mainly synthesized by subepithelial tissues (58, 65) and are then degraded and inactivated by the epithelial cells (65). In the rabbit ileum, the epithelial cell fraction constitutes 67% of the total protein of intestinal tissue, yet it produced only 0.2% of the total PGE_2. In contrast,

the lamina propria and submucosa make up 12% of the protein, yet these fractions together produce 90% of all the PGE_2 produced by this tissue. This is not the case with leukotrienes, which appear to be produced in almost equal amounts by the epithelial and the subepithelial elements (58, 66).

The intestinal secretory effects of PG appear to be receptor mediated, although it has bee difficult to prove the existence of a PG receptor on the epithelial cell membrane (67, 68). Most likely, this is a technical problem that results from attempts to quantitate the binding of a lipid agonist to a small amount of protein receptor embedded in a large amount of cell membrane lipid matrix. Therefore, a role for PG in the intestinal secretory response must be discerned from directly studying the effect of these compounds on isolated T-84 cells and on mammalian intestinal systems. Prostaglandin synthesis inhibitors such as indomethacin or piroxicam are useful to define whether prostaglandins are being released by mast cells or phagocyte stimulants.

Prostaglandins inhibit neutral NaCl absorption and stimulate electrogenic Cl^- secretion in both the small intestine and colon through the cAMP-mediated intracellular messenger-protein kinase A systems (69). In the Ussing-chambered mammalial intestine, the potency profile for cAMP elevation and for electrogenic Cl^- secretion is $PGE_2 = PGI_2 > PGD_2$ (70). Furthermore, there is emerging evidence that PGE_2 and PGI_2 act on different elements in the intestine (52, 71), e.g., the epithelial cell for PGE_2 and the enteric nervous system for PGI_2 (Fig. 2). In addition, PGD_2 may be an inhibitor of the secretory response (72). It is important to note that cyclooxygenase blockers such as indomethacin or piroxicam inhibit by 30 to 100% the Isc in the mast cell degranulation models (73) and in the models of phagocyte-mediated secretion (34). Furthermore, it is clear that part of the secretory action of histamine, 5-HT, BK, PAF, and ROM comes through the release of PGE_2 and PGI_2, with the subsequent stimulation of the epithelial cell or the enteric nerves by these eicosanoids (2, 34, 43, 58, 63).

Enteric Nervous System—Immune System Interactions

Functional Anatomy. There is a close anatomical relationship between the enteric nervous system and the immune system. Acetylcholine, noradrenaline, and various peptide neurotransmitter-containing fibers (particularly substance P and calcitonin gene-related peptide) are found in lymphoid fields of the lamina propria (74). Furthermore, neuropeptide receptors for substance P, somatostatin, and VIP have been localized to the cell membranes of immunoregulatory T lymphocytes and monocyte/macrophages (75). Substance P appears to be a proinflammatory regulator of immune cells, while VIP and somatostatin inhibit immunocyte activity.

Recently, an extensive and intimate anatomic association has been defined between the intestinal mast cell and substance P and calcitonin gene-related peptide nerves of the lamina propria (76). In the *N. brasiliensis*-infected rat jejunum, approximately 87% of all mast cells in the lamina propria were either touching or within 2 μm of these nerves. Substance P is thought to be important in sensory transmission in the gastrointestinal tract. As noted above, receptors for this neurotransmitter are present on mast cells, macrophages, and T lymphocytes. Therefore, this tachykinin may be an important messenger between the enteric nervous system and immune cells. Substance P seems to have an

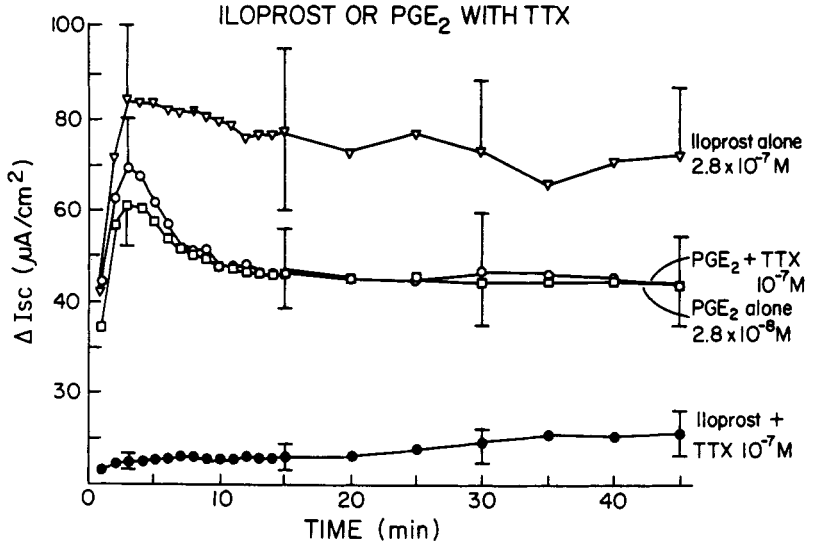

Figure 2. The short circuit current response (ΔIsc = Cl^- secretion) of rat colon to a stable PGI_2 analog (Iloprost $2.8 \times 10^{-7}M$) is inhibited by TTX ($10^{-7}M$). The response to PGE_2 ($10^{-7}M$) is unaffected by TTX blockade of the enteric nervous system. From data in (52).

important role in so-called "neurogenic inflammation," as studied in arthritis models (77, 78). By analogy to that system, substance P is likely to be important in intestinal inflammation as well.

Immune Mediator Activation of Enteric Nervous System. Studies of mast cell-intestinal anaphylaxis models and phagocyte-intestinal inflammation models, or of the effects of specific inflammatory mediators or prostaglandin to Ussing-chambered mammalian intestine, all suggest an important role for the enteric nervous system in immune mediator-stimulated secretion (2, 34, 52). With each of these stimulants, a considerable portion (20–100%) of the Isc response can be inhibited by blockers of nerve action potential transmission, e.g., TTX, or by specific antagonists of neurotransmitter action such as HEX or ATR. Thus, in these immune cell secretory models, inflammatory mediators released from phagocytes and mast cells may act directly on the epithelium, but seem to have their predominant effect by activating receptors on the enteric nervous system.

There have been few specific studies of the effects of inflammatory mediators on enteric nervous system ganglia. The best studied is histamine, which elicits excitatory postsynaptic potentials in the myenteric plexus (79). Both PGE_2 and PGI_2 have been shown to release acetylcholine from the guinea pig myenteric plexus (80) and to suppress norepinephrine release from adrenergic nerves in the rat colon (81). Studies by several investigators suggest that enteric nerves have receptors specific for PGI_2, whereas the receptors of the epithelium proper have more affinity for PGE_2 (52, 71) (Fig. 2). PAF has been shown to release norepinephrine in rat intestine (82) and to elicit calcium-mediated neurotransmitter release in cultured rat enteric nervous system preparation (83). Although it is difficult to be certain which inflammatory mediator is responsible for stimulating the enteric nerves in the mast cell and phagocyte degranulation models, certainly PGI_2 is a prime candidate. The degree of inhibition of the response by indomethacin and by TTX are similar and, when added together, neither inhibitor significantly increases the inhibitory response of either inhibitor alone (34).

The fact that certain of these inflammatory mediators are capable of releasing epinephrine, a pro-absorptive neurotransmitter, from nerve terminals in the intestine suggests the possibility that inflammatory mediators might, under certain conditions, promote intestinal absorption rather than secretion. Indeed, there are *in vivo* studies in which PGI_2 and PGD_2 have been reported to inhibit the intestinal secretion elicited by other secretagogues (72).

Amplification and Regulation of the Immune Response

Amplification. The immune response initiated by either mast cell or phagocyte degranulation can be instantly amplified by the release of inflammatory mediators from other immune cells (mast cells and phagocytes) and mesenchymal cells (myofibroblasts of the pericryptal fibroblastic sheath and the endothelium of the extensive lamina propria capillary network) in the lamina propria. Instantaneous augmentation of the inflammatory response comes via the fact that mast cells, phagocytes, and mesenchymal cells all have receptors for such inflammatory mediators as histamine, BK, 5-HT, LT, and PAF (2, 11, 63, 84, 85). These cells also respond to H_2O_2, although it is unclear if this is a receptor-mediated event. Although autocrine and paracrine activation of mast cells and phagocytes would release the whole panoply of inflammatory mediator response, the myofibroblasts and endothelium amplify the intestinal secretory response predominantly through the release of PGE_2 and PGI_2 and PAF (2, 63, 86).

Cytokines as Upregulators of the Immune Response. *Tumor necrosis factor and interleukin 6.* TNF is a nonglycosylated protein produced by both monocytes and macrophages (87). Its amino acid sequence is highly conserved among different animal species and, therefore, activity is generally not species specific. Although it is known for its cytotoxic and cytostatic effects on tumor cells in culture, it has a broad range of cytoregulatory actions, including modulation of fibroblast growth and stimulation of prostaglandin synthesis in a synergistic fashion with IL-1 and IFN-γ. IL-6 (formerly called IFN-β) is produced by T cells, macrophages, and fibroblasts (88). It acts on B lymphocytes as a differentiation and growth factor, but it is also capable of inducing acute phase reactant secretion by the liver. The roles of TNF and IL-6 as regulators of intestinal enterocyte transport have not been well-studied. Interleukin-1, however, has been investigated in the intestine and its regulatory effects are noted below.

Interleukin 1. IL-1 is one of the many soluble factors released by monocytes and macrophages, as well as, to a lesser extent, by phagocytes and mesenchymal cells such as fibroblasts and endothelial cells (89). Two forms of IL-1 are secreted, α and β, which appear to recognize the same receptor and initiate similar reactions despite the fact that they have only 26% amino acid homology. Furthermore, although there is only partial amino acid homology between different species (murine, human, and rat), there seems to be good cross-species reactivity (89, 90). Macrophages release IL-1 upon stimulation with endotoxin lipopolysaccharide, which increases the translation of IL-1 protein. Once released, IL-1 stimulates the helper T cell to release IL-2 and other cytokines, leading to the clonal expansion of several T cell classes (89, 90). IL-1 also stimulates arachidonic acid metabolism by the macrophage itself (an autocrine response), as well as by mesenchymal cells such as the fibroblast and endothelium (91, 92). The fibroblasts proliferate and increase collagen synthesis, while endo-

thelial cells alter expression of adhesion molecules that promote adherence of monocytes, neutrophils, and lymphocytes to the capillary surface (29, 30, 93, 94). Other organs and cells respond to IL-1 as well. For example, the central nervous system effects include the induction of fever and the release or corticotropin releasing factor (see below).

In rabbit colon, large intraluminal doses of IL-1 stimulate PGE_2, PGI_2, and thromboxane A_2 release (95, 96). IL-1α is more potent than IL-1β. Following pretreatment with IL-1, there is augmented PGE_2 production with superimposed BK stimulation. Recent studies in our laboratory indicate that IL-1 is capable of enhancing prostaglandin production in fibroblasts in response to inflammatory mediators such as histamine and BK (97). Whether this represents an effect of IL-1 on cyclooxygenase transcription or translation or an activation of phospholipase A_2 remains to be determined (92, 97, 98).

Down-regulation of Inflammation. The beneficial effects of inflammation in the intestine are to increase the secretion of water and mucus, the exfoliation of intestinal epithelial cells, and the propulsive contraction of intestinal smooth muscles, all of which serve to wash out or expulse offending dietary or microorganism antigens. However, there is a delicate balance between host protection and pathologic injury, and this balance is governed by a down-regulation of the inflammatory response once it has been initiated. This is accomplished through several mechanisms that act locally, in the vascular compartment, and systemically (2, 3).

Local down-regulation is accomplished by the induction of suppressor T lymphocytes and suppressor macrophages, the secretion of competitive inhibitors of IL-1 or PAF (presumably by the same cells that secrete these agonists), and the secretion of acutely acting down-regulators of immune cells such as prostaglandins of the E and I classes (95, 99–102). The local prostaglandin down-regulatory response comes about via an autocrine- and paracrine-mediated increase in cAMP content in the immune cells which inhibits mediator secretion. The vascular phase includes the production and secretion of soluble receptors for IL-1, IL-2, TNF, and IFN-γ, which bind excess cytokines (15, 103–105). Finally, a central nervous system-endocrine-immune system interaction down-regulates via IL-1 and TNF stimulation of the hypothalamus to secrete corticotropin-releasing hormone and, subsequently, adrenocorticotropic hormone and corticosteroids (106, 107). Corticosteroid inhibition occurs through production of the proteins (lipomodulin and macrocortin) in the immune cells which inhibit phospholipase A_2 activity and, thus, the subsequent production of eicosanoids and PAF by these effector cells.

Summary and Conclusions

The immune system takes part in the regulation of intestinal water and electrolyte transport through the release of inflammatory mediators that act both directly and via the enteric nervous system to inhibit NaCl absorption and stimulate electrogenic Cl^- secretion. It is likely that immune system activation is a normal physiologic event. The intestinal tract is filled with antigens and, although the barrier function of the epithelium usually serves to prevent their transmigration into the lamina propria, it probable that, on occasion, antigen presentation does occur. Under these instances, the phagocytes may instantly respond by initiating an intestinal secretory response that washes these antigens away. Similarly, previous sensitization to dietary antigens may allow mast cell degranulation to initiate a cleansing secretory response. Certainly under pathological conditions such as infection with parasites, bacteria, and viruses, the immune-mediated intestinal secretory response can either wash away these offending microorganisms or, by exfoliating infected or colonized cells and initiating muscle contraction, may actually physically expulse them from the gastrointestinal tract. In chronic idiopathic inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, this inflammatory response seems to be uncontrolled; thus, what is normally a protective mechanism promulgates disease.

Many issues remain to be clarified concerning intestinal inflammation and the responses of target cells such as the epithelium, the vasculature, and the smooth muscle. For example, recent studies showing that Pavlovian conditioning can degranulate mast cells (108) suggests the involvement of the immune system in stress-related or behavioral/functional diarrheas. The next decade will clarify both the normal, pathological, and central nervous system-mediated intestinal secretory responses to immune system activation. Such studies will further our understanding of both normal and pathologic control of intestinal water and electrolyte transport.

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