

## Nutrient Tasting and Signaling Mechanisms in the Gut II. The intestine as a sensory organ: neural, endocrine, and immune responses\*

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**Furness, John B., Wolfgang A. A. Kunze, and Nadine Clerc.** Nutrient Tasting and Signaling Mechanisms in the Gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses. *Am. J. Physiol.* 277 (*Gastrointest. Liver Physiol.* 40): G922–G928, 1999.—The lining of the gastrointestinal tract is the largest vulnerable surface that faces the external environment. Just as the other large external surface, the skin, is regarded as a sensory organ, so should the intestinal mucosa. In fact, the mucosa has three types of detectors: neurons, endocrine cells, and immune cells. The mucosa is in immediate contact with the intestinal contents so that nutrients can be efficiently absorbed, and, at the same time, it protects against the intrusion of harmful entities, such as toxins and bacteria, that may enter the digestive system with food. Signals are sent locally to control motility, secretion, tissue defense, and vascular perfusion; to other digestive organs, for example, to the stomach, gallbladder, and pancreas; and to the central nervous system, for example to influence feeding behavior. The three detecting systems in the intestine are more extensive than those of any other organ: the enteric nervous system contains on the order of  $10^8$  neurons, the gastroenteropancreatic endocrine system uses more than 20 identified hormones, and the gut immune system has 70–80% of the body's immune cells. The gastrointestinal tract has an integrated response to changes in its luminal contents. When this response is maladjusted or is overwhelmed, the consequences can be severe, as in cholera intoxication, or debilitating, as in irritable bowel syndrome. Thus it is essential to obtain a full understanding of the sensory functions of the intestine, of how the body reacts to the information, and of how neural, hormonal, and immune signals interact.

primary afferent neurons; gut hormones; immune system; inflammation; enteric nervous system

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THE NEURAL, ENDOCRINE, AND IMMUNE detecting systems provide direct input to local (intramural) regulatory systems and information that passes to the central nervous system and to other organs (Fig. 1).

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\*Second in a series of invited articles on Nutrient Tasting and Signaling Mechanisms in the Gut.

### SENSORY NEURONS

The neurons that detect the states of tissues are primary afferent neurons, primary because they are the first neurons in reflex pathways and afferent because they run toward reflex control centers. Three broad classes of primary afferent neurons are associated with the gut: 1) intrinsic primary afferent neurons (IPANs, also called intrinsic sensory neurons), with cell bodies and connections in the gut wall, 2) extrinsic primary afferent neurons, with cell bodies in vagal and dorsal root (spinal) ganglia, and 3) intestinofugal neurons, with cell bodies in the gut and projections to neurons outside the gut wall (Fig. 2) (9).

### IPANs

Intrinsic primary afferent (sensory) neurons are necessary for the generation of appropriate reflex responses to intestinal contents; intrinsic reflexes generate mixing and propulsive movements of the muscle, cause local changes in blood flow, and modulate secretion of water and electrolytes. Intrinsic sensory neurons also participate in reflexes between organs, for example, between the duodenum and stomach, pancreas, and biliary system.

Experiments conducted in the first decade of this century showed that motility reflexes could be elicited in the intestine after the axons of extrinsic neurons had been severed and allowed to degenerate. The obvious implication of this discovery was that the complete circuits of reflexes, including primary afferent neurons, were in the gut wall. However, it was not until 90 years later that IPANs were unequivocally identified (9, 13). These neurons have only been studied in detail in the ileum of the guinea pig, although there is evidence for similar neurons in other regions and species (e.g., see Ref. 19). IPANs react to three types of stimuli: chemical changes in the intestinal lumen, distension of the intestine, and mechanical distortion of the mucosa.

*Chemosensitive IPANs.* Intracellular records taken from nerve cell bodies in the guinea pig small intestine have identified a class of intrinsic neurons that responds to chemicals (e.g., inorganic acid and short-chain fatty acids at neutral pH) applied to the luminal

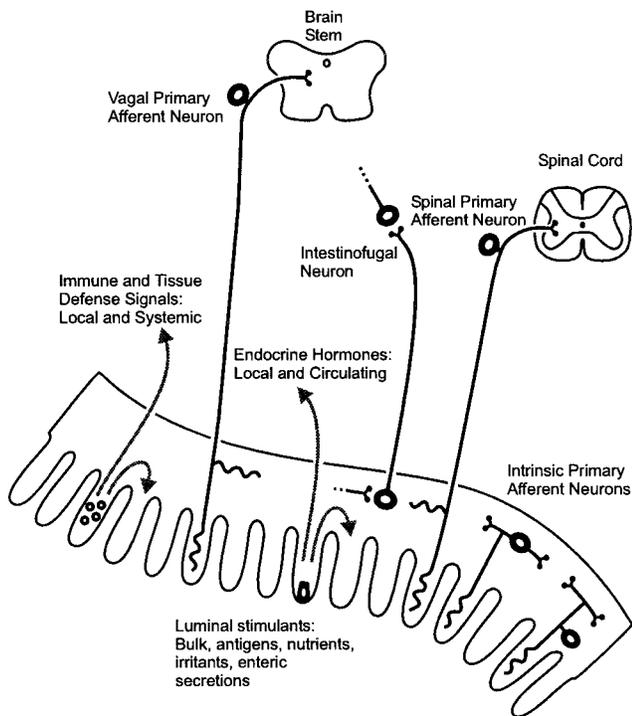


Fig. 1. Three systems for detecting changes in tissues are located in the wall of the intestine: neural, endocrine, and immune detecting systems. Neural sensations are conveyed by extrinsic and intrinsic primary afferent neurons (IPANs) and intestinofugal neurons (see Fig. 2). Endocrine messages are in the form of hormones released from cells in the mucosal epithelium. The hormones enter the circulation and thus act at remote sites, but they also act locally, on nerve endings, epithelium, microvasculature, and cells of the immune system. Immune messages are conveyed by local activation of lymphocytes and augmented by circulating lymphocytes that are activated by antigens from the lumen.

surface of the mucosa of the small intestine (1). These neurons have a distinctive shape, known as Dogiel type II morphology. Interestingly, when Dogiel first identified these neurons, he predicted that they would be sensory. The neurons are multipolar, with one or more processes that lead to and branch in the lamina propria of the mucosa, just beneath the absorptive epithelium, and axons that lead into the myenteric ganglia and supply terminals around several nerve cells, which include other IPANs, interneurons, and motoneurons. IPANs have distinct electrophysiological properties. They have broad action potentials that are carried by both sodium and calcium currents and are followed by early and, generally, by late afterhyperpolarizing potentials. Late afterhyperpolarizing potentials are suppressed by the actions of several neurotransmitters and hormones and are thus not always observed. IPANs receive slow excitatory synaptic inputs; this is unusual for primary afferent neurons, which generally do not receive any synapses on their cell bodies. IPANs seem to be unique among sensory neurons in that their excitabilities can be modified by synapses at the soma. In fact, many inputs to IPANs arise from other IPANs, suggesting that these neurons form self-reinforcing networks (9).

The intrinsic neurons that detect changes in the chemical content of the gut lumen may do so indirectly via the release of hormones from enteroendocrine cells. One reason to propose an indirect action is that the mucosal epithelium separates the nerve endings from the luminal environment (Fig. 2). A possible intermediate for transduction of signals from the mucosa is 5-hydroxytryptamine (5-HT), which is a potent stimulant of the endings of IPANs (9, 14). 5-HT is released when the mucosa is mechanically stimulated, and the consequent reflex responses are antagonized by drugs that block 5-HT receptors. Mechanical stimulation also causes *c-fos* induction in IPANs with cell bodies in submucosal ganglia, and this induction is blocked by 5-HT receptor antagonists (14). Other hormones that are contained in gut endocrine cells, such as CCK and motilin, are released by nutrients and act on neurons but have not been tested for their possible roles as intermediates in enteric reflexes.

*Stretch-sensitive IPANs.* A majority of myenteric Dogiel type II neurons respond directly to tension in the

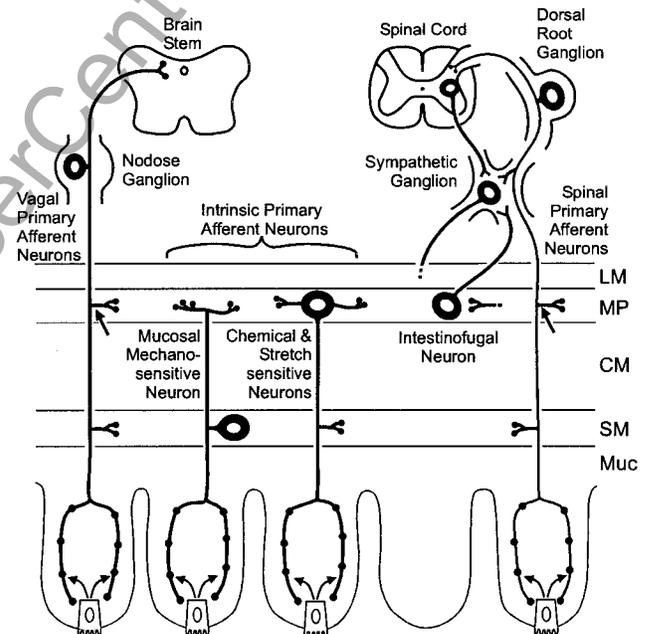


Fig. 2. Simplified diagram to illustrate the arrangement of primary afferent neurons of the intestine. See text for a more complete description. Intestinal primary afferent neurons include IPANs, vagal and spinal primary afferent neurons, and intestinofugal neurons. IPANs are multipolar, and their terminals are confined within the wall of the intestine. Vagal and spinal primary afferent neurons are pseudounipolar and have collaterals that run to enteric ganglia (e.g., arrows). Subgroups of these that respond to specific modalities may have specific patterns of ending in the gut wall (not shown). Vagal primary afferent neurons have cell bodies in the nodose ganglia, and their outputs are via terminals in the nucleus tractus solitarius within the brain stem. Cell bodies of spinal primary afferent neurons are in dorsal root ganglia, their central processes end in the dorsal horns of the spinal cord, and their peripheral axons pass through sympathetic ganglia to innervate the intestine. In many cases, primary afferent neurons are excited by hormones released by gut endocrine cells. Intestinofugal neurons are part of the afferent limb of intestinointestinal reflexes that pass through sympathetic ganglia. LM, longitudinal muscle; CM, circular muscle; MP, myenteric plexus; SM, submucosa; Muc, mucosa.

muscle (16). Two types of response were detected: a phasic response at the onset of stretch and an ongoing action potential discharge during maintained stretch. The onset response was recorded when the muscle itself was paralyzed with nicardipine, but ongoing discharge during maintained stretch was abolished if muscle contraction was prevented by muscle relaxants. This indicates that active tension in the muscle (induced by stretch) contributes to the excitation of the tension-sensitive IPANs.

**Mucosal mechanoreceptors.** Functional evidence for IPANs with cell bodies in submucosal ganglia comes from experiments in which activity-dependent induction of *c-fos* and activity-dependent uptake of dyes were localized; *c-fos* immunoreactivity was detected in submucosal nerve cells after the mucosa had been distorted by puffs of nitrogen gas (14). The *c-fos* expression was abolished by TTX but not by hexamethonium, which was utilized as an antagonist of fast excitatory transmission between neurons, suggesting that *c-fos* was produced in the cell bodies of IPANs that had processes in the mucosa. Styryl dyes, which are taken up by the endings of active neurons and transported back to the cell bodies, also identify neurons that respond to movement of the villi (13). Distortion of the mucosa by puffs of nitrogen gas caused styryl dye labeling in numerous submucosal and in a few myenteric neurons in the presence of hexamethonium. Fibers in myenteric ganglia, presumed to be axons from submucosal IPANs, were labeled. These results suggest that cell bodies of mucosal mechanoreceptors are in submucosal ganglia and project to the myenteric plexus (Fig. 2).

#### ROLES OF IPANs

Intrinsic reflexes that affect motility, water and electrolyte secretion, and blood flow all occur in the small intestine (8). Motility reflexes are evoked by distension of the muscle (without distortion of the mucosa), chemicals applied to the mucosal surface, and mucosal distortion. Secretomotor reflexes are initiated physiologically by chemical or mechanical interaction of luminal contents with the mucosa or pathologically by toxins, such as cholera toxin or enterotoxins, in the lumen (7). The enteric secretomotor circuits consist of IPANs with their endings in the mucosa and nerve circuits that pass through the myenteric and submucosal plexuses and feed back to secretomotor neurons with cell bodies in the submucosal ganglia. The secretomotor neurons stimulate epithelial cells to pump chloride ions, which are accompanied by water, into the lumen.

Local vasodilator reflexes in the small intestine are caused by mechanical or chemical irritation of the mucosa, and substantial evidence indicates that the vasodilator neurons are intrinsic to the intestine and transmission from them is predominantly noncholinergic (25). The same motoneurons have axons that branch to supply both the secretory epithelium and arterioles; thus some secretomotor and vasodilator reflexes share the same final neurons (e.g., see Ref. 12). This makes physiological sense, as at least part of the secreted

water and electrolytes come indirectly from the vasculature.

Thus the role of IPANs is to detect changes in the state of the intestine that are consequences of the presence and nature of the intestinal contents. The information is conveyed to other neurons of the enteric nervous system, which then integrate the information and cause appropriate changes in mixing and propulsive activity, in water and electrolyte transport, in local blood flow, and possibly in endocrine secretion. Responses of muscle, epithelium, and vasculature are evoked by similar stimuli, so it is likely that overlapping populations of IPANs contribute to motility and secretomotor and vasomotor reflexes. However, the integration of each type of response with the others still requires resolution.

#### EXTRINSIC PRIMARY AFFERENT NEURONS

Extrinsic primary afferent neurons carry information about the state of the gastrointestinal tract to the central nervous system. They appear to monitor all aspects of gut function, and they also carry nociceptive information (22).

Vagal primary afferent neurons have cell bodies in the nodose ganglia and axons that reach the gut via the vagus nerves, and spinal primary afferent neurons have cell bodies in the dorsal root ganglia (Fig. 2). The axons of spinal primary afferent neurons in the thoracic and lumbar regions pass through sympathetic ganglia to reach the gut via splanchnic and mesenteric nerves. The axons of most spinal primary afferent neurons with cell bodies in sacral ganglia follow the pelvic nerves to reach the colon and rectum.

Direct recordings of extrinsic primary afferent neurons have been made by placing electrodes in nerves or on their cell bodies in sensory ganglia, and the existence of these neurons has been deduced indirectly by monitoring behavioral or physiological consequences of their activation. Some of the information conducted by extrinsic primary afferent neurons is directly perceived, for example, sensation of gastric or intestinal fullness, various pain sensations (cramp, colicky pain, sharp pain), warmth, and the sensation of gastric emptiness. Perception of the state of the gastrointestinal tract is subject to psychosensory modulation. Perception is enhanced when attention is paid to the gut and is diminished with inattention. Sensation is also diminished when painless somatic stimuli are simultaneously applied. Other information is indirectly perceived; for example, the feeling of satiety after a meal is not directed to a particular organ. However, most of the information carried by gastrointestinal primary afferent neurons is not consciously perceived. This is nicely demonstrated by tests on fistula patients who report no sensation when the healthy stomach is probed or in patients that have had the intestinal lining cut to take a biopsy.

Low- and high-threshold mechanosensitive afferent neurons have been defined. Low-threshold neurons respond to tissue states that occur in the normal course of digestion, and high-threshold neurons respond to

stimuli that are at the extreme of normal or are pathological. For example, moderate distension of the stomach stimulates low-threshold mechanoreceptors, which cause reflex relaxation of the proximal stomach and rhythmic mixing contractions in the distal stomach. This is unnoticed by the subject. Greater distension activates higher-threshold mechanoreceptors, leading to feelings of fullness. Further distension can lead to discomfort and pain.

Vagal afferent fibers respond to a wide range of stimuli, including mechanical probing of the esophageal, gastric, or duodenal mucosa, distension of the gut wall, and muscle contraction, and respond to intraluminal chemicals, including acid, absorbable carbohydrate, lipid, and fatty acids (22). Vagal afferent fibers also respond to changes in osmolarity and temperature (22). However, it is not entirely clear whether vagal afferents are selectively and directly activated by nutrients; activation by carbohydrates might be secondary to motility reflexes, or responses may be initiated by endocrine hormones that are released by nutrients (see GUT ENDOCRINE SYSTEM).

Because the majority of the information that is communicated to the central nervous system does not come to conscious sensation, it is impossible to know how specific and fine detailed is the information. It may, in fact, be a summed information that informs the central nervous system of the general state of the digestive organs. This is suggested by the substantial sizes of receptive fields of the afferent neurons (e.g., see Ref. 20). It is also suggested by the reflex responses of organs, e.g., acid or enzyme secretion, gallbladder contraction, or gastric relaxation; none of these appear to be finely graded. Moreover, hormones can be expected to diffuse locally and, via the bloodstream, may also affect many afferent nerve endings.

Pain and visceral discomfort are conducted to the central nervous system via spinal afferent neurons. In humans, cutting the spinal afferent nerves abolishes pain caused by strong distension of the stomach, intestine, or gallbladder (2). Painful sensations are more likely and occur at lower thresholds if the gut is inflamed. This is because the nerve endings in inflamed tissues are sensitized, almost certainly by mediators released from immune or mast cells. In general, low-threshold afferent endings are vagal in origin and high-threshold nerve endings are of spinal origin. However, some spinal primary afferent neurons can also be activated by low-threshold stimuli, which suggests that some nonnociceptive information is carried by spinal afferent neurons.

#### ROLES OF EXTRINSIC PRIMARY AFFERENT NEURONS

One of the roles of extrinsic primary afferent neurons is to signal to the central nervous system information that is necessary for regulation of organs and behaviors that are beyond the immediate local territories of the afferent endings, although some reflexes, notably vagovagal reflexes, are signaled back to their regions of initiation. The information that reaches the central nervous system from the detection of several qualities

of the gastrointestinal tract, including the state of distension, chemicals in the lumen, and the presence and degrees of tissue injury and inflammation, can be decoded and interpreted consciously as satiety, pain, hunger, or nausea. The afferent information is also used to direct functions automatically, for example, esophageal propulsion, gastric relaxation in response to a meal, gastric acid secretion, all through the vagus, defecation through the pelvic nerves, and control of water and electrolyte transport and blood flow in relation to the relative needs of all organs, via sympathetic motor pathways.

#### INTESTINOFUGAL NEURONS

The intestinofugal neurons are an unusual class of neurons. Their cell bodies are in the gut wall, and their processes form synapses in prevertebral sympathetic ganglia (Fig. 2). Their presence was deduced during the 1930s, when it was discovered that distension of one region of the gastrointestinal tract caused inhibition of motility in other regions and that these enteroenteric inhibitory reflexes persisted after connections with the central nervous system were severed so long as the integrity of connections with prevertebral sympathetic ganglia were maintained (15). Methods to study these reflexes *in vitro* were developed in the early 1970s, and the organization of the pathways has been subsequently studied in considerable detail (23). The cell bodies of intestinofugal neurons are in the myenteric plexus. They are most numerous in the large intestine, in the small intestine they increase in number distally, and they are rare in the stomach. The axons of intestinofugal neurons make excitatory, cholinergic synapses with the cell bodies of sympathetic neurons that project back to the gut.

#### ROLES OF INTESTINOFUGAL NEURONS

The functions of intestinofugal neurons have been analyzed almost exclusively in relation to motility control, although they also innervate sympathetic neurons whose function is to inhibit secretion of water and electrolytes in the intestine (8, 23). The intestinofugal neurons that affect motility are in the afferent limbs of enteroenteric inhibitory reflexes. These reflexes appear to act primarily on regions of the gastrointestinal tract that are more oral than the sites from which they are initiated (23). Thus the reflexes are one of the feedback mechanisms by which more distal parts of the intestine regulate the more proximal regions from which they receive products of digestion. Other mechanisms of distal-to-proximal regulation include actions of hormones that are released in response to nutrients, for example, the ileal brake (in which signals from the distal ileum cause slowing of gastric emptying) and reflexes that pass from the small intestine through the central nervous system and return via vagal motoneurons (10).

#### GUT ENDOCRINE SYSTEM

Hundreds of thousands of endocrine cells, producing more than 20 hormones, are dispersed among the

epithelial cells of the luminal surface of the intestine and react to changes in gut contents by releasing hormones that are, in general, targeted to other parts of the digestive system (18). For example, CCK is released from the duodenum in response to a meal; the major chemicals signaling this release are the products of the breakdown of fats and proteins. CCK then acts on the pancreas to release digestive enzymes and on the gallbladder to trigger the emptying of bile salts into the duodenum. Most gut endocrine cells have surfaces bearing microvilli that are directly apposed to the gut lumen. These surfaces are detectors that "taste" the luminal contents, in response to which the endocrine cells are excited to release hormones from their basal surfaces, close to afferent nerve endings, immune cells, and the perfusing vasculature.

The targets of gut hormones include neurons; conversely, enteric neurons modify hormone release. CCK stimulates the endings of vagal afferent neurons, resulting in reflex inhibition of gastric emptying and satiation (18). CCK also stimulates neurons of the gallbladder; this appears to be the major mechanism through which gallbladder emptying is induced when CCK is released (17). Vagal afferent neurons are also stimulated by 5-HT; in this case, nausea occurs. Motilin, which is released from duodenal endocrine cells, activates a motor program in the enteric nervous system, which results in migrating myoelectric complexes that sweep the contents of the small intestine in an anal direction. Many of the classes of gut endocrine cells are under neural control. For instance, release of gastrin is caused by activity in vagal and intrinsic nerve pathways, and vagal stimulation also causes 5-HT release.

#### GUT IMMUNE SYSTEM

The vast surface area presented by the lining of the gastrointestinal tract must defend the body against many potentially injurious substances in food, accompanying food or drink, or produced by bacteria or degradation of food. Some level of assault on the intestine from its contents occurs at all times; thus it is the natural state of the intestine to be immunologically and chemically challenged. To defend the otherwise highly permeable epithelial membrane, the small and large intestines have developed a number of specializations, which are collectively called gut-associated lymphoid tissue (GALT). Within the gut wall, the GALT includes antigen sampling cells (M cells) in the epithelial lining, collections of lymphocytes and immune-associated cells, including macrophages, eosinophils, mast cells, and neutrophils (3). Lymphocytes of the GALT are present as organized lymphoid aggregates, represented by Peyer's patches in the small intestine, the mesenteric lymph nodes, and solitary lymphoid nodules plus numerous immune cells that constitute the nonorganized lymphoid elements in the mucosa and include the intraepithelial lymphocytes and lymphocytes in the lamina propria. Overall, 70–80% of the immune cells of the body are in the gut (5). Antigens are sampled from the lumen by M cells, which are modified enterocytes. The antigen that is transported across the epithelium

by the M cell is taken up and processed by macrophages and dendritic cells and then presented to local T lymphocytes, which in turn stimulate local B lymphocytes. The B lymphocytes ultimately migrate to and proliferate in the lamina propria of the mucosa and produce antibody, primarily IgA. A proportion of the lymphocytes first migrate from Peyer's patches to mesenteric lymph nodes. These then enter the circulation and localize to intestinal and nonintestinal mucosa-associated lymphoid tissue (MALT), utilizing specific receptors on postcapillary venules to guide their localization (5). MALT in the gut and elsewhere is characterized by the predominance of local IgA production and by localization signals through which activated lymphocytes derived from one mucosal surface can recirculate and localize selectively to the same and other mucosal surfaces. The connection between different mucosal surfaces permits immunity initiated in one organ to protect other mucosal sites. For example, localization signals for gut-derived lymphocytes are in the breast and conjunctiva.

The immune system of the intestine is involved during the course of inflammatory bowel disease, microbial infection, allergy, and various injuries. The mucosa can become infiltrated with increased numbers of granulocytes, lymphocytes, macrophages, eosinophils, and mast cells. These, in turn, release a host of soluble mediators of inflammation, including cytokines, prostaglandins, leukotrienes, and histamine. Several of these substances excite enteric neurons and the extrinsic afferent endings in the gut. Considerable evidence now indicates that neuroimmune interactions are important factors in sensitizing the inflamed bowel (6). In addition to immune messengers affecting neurons, there is innervation of Peyer's patches by enteric neurons, and receptors for enteric neurotransmitters are located on lymphocytes (6).

#### INTERACTIONS BETWEEN AFFERENT NEURONS AND IMMUNE AND ENDOCRINE SYSTEMS

The lamina propria is a milieu in which the secreted products of inflammatory cells, endocrine hormones, and afferent nerve endings interact with receptors on nerve endings and on cells of each of the other two systems. The products of immune and inflammatory cells sensitize afferent nerve endings, depolarize enteric neurons, and stimulate smooth muscle and mucosal epithelial cells; neurotransmitters affect immune cells, the arteriole diameter, vascular permeability, and epithelial fluid transport; and endocrine cell products affect nerve endings and immune cells (4–6).

Cells in damaged or inflamed tissue produce neuroactive substances, including cytokines [interleukins (IL), tumor necrosis factor- $\alpha$ , leukemia inhibitory factor (LIF)], prostaglandins, bradykinin, and histamine. Each of these substances acts on neurons. It has been long established that intestinal inflammation causes intestinal hyperalgesia and that motility disorders are associated with, and outlast, periods of inflammation (6). These changes may be contributed to by a number of substances released as part of the inflammatory reac-

tion. For example, visceral afferents are stimulated by bradykinin, and intraperitoneal bradykinin causes abdominal pain. 5-HT is released in experimental intestinal anaphylaxis and stimulates the endings of vagal afferent fibers via 5-HT<sub>3</sub> receptors (4). 5-HT is also a potent stimulator of the mucosal endings of IPANs. Pharmacological experiments suggest that tachykinins, presumably released by axon reflexes, contribute to sensitization of gut afferent nerve endings (4). The mechanisms by which inflammatory mediators cause long-term effects are only partially investigated. However, they are known to stimulate increased synthesis of nerve growth factor (NGF) by fibroblasts and its production from mast cells. Both NGF and LIF are neurotrophic factors, notably in the case of NGF for spinal afferent neurons. Interplay between cytokines and neurotransmitters also occurs at the level of the smooth muscle (5, 24). The inflammatory product, IL-1, stimulates smooth muscle cells to produce IL-6, an effect that is enhanced by the neurotransmitters vasoactive intestinal peptide, calcitonin gene-related peptide (CGRP), and norepinephrine and diminished by substance P.

Tachykinins, usually measured as substance P, and CGRP are contained in a majority of spinal afferent neurons and are also in IPANs, at least in the guinea pig (4, 8). Tachykinins and CGRP cause vasodilatation and plasma cell extravasation, thus contributing to increased blood flow and the access of immunocytes to the tissue. Thus these substances may have significant effects in restricting the deleterious consequences of tissue damage, as well as in neurogenic inflammation. In the stomach, CGRP released from afferent nerve endings after injury contributes to mucosal protection and reduces the degree of ulceration (11). Transmitter release from afferent endings in the colon also reduces the severity of damage consequent on inflammation, at least in the acute phase (21).

## CONCLUSIONS

The thesis pursued in this themes article is that the intestine can properly be regarded as a sensory organ with three detecting systems: neurons, endocrine cells and immune cells. A richness of knowledge now exists about each system, and there is growing knowledge of their interactions. In pathological conditions, such as inflammation, it has been easy to reveal that factors from neurons, immune cells, and endocrine cells are released within the mucosa, but it remains difficult to analyze how the interactions between these factors produce the overall inflammatory response. It is probable that changed neuronal sensitivities are involved in disorders such as irritable bowel syndrome; how these changes are brought about and how they may be modified to alleviate the pathology require further investigation.

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