ABSTRACT: Neurogastroenterology is a subspecialty encompassing relations of the nervous system to the gastrointestinal tract. The central concept is emergence of whole organ behavior from coordinated activity of the musculature, mucosal epithelium, and blood vasculature. Behavior of each effector is determined by the enteric nervous system (ENS). The ENS is a minibrain positioned close to the effectors it controls. The ENS neurophysiology is in the framework of neurogastroenterology. The digestive tract is recognized as the largest lymphoid organ in the body with a unique complement of mast cells. In its position at the “dirtiest” of interfaces between the body and outside world, the mucosal immune system encounters food antigens, bacteria, parasites, viruses, and toxins. Epithelial barriers are insufficient to exclude fully the antigenic load, thereby allowing chronic challenges to the immune system. Observations in antigen-sensitized animals document direct communication between the mucosal immune system and ENS. Communication is functional and results in adaptive responses to circumstances within the lumen that are threatening to the functional integrity of the whole animal. Communication is paracrine and incorporates specialized sensing functions of mast cells for specific antigens together with the capacity of the ENS for intelligent interpretation of the signals. Immuno-neural integration progresses sequentially, beginning with immune detection, followed by signal transfer to the ENS, followed by neural interpretation and then selection of a neural program with coordinated mucosal secretion and a propulsive motor event that quickly clears the threat from the intestinal lumen. Operation of the defense program evokes symptoms of cramping abdominal pain, fecal urgency, and acute watery diarrhea. Investigative approaches to immuno-ENS interactions merge the disciplines of mucosal immunology and ENS neurophysiology into the realm of neurogastroenterology.

Key words: abdominal pain, diarrhea, enteric nervous system, food allergy, mast cell, neurogastroenterology

INTRODUCTION

Study of the involvement of the enteric nervous system (ENS) in gastrointestinal allergic responses is part of a newly recognized science called neurogastroenterology (Wingate and Grundy, 2000; Wingate, 2008). The ENS cooperates with the enteric immune system to establish a line of defense against foreign invasion at a vulnerable interface between the body and the outside environment. Electrophysiological recording in ENS neurons shows that mediators released in paracrine fashion from immune/inflammatory cells alter electrical and synaptic behavior of enteric neurons. All types of immune/inflammatory cells are sources of paracrine signals to the ENS. Most is known about signaling between mast cells and the neural elements of the ENS. This review is directed toward enteric neuroimmune interactions in food allergy, parasitic intestinal infection, and relations to inflammatory bowel syndrome (IBS) in humans and animal models.

Neurogastroenterology is a scientific and clinical subspecialty that deals with the neural mechanisms that influence function of the digestive tract and that underlie projection of conscious sensations to the gut. It derives from both the basic medical sciences and clinical medicine. Neurogastroenterology embraces research in the basic medical sciences and diagnosis disciplines including physiology, biochemistry, neurobiology, anatomy and histology, endocrinology, microbiology, immunology, and pharmacology into a unified subspecialty.
focused on the digestive tract. In clinical medicine, neurogastroenterology specializes further the subspecialty of gastroenterology. Neurogastroenterology encompasses the central nervous system, sensory systems, autonomic nervous system, and effector systems that do the work of the digestive tract.

Gastrointestinal symptoms associated with common food allergies, involving type I IgE-mediated responses, are 1) cramping abdominal pain, 2) fecal urgency, 3) acute explosive watery diarrhea, and 4) generalized abdominal malaise. These are common symptoms also for 1) postprandial IBS; 2) enteritis, both infectious and radiation induced; 3) ulcerative colitis; 4) Crohn’s disease; 5) microscopic colitis; and 6) collagenous colitis. They reflect an output of one of the gut behavioral programs stored in the ENS program library.

ENTERIC NERVOUS SYSTEM

The ENS is an independent integrative nervous system that, like digital hard drives, flash memory sticks, and other forms of memory storage, holds a library of programs for a variety of patterns of small or large intestinal functional behaviors. Output of one program determines motility and secretory behavior in the postprandial state, and another establishes the pattern of intestinal motility that characterizes the fasting state. The specialized propulsive motility in the upper one-third of the small intestine during emesis reflects output of another of the programs in the library, called power propulsion. During emesis, peristaltic propulsion in the upper one-third of the small intestine is reversed for rapid movement of the luminal contents toward the stomach. The emetic program can be “called up” from the library either by commands from the central nervous system or by local sensory detection of threatening substances in the lumen (Lang and Sarna, 1989).

An overlay of signals released from enteric inflammatory/immune cells brings up a defensive program, which when in operation in the distal intestinal tract, functions to rapidly remove threats (e.g., parasites, food antigens, and toxins) that have appeared in the lumen (Wood, 2004).

Power Propulsion

Power propulsion, during emesis and in the distal small bowel and large intestine, is a specialized form of intestinal motility that forcefully and rapidly propels the luminal contents over long distances to effectively empty the lumen. Its occurrence in the distal bowel is accompanied by cramping abdominal pain, fecal urgency, and watery diarrhea in animal models and in humans (Sethi and Sarna, 1991; Phillips, 1995).

Power propulsion is a component of a program in a library of behaviors in the ENS that reproduces the same stereotyped propulsive motor behavior in antigenic detection by the sensitized enteric immune system, radiation-induced enteritis or mucosal contact with noxious stimulants (Otterson et al., 1988; Sarna et al., 1991; Otterson et al., 1992). Stimulated secretion of NaCl and H2O precedes power propulsion when the program “runs.” Strong propulsive contractions of the intestinal circular muscle coat account for the sensations of cramping abdominal pain in humans (Kamath et al., 1990; Figure 1).

Power propulsion in the small bowel can be programmed to travel in oral or aboral directions. During the act of vomiting, power propulsion starts in the middle of the small intestine, travels in the oral direction, and rapidly transports the luminal contents toward the open gastric pylorus (Weisbrodt and Christensen, 1972). Power propulsion in the ileum travels in the aboral direction and rapidly empties the luminal contents into the colon.

Power propulsion, when it occurs in the antigen-sensitized or in the inflamed large intestine, generally starts in the proximal colon and strips the lumen clean as it travels rapidly toward the recto-sigmoid region (Figure 1). It takes place in concert with diarrheal states where large volumes of watery stool may be propelled quickly into the distal large bowel. Rapid distension
of the recto-sigmoid region by the advancing luminal contents triggers the recto-anal reflex and relaxation of the internal anal sphincter. Relaxation of the internal anal sphincter and conscious realization of need for contraction of the external sphincter and puborectalis muscle occur at this time coincident with the sensation of urgency and concern about incontinence.

### Histoanatomy

The ENS has as many neurons as the spinal cord. About 100 million neurons are required for programmatic control of the gastrointestinal functions that account for the different digestive states (e.g., postprandial state, interdigestive state, and emesis). The volume occupied by the central nervous system in the skull and spinal cord would be greatly expanded if the required numbers of specialized types of neurons, together with accompanying glia, were placed there. As an alternative to bundling the ENS control circuits exclusively within the central nervous system and transmitting control signals over long, unreliable transmission lines to several meters of gut, vertebrate animals have evolved with the neural control networks distributed along the length of the digestive tract in close apposition to the muscles, glands, and blood vessels that must be controlled and their activity integrated for effective function of the whole organ (e.g., stomach) in relation to neighboring organs (e.g., the upper small intestine).

Cell bodies of ENS neurons are in ganglia inside the walls of most of the specialized compartments of the digestive tract. The ganglia are interconnected by fiber tracts to form ganglionated plexuses (Figure 2). Interganglionic fiber tracts contain projections from ganglion cell bodies in 1 ganglion that connect synaptically with neurons in neighboring ganglia. The myenteric and submucosal plexuses are the prominent ganglionated plexuses of the ENS (Figure 2). The myenteric division of the ENS, known also as Auerbach's plexus, is located between the longitudinal and circular muscle coats of most regions of the gut. It is a 2-dimensional array of flat disc-like neurons, ganglia, and interganglionic fiber tracts sandwiched between the longitudinal and circular muscle coats of most regions and under and between the taenia coli of the colon of humans and some other species. Unlike other autonomic ganglia, the cell bodies of ENS neurons are not in grape-like clusters; they lay edge-to-edge like a single layer of coins in a 2-dimensional plane (Hanani et al., 1998). The single-layered, 2-dimensional arrangement is hypothesized to be an adaptation for sustaining the neural networks in a functional state as the ENS is subjected to the mechanical forces and deformations that occur during contraction of the musculature or expansion and stretching of the wall as the lumen fills. Most of the motor neurons that innervate the circular and longitudinal muscle coats reside in the myenteric plexus (Brookes, 2001a, b).

The submucosal plexus is a ganglionated plexus situated throughout the submucosal region between the mucosa and circular muscle coat. It is most prominent as a ganglionated network in the small and large intestine. Ganglion cells in the submucosal plexus supply motor innervation to the intestinal secretory glands and possibly to the muscularis mucosae. Neurons in submucosal ganglia project fibers to the myenteric plexus and also receive synaptic input from axons projecting from the myenteric plexus (Song et al., 1991; Hu et al., 2003). The interplexus connections link the 2 networks into a functionally integrated nervous system (i.e., the brain-in-the-gut).

### Brain-in-the-Gut

The ENS has all of the neural elements and integrated circuitry necessary for independent processing of sensory information and programming of organized behavior of the intestinal effector systems (i.e., musculature, secretory glands, and blood vasculature) in the control of the intraluminal environment of the gut. Like the spinal cord, the ENS is “wired” with sensory neurons, interneurons, and motor neurons (Figure 3). The 3 kinds of neurons are synaptically interconnected into integrated circuits that process sensory information and program for the variety of digestive functions found in the specialized compartments of the digestive tract during ever-changing demands of the digestive, digestive, and defensive states of the functioning bowel. The kinds of output from the integrated circuits determine the distinctive patterns of motility that characterize the digestive and protective states of the gastrointestinal tract. The programs for physiological ileus (i.e., absence of motility), digestive state (i.e., mixing), interdigestive state (i.e., migrating motor complex), and small intestinal retropulsion during emesis are all stored in the ENS library.

Neural networks in the myenteric division of the ENS have motor neurons that innervate and control individualized behavior of the gastrointestinal circular and longitudinal muscle coats (Figure 3). One subpopula-

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**Figure 2.** Structural relations of the intestinal musculature and the enteric nervous system. Longitudinal and circular muscle coats are the main components of the musculature involved in propulsive motility. Ganglia and interganglionic fiber tracts of the myenteric and submucosal plexuses are main constituents of the enteric nervous system. The myenteric plexus is situated between the circular and longitudinal muscle coats; the submucous plexus is between the mucosa and circular muscle coat.
tion of excitatory musculomotor neurons activates contraction of the musculature; another inhibitory subpopulation suppresses muscle contraction. Neural networks in the submucosal division of the ENS are populated with secretomotor neurons. Secretomotor neurons have a single axon that innervates and determines the secretory volume released into the intestinal lumen from its secretory glands (Figure 4). Understanding the cellular neurophysiology and integrated control of secretomotor neurons is basic to understanding secretory diarrhea and constipation. Firing of secretomotor neurons stimulates secretion of water, NaCl, HCO₃⁻, and mucus. Collaterals leaving the single axon of submucosal secretomotor neurons project to the submucosal vasculature (Andriantsitohaina and Surprenant, 1992). When the neurons fire to stimulate secretion, the axon collaterals simultaneously release neurotransmitters that dilate periglandular arterioles and thereby increase mucosal blood flow in support of the demands for stimulated secretion (Vanner and Surprenant, 1996).

ENTERIC MAST CELLS

Interaction of enteric mast cells with the ENS is basic for understanding the intestinal symptoms associated with food allergies, as well as understanding essentially the same kind of symptoms for inflammatory bowel disease, infectious enteritis, and stress-induced irritable bowel. Enteric mast cells are filled with granules that are sites of storage for a broad mix of preformed chemical signaling mediators. Antigen binding to the mast cells stimulates release of the mediators, which diffuse, in paracrine manner, into the extracellular milieu to influence other cell types. Enteric mast cells express high-affinity receptors for IgE antibodies or other immunoglobulins on their surfaces. A flood of mediators is released from the mast cells when antibodies to a sensitizing antigen occupy the receptors and cross-linking occurs by interaction of the sensitizing antigen with the bound antibody (Figure 3).

A second class of mediators that includes eicosanoids and platelet-activating factor (PAF) is not preformed and stored in granules in mast cells. Rather, synthesis that precedes release is initiated in response to stimulation. Antigen-antibody reactions are among the factors that stimulate synthesis and release of these mediators. Oral allergen-induced diarrhea in mice is mast cell-, IgE-, serotonin-, and PAF-dependent (Caplan et al., 1994). Synthesis starts with the action of phospholipase A₂ and the formation of 1-O-alkyl-2-lyso glycerophosphocholine (lyso-PAF) and arachidonate or another FFA (Chilton et al., 1984).

Figure 3. Heuristic model for enteric neuroimmune interactions and the brain-mast cell connection during stress. The enteric nervous system (ENS) is a minibrain, with sensory neurons, interneuronal synaptic microcircuits, and motor neurons, located in close apposition to the gastrointestinal effectors it controls. Enteric mast cells are positioned strategically to detect foreign antigens and signal their presence to the ENS. When stimulated by foreign antigens or neuronal input, mast cells release several paracrine mediators simultaneously. Some of the mediators signal the ENS whereas others act as attractant factors for polymorphonuclear leukocytes responsible for acute inflammatory responses. The ENS responds to signals from the mast cells by “running” a defensive program of coordinated secretion and propulsive motility that functions to rapidly expel the source of antigenic stimulation from the bowel. Symptoms of abdominal pain, fecal urgency, and watery diarrhea are side effects of operation of the defense program. Neural inputs to enteric mast cells from the central nervous system stimulate simultaneous release of chemoattractant factors for inflammatory cells and chemical signals to the ENS with effects that mimic the symptoms of antigenic detection by the mast cells. Stress activates the brain-to-mast-cell connection.
Infections with nematode parasites stimulate proliferation of intestinal mast cells in animal models used for study of mast cell involvement in detection and signaling for the presence of sensitizing antigens and infectious invaders that breach the mucosal barrier (Broaddus and Castro, 1994; Santos et al., 1996; Saunders et al., 2002). Results from studies in food allergic models and nematode-infected animals have expanded our understanding of mast cell involvement in ENS immuno-neural communication. This work shows that a second exposure to antigens isolated from the infectious agent (e.g., intestinal nematodes in rats, guinea pigs, or dogs) or food products (e.g., β-lactoglobulin in milk-sensitized guinea pigs) evokes predictable integrated intestinal motor and secretory behavior (Baird and Cuthbert, 1987; Harari et al., 1987; McKay and Perdue, 1993; Santos et al., 1999). Recognition of an antigen by an antibody, bound to a sensitized mast cell, triggers release of a barrage of mediators from mast cells. Once released, the mediators become paracrine messages to the ENS, which responds by suspending operation of other programs in its library and running a defensive program designed to move any remaining antigen out of the lumen. Copious secretion and increased blood flow followed by orthograde power propulsion of the luminal contents are the behavioral outputs of the program (Figures 3 and 4).

Mast cells are equipped and strategically placed to recognize foreign agents that threaten whole-body integrity. When a threat is detected, signals are sent to the ENS, which in response starts a programmed response organized to eliminate the threat. Operation of the immuno-neural defensive program in the lower one-half of the intestinal tract is an analog of the emetic program, which provides a similar form of defense in the upper gastrointestinal tract.

Mast cell function in immuno-neural communication is homologous with sensory detection and information coding in sensory neurophysiology. In sensory physiology, sensory neurons are genetically programmed to express detection mechanisms for specific stimuli (e.g., touch, temperature, or pH) that remain fixed throughout the life of the individual. Mast cells, on the other hand, acquire specific detection capabilities through the flexibility of recognition functions inherent in synthesis by the immune system of new antibodies that become attached to the mast cells. Detection specificity for foreign antigens is acquired and reinforced throughout life as a result of formation of new antibodies that bind to and remain on immunoglobulin receptors on mast cells. The output signals from mast cells, which are triggered by cross-linking of antigens with the attached antibodies, are chemical in nature and analogous to chemical output signals (i.e., neurotransmitters) from sensory neurons to second-order neurons in the central nervous system. Both mast cells and sensory neurons ultimately code information on the sensed parameter by releasing a chemical message.
that is decoded by information processing circuits in the nervous system.

**Mast Cells in Brain-Gut Connections**

Apart from their sensing function, enteric mast cells are switching stations for relay of commands from the central nervous system to the ENS. This constitutes a brain-gut connection in which central psychological status (e.g., stress) becomes linked to irritable states of the digestive tract by way of mast cell activation and release of mediators. Mast cell activation, evoked by psychogenic stress, releases mediators that start the defense program in the ENS library and thereby evoke the same symptoms of diarrhea and abdominal distress as antigen-evoked degranulation. Evidence for a brain-mast cell connection first appeared in reports of Pavlovian conditioning of enteric mast cell degranulation (MacQueen et al., 1989). Assays that measure release of mast cell proteases into the systemic circulation and intestinal lumen are methods used to establish when degranulation of enteric mucosal mast cells occurs. Release of proteases into the circulation can be evoked as a conditioned response in laboratory animals by either light or auditory stimuli after repeated trials of pairing the stimuli with a sensitizing antigen, such as ovalbumin in rats (MacQueen et al., 1989). In humans, release of mast cell proteases into the jejunal lumen occurs as a conditioned response to cold-pressor stress, which like the findings in laboratory animals, reflects a brain-to-enteric-mast-cell connection (Santos et al., 1998). A neural framework for central nervous influence on mast cells in the intestinal tract is indicated by close histological proximity of intramural vagal and spinal afferent terminals and enteric mast cells and by increased expression of histamine in intestinal mast cells in response to vagal nerve stimulation (Gottwald et al., 1995; Williams et al., 1997). Stimulation of neurons in the brain stem by intracerebroventricular injection of thyrotropin-releasing hormone (TRH) evokes degranulation of mast cells in the rat small intestine and adds to evidence for the brain-to-mast-cell connection (Santos et al., 1996).

Intracerebroventricular injection of TRH in rats evokes the same kinds of inflammation and erosions in the stomach as cold-restraint stress. In the large intestine, restraint stress exacerbates nociceptive responses to distension that are associated with increased release of histamine from mast cells (Gué et al., 1997). Like effects of central TRH on gastric mucosal pathology, intracerebroventricular injection of corticotropin-releasing factor mimics responses to stress in the large intestine. Injection of a corticotropin-releasing factor receptor antagonist or pretreatment with mast cell stabilizing drugs suppresses stress-evoked responses in the lower gastrointestinal tract. The brain-mast cell connection is significant for irritable bowel symptoms because the gastrointestinal symptoms associated with mast cell degranulation are expected to be the same whether the mast cells are degranulated by antigen-antibody cross-linking in allergies and infections or by input from the brain during stress.

**Mast Cells and Visceral Pain**

Degranulation of mast cells releases mediators that sensitize pain receptors on spinal afferents in the large intestine (Gebhart, 2000). Degranulation of enteric mast cells, in animals, results in reduced threshold for pain responses to intestinal distension that is prevented by treatment with mast cell stabilizing drugs (Coelho et al., 1998). The terminals of vagal and spinal sensory afferent neurons express receptors for multiple mast cell mediators. Sensitization of sensory nerve terminals by mast cell mediators is reminiscent of the characteristic hypersensitivity to intestinal distension found in a subset of irritable bowel patients (Whitehead et al., 1990; Munakata et al., 1997; Camilleri et al., 2001). Colonic mucosal biopsies from patients with IBS have increased numbers of mast cells, which raises a question of whether the hypersensitivity to distension and strong muscle contractions reflects sensitization of intramural endings of spinal mechanosensitive nerves by mediators released from mast cells (O’Sullivan et al., 2000; Barbara et al., 2004).

**Mast Cells, Inflammation, and ENS-Programmed Defense**

Mast cells release mediators, which signal the ENS that degranulation has taken place while simultaneously attracting immune/inflammatory cells into the intestinal wall from the mesenteric circulation. This has been demonstrated experimentally by introducing purified *Clostridium difficile* toxin-A into intestinal loops and observing stimulation of an influx of acute inflammatory cells coincident with activation of the ENS defense program. Activation of the defense program in this case becomes obvious as copious mucosal secretion of H2O and electrolytes and powerful propagating propulsive contractions in the anal direction. Blockade of the ENS and sensory afferents by exposure of the preparations to a nerve-blocking agent, treatment with tachykinin NK-1 receptor antagonists, or application of mast cell stabilizing drugs suppresses the acute inflammatory response to the toxin (Pothoulakis et al., 1993, 1994; Castagliuolo et al., 1994, 1998). None of the responses to *C. difficile* toxin-A occur in preparations from mast cell-deficient mice (Wershil et al., 1998).

The neurokinin, substance P, is a known mediator in the cascade of events leading to toxin-A-induced mast cell degranulation and release of chemotaxant factors for inflammatory cells (Cocchiara et al., 1995, 1999). Substance P is expressed by enteric neurons and vagal and spinal sensory afferent neurons. It is a neurotransmitter released by enteric neurons and a transmitter for axonal reflexes, which are mediated by spinal sensory afferents within the intestinal wall.
Substance P is a secretagogue for histamine and cytokine release from mast cells in human and guinea-pig intestine (Cocchiara et al., 1997, 1999). A known excitatory action of *C. difficile* toxin-A on enteric neurons is expected to release neuronal substance P, which would then act to degranulate mast cells in the neighborhood of release (Xia et al., 2000).

Exposure of myenteric and submucosal neurons in the ENS to toxin-A in vitro depolarizes the membrane potential and increases excitability. This occurs coincident with presynaptic suppression of nicotinic fast excitatory synaptic transmission in both plexuses and with suppression of inhibitory noradrenergic neurotransmission to secretomotor neurons in the submucosal plexus, which is discussed subsequently (Xia et al., 2000). Suppression of noradrenergic neurotransmission removes sympathetic braking action from secretomotor neurons, and this facilitates stimulation of secretion (Figure 4). Toxin-A evoked excitation of secretomotor neurons, and removal of the sympathetic brake is most likely an underlying factor in the diarrhea associated with *C. difficile* overgrowth in the large intestine.

**MAST CELL SIGNALING TO THE ENS**

Evidence for communication from mast cells to the ENS is derived from electrophysiological recording in enteric neurons in intestinal preparations from antigen-sensitized animal models and electrophysiological recording of the actions of known mast cell mediators on the electrical and synaptic behavior of ENS neurons (Figure 5; Wood, 2004). Evidence obtained in this manner is consistent with the hypothesis that mast cell signals “call up” a neural program for defensive intestinal behavior in response to circumstances within the lumen that are threatening to the functional integrity of the whole animal. Signaling is chemical (i.e., paracrine) and incorporates specialized sensing functions of intestinal mast cells for antigens, as indicated previously, together with the capacity of the ENS for interpretation of the mast cell signals, which may be evoked either by binding of an antigen or neural input (Figure 3). Immuno-neural integration cascades sequentially starting with mast cell detection followed by signal transfer to the ENS, followed by neural interpretation and then by selection of a specific neural program of coordinated mucosal secretion and powerful motor propulsion that effectively clears the antigenic threat from the intestinal lumen.

**Mast Cell Signals**

Several mast cell-derived mediators have neuropharmacological actions on electrical and synaptic behavior of neurons in the ENS, on spinal and vagal afferent terminals, and on sympathetic nerve endings in the ENS (Figure 5). Some key mast cell mediators known to act at their receptors on neural elements in the ENS are 1)
Histamine is best understood as one of the mast cell signals to the ENS due to data derived from animals after sensitization to food antigens or parasites (Wang et al., 1991; Frieling et al., 1994; Liu et al., 2003). Histamine is not synthesized by enteric neurons and is not thought of as a neurotransmitter in the ENS (Pamula et al., 1985). Mast cells and neutrophils are sources of histamine in the intestine. Electrophysiological and immunohistochemical studies on single enteric neurons in animals are responsible for our insight into histaminergic actions on ENS neurons. Application of histamine, to mimic release from mast cells and neutrophils, excites neurons in the small and large intestinal myenteric and submucosal plexuses of the guinea pig (Nemeth et al., 1984). Unlike the small and large intestine, enteric neurons in the guinea-pig stomach do not express histamine receptors and do not respond to experimental applications of histamine (Liu et al., 2003).

Histamine has 3 major actions on neural elements in the guinea-pig intestine. One action, which occurs at the level of neuronal cell bodies, is long-lasting excitation mediated by histamine H2 receptors (Figure 5D; Nemeth et al., 1984). The second is at fast excitative nicotinic synapses, where it acts at presynaptic inhibitory histamine H3 receptors to suppress cholinergic synaptic transmission (Tamura et al., 1988; Liu et al., 2000). A third action is to prevent inhibition by the sympathetic innervation of secretomotor-evoked mucosal secretion (Figure 4). Histamine acts at presynaptic histamine H3 inhibitory receptors on sympathetic noradrenergic fibers to suppress sympathetic inhibitory input to submucosal secretomotor neurons and at H3 presynaptic terminals of enteric somatostatinergic neurons that also provide inhibitory input to secretomotor neurons (Liu et al., 2000).

Mast cells in colonic mucosal biopsies from patients with diarrhea-predominant IBS release more histamine than normal subjects (Barbara et al., 2004). Increased release of histamine onto the neural networks that control the secretomotor innervation of the intestinal crypts, in this set of IBS patients, can be expected to enhance intestinal secretion and lead to secretory diarrheal symptoms like those associated with infectious agents and food allergies.

Histaminergic receptor antagonists are used effectively in treatment of food allergies, as well as watery diarrheal symptoms associated with mastocytosis and microscopic colitis (Baum et al., 1989; Ferrer et al., 2010). The histamine H2 receptor antagonist cimetidine is an effective antidiarrheal drug for treatment of pediatric diarrhea. It also has been used effectively for treatment of diarrhea associated with short-bowel syndrome in patients with Crohn’s disease (Aly et al., 1980). Moreover, mast cell stabilizing drugs, which act to suppress histamine release, are efficacious in the treatment of diarrhea-predominant IBS (Santos et al., 2006; Kloeker et al., 2010).

**Neuromodulatory Function of Histamine**

As mentioned previously, the ENS has a library of programs for specific patterns of intestinal motor behavior. Each program adapts the bowel for a specific digestive state or, in some cases, adverse condition in the intestinal lumen (e.g., inflammation, infectious agents, or food allergens). One or the other program may be “called up” by endocrine or paracrine release of a neuromodulator that floods over the circuit or by neuromodulatory inputs from the CNS.

Histamine release from enteric mast cells and the overlay of histamine on the neural networks in the intestinal submucosal plexus starts a protective program, the output of which generates a rhythmic pattern of secretion and coordinated muscle contractions. Experimental application of histamine to simulate degranulation of mast cells or actual degranulation of mast cells in the intestine of antigen-sensitized animal models evokes cyclical bursts of secretion of electrolytes, H2O, and mucus coordinated with contractions of the muscularis externe (Cooke et al., 1993). Blockade of the ENS with tetrodotoxin stops the patterned response to histamine.

Two modulatory actions of histamine at the single neuron level account for the emergent pattern of enteric network output that is subsequently transformed into a rhythmic pattern of behavior at the level of the secretory epithelium and musculature. One neuromodulatory...

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**Figure 6.** An overlay of histamine on the microcircuits of the submucosal plexus, which mimics mass cell release, evokes repetitive cycles of mucosal secretion and coordinated contractions of the muscularis externa. A full-thickness preparation from the wall of guinea pig colon was placed in an Ussing flux chamber with a small strain gauge attached to the serosal surface. The upper trace shows cyclical increases in short-circuit current, which reflect secretion of NaCl and H2O; the lower trace is muscle contraction recorded by the strain gauge. Courtesy of H. J. Cooke, The Ohio State University College of Medicine, Columbus.
action is at histamine H$_2$ receptors to increase the excitability of the cell bodies of neurons that make up the circuit (Figure 5D). This results in long-lasting firing of action potentials and mimics slow synaptic excitation (Tamura and Wood, 1992).

The second neuromodulatory action of histamine is at synaptic connections between the neurons that form the integrative networks. Histamine acts at receptors on the presynaptic terminals to suppress the release of neurotransmitter and thereby suppress transmission at the synapses. The presynaptic inhibitory action of histamine at enteric cholinergic synapses is mediated by the histamine H$_3$ receptor subtype in the guinea pig (Tamura et al., 1988; Liu et al., 2000). The third action is to prevent inhibition by the sympathetic innervation of secretomotor-evoked mucosal secretion (Figure 4). Histamine acts at presynaptic histamine H$_3$ inhibitory receptors on sympathetic noradrenergic fibers to suppress sympathetic inhibitory input to submucosal secretomotor neurons and at H$_3$ presynaptic terminals of enteric somatostatinergic neurons that also inhibit the excitability secretomotor neurons (Liu et al., 2000).

**Mast Cells in the Brain-Gut Connection**

Communication links from the brain to mast cells and from mast cells to the ENS are a reasonable explanation for the often recognized relationship between stress and symptoms from an irritated gut. Activation of sympathetic nervous input is not a plausible explanation for stress-evoked gut irritability. Activation of the sympathetic nervous system accounts for increases of blood pressure and heart rate in stressed individuals, but cannot explain the symptoms of cramping lower abdominal pain, watery diarrhea, and fecal urgency. Advances in understanding the sympathetic interface with the ENS rule out sympathetic involvement because sympathetic activation inhibits secretomotor neurons and constricts periglandular arterioles and thereby suppresses the neurogenic secretion necessary for generation of loose stools (Figure 4; Wood, 1999). Sympathetic activation and the release of norepinephrine likewise suppress nicotinic synaptic transmission in the ENS and are, therefore, unlikely to initiate the powerful propulsive motility in the colon that accounts for cramping lower abdominal pain (Wood, 1999).

The concept of a brain-to-mast-cell connection implies a mechanism that links central psycho-emotional status to irritable states of the digestive tract, as demonstrated several years ago by T. P. Almy, for humans (Almy, 1951). The irritable state of the bowel (i.e., abdominal discomfort, cramping lower abdominal pain, diarrhea, and urgency) known to result from degranulation of intestinal mast cells and release of signals to the ENS, is anticipated regardless of the mode of stimulation of the mast cells (Figure 3). Degranulation and release of mediators evoked by neural input to the mast cells trigger a program of secretion and power propulsion in the same way as degranulation triggered by cross-linking of a sensitizing antigen to antibodies on the mast cells. This most likely explains the similarity of bowel symptoms between those associated with food allergens and infectious agents and those associated with psychogenic stress in susceptible individuals.

The immuno-neuropsychological evidence reinforces the neurogastroenterological concept that moment-to-moment behavior of the gut, whether normal or pathological, is determined mainly by the ENS. The ENS receives and processes input signals derived from immune/inflammatory cells, including mast cells, sensory receptors, and the CNS. Enteric mast cells use the capacity of the immune system for detection of new antigens and long-term memory that permits recognition of the antigen if it ever reappears in the gut lumen. Should the antigen reappear and breach the mucosal barrier, the mast cells signal its presence to the ENS. The ENS interprets the mast cell signal as a threat and calls up from its program library secretory and propulsive motor behavior organized for quick and effective eradication of the threat. Operation of the program protects the integrity of the bowel and the individual, but at the expense of the side effects of abdominal distress and diarrhea. The same symptomatology is expected to result from activation of neural pathways that link psychological states in the brain to degranulation of mast cells in the gut.

Conjuring up an explanation for the functional significance of the brain-mast cell connection in stress is a challenge for evolutionary biology. There no doubt have been selective pressures for evolution of mechanisms for signaling from the brain to mast cells in the gut. A plausible hypothesis emerges from the reality that the only mechanical barrier between a very “dirty” intestinal lumen and the interior of the body is a single epithelial cell layer. Physical stress and the potential for trauma (e.g., predacious attack, fright, and flight) carry a high probability for a break in the barrier. That stress factors compromise mucosal barrier function is well documented (Saunders et al., 1994, 2002). The “emotional brain” seems to respond to stress by increasing immune surveillance, at a dangerous interface between the body and the outside world, when it perceives a threat that a breach in the mucosal barrier might be imminent. The mechanism used by the brain to elevate protective surveillance appears to be activation of enteric mast cells to release chemotaxant factors, which in turn call in additional numbers of inflammatory cells from the circulating blood (Figure 3).

**SUMMARY AND CONCLUSIONS**

The ENS contains a library of programs for specific patterns of intestinal motor behavior that are adaptive for one or the other of the intestinal digestive states. The ENS runs a defensive program characterized by powerful propulsive motility when threatening agents (e.g., toxins, infective agents, or food allergens) find their way into the intestinal lumen. Cramping abdomi-
nal pain, fecal urgency, and explosive watery diarrhea are hallmark symptoms of food allergies, diarrhea-predominant irritable bowel syndrome, infectious enteritis, and radiation-induced enteritis. Mast cells signal the presence of luminal threats to the ENS (i.e., the brain-in-the-gut), which uses one of the specialized programs from its library of programs to remove the “threat.” Removal is accomplished by first stimulating mucosal secretion, which flushes the threatening agent into the lumen and maintains it in suspension. The secretory response then becomes linked to powerful propulsive motility, which propels the secretions together with the offending agent rapidly in the anal direction. Cramping abdominal pain accompanies the strong propulsive contractions. Urgency is experienced when arrival of the large bolus of liquid distends the recto-sigmoid region and reflexively opens the internal anal sphincter muscles. Sensory information arriving in the brain from receptors in the rapidly distending recto-sigmoid accounts for the conscious sensation of urgency and might exacerbate the emotional stress of the individual. The symptom of explosive watery diarrhea is self-explanatory in this situation.

LITERATURE CITED


