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EDITORIAL

Neuropathophysiology of functional gastrointestinal disorders

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Abstract

The investigative evidence and emerging concepts in neurogastroenterology implicate dysfunctions at the levels of the enteric and central nervous systems as underlying causes of the prominent symptoms of many of the functional gastrointestinal disorders. Neurogastroenterological research aims for improved understanding of the physiology and pathophysiology of the digestive subsystems from which the arrays of functional symptoms emerge. The key subsystems for defecation-related symptoms and visceral hypersensitivity are the intestinal secretory glands, the musculature and the nervous system that controls and integrates their activity. Abdominal pain and discomfort arising from these systems adds the dimension of sensory neurophysiology. This review details current concepts for the underlying pathophysiology in terms of the physiology of intestinal secretion, motility, nervous control, sensing function, immuno-neural communication and the brain-gut axis.

Key words: Neurogastroenterology; Visceral pain; Diarrhea; Irritable bowel syndrome; Constipation; Stress; Enteritis; Enteric nervous system; Neuroimmune communication; Mast cells

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INTRODUCTION

Functional gastrointestinal disorders are those in which no abnormal metabolic or physical processes, which can account for the symptoms, can be identified[1]. The irritable bowel syndrome (IBS) is an example of a significant functional disorder, which affects 10-20 percent of the population worldwide[2-6]. Predominant symptoms of IBS are abnormal defecation associated with abdominal pain, both of which may be exacerbated by psychogenic stress[7]. The abnormal defecation in IBS is predominately diarrhea or constipation. A subgroup of IBS patients alternates from one to the other over time. In the absence of abdominal pain, persistent diarrheal states or states of constipation may also fall into the category of a functional disorder. Urgency to stool and incontinence for fecal liquid are often coincident with the diarrheal state. Patients with constipation-predominant IBS, and oftentimes functional constipation, often report bloating, straining and sensations of incomplete fecal evacuation. Significant subpopulations of IBS patients and functional dyspeptic patients are hypersensitive to distension of the recto-sigmoid region of the large bowel and the hypersensitivity can extend to other regions of the digestive tract (e.g. esophagus)[7,8].

The basic gastrointestinal physiology in this review deals with the normal and disordered physiology of the systems out of which the symptoms of IBS and functional diarrhea or constipation emerge. Knowledge of this kind is necessary for understanding the pathophysiology, which underlies the symptoms, and for rational therapeutic strategies. The subsystems involved in the defecation-related symptoms are the intestinal secretory glands, the musculature and the nervous system that controls their activity. Abdominal pain and discomfort, which arise from these systems, falls into the domain of sensory neurophysiology. This review will explore the pathophysiology in terms of current concepts of the physiology of intestinal secretion, motility, nervous control and sensing functions.

THE BRAIN-IN-THE-GUT

Gastrointestinal behavior reflects the integrated functioning of the musculature, mucosal epithelium and blood-lymphatic vasculature. The enteric division of the autonomic nervous system (i.e. brain-in-the-gut) organizes and coordinates the activity of the three effector systems to generate functionally effective patterns of behavior that are adaptive for differing digestive states. The enteric nervous system (ENS) is a local minibrain that contains a library of programs for the necessary patterns of intestinal behavior. Mixing in the digestive state, the migrating motor complex in the interdigestive state and emetic patterns of small intestinal motor behavior and haustral formation in the large intestine are examples of outputs from four of the neural programs in the ENS library. During emesis, the

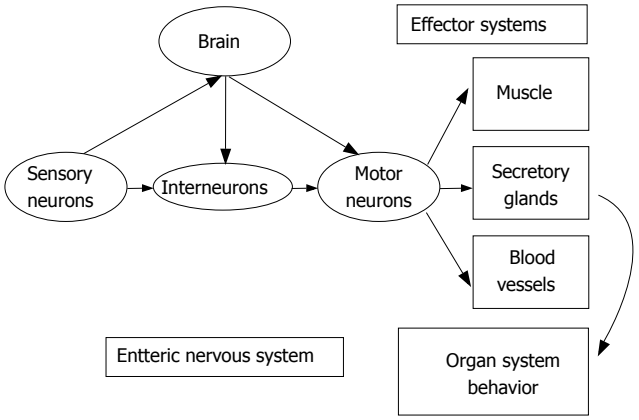

Figure 1 The heuristic model for the enteric nervous system is the same as for the central nervous system. Sensory neurons, interneurons and motor neurons are synaptically interconnected to form the neural networks of the ENS. Like the central nervous system, sensory neurons, interneurons and motor neurons are connected by chemical synapses for directional flow of information from sensory neurons to interneuronal integrative networks to motor neurons to effector systems. The ENS organizes and coordinates the activity of each effector system into meaningful behavior of the whole organ. Bidirectional communication occurs between the ENS and the central nervous system.

program output includes reversal of peristaltic propulsion in the upper jejunum and duodenum to rapidly propel the contents toward the open pylorus and relaxed gastric antrum and corpus.

Structure, function and neurochemistry of the ganglia of the enteric nervous system are unlike other autonomic ganglia. Neurons in the ganglia of the ENS are interconnected by chemical synapses to form an independent nervous system with mechanisms for integration and processing of information like those in the brain and spinal cord. Instead of housing neural control entirely within the central nervous system (CNS), a minibrain has evolved within the walls of the digestive tract placed in close proximity to the effector systems that must be controlled and regulated along several meters of bowel.

The ENS has as many neurons as the spinal cord. The large number of neurons, required for program control of digestive functions, would overly expand the CNS if housed there. Rather than crowding the neural control circuits exclusively within the skull or vertebral column and transmitting nerve impulses over long transmission lines to the gut, vertebrate animals have evolved with most of the neural networks, required for automatic feedback control, spatially distributed along the digestive tract close to the effector systems that must be controlled and integrated for whole organ function.

Like the CNS, the ENS has interneurons and motor neurons that are interconnected by chemical synapses into functional neural networks (Figure 1). Moreover, like the CNS, the ENS networks receive synaptic input from sensory neurons. The sensory neurons, most of which have their cell bodies in spinal dorsal root or nodose ganglia and their terminations in the intestinal wall and spinal cord, express receptor regions specialized for detecting and coding information on changes in thermal, chemical or mechanical stimulus energy within the environment of the receptor region. The receptor regions transform changes in stimulus energy into signals coded by action potentials that subsequently are transmitted along sensory nerve fibers to be received and processed in both the ENS and CNS.

Interneurons are connected by synapses into networks that process sensory information and determine the behavior of motor neurons. Multiple connections among many interneurons use the same mechanisms of chemical neurotransmission as the CNS to form "logic" circuits that decipher inputs from sensory neurons. Some of the circuits are reflex circuits that organize reflex responses to sensory inputs and others are integrative circuits that contain the programs for motor behavioral patterns, such as the migrating motor complex, haustral formation in the colon and postprandial mixing movements in the small intestine. Motor neurons are the final common output pathways for transmission of control signals from the interneuronal networks to the effector systems.

Enteric motor neurons

Motor neurons in the ENS are excitatory or inhibitory motor neurons (Figure 1). The excitatory motor neurons release neurotransmitters, which evoke contraction of the musculature and secretion from mucosal glands. Acetylcholine and substance *P* are the main excitatory neurotransmitters released at neuromuscular junctions to stimulate muscle contraction. Acetylcholine, vasoactive intestinal polypeptide and ATP are excitatory neurotransmitters responsible for evoking secretion from the intestinal glands.

Enteric inhibitory motor neurons release neurotransmitters at neuromuscular junctions where they act to suppress contractile activity of the musculature. Vasoactive intestinal polypeptide, nitric oxide and ATP are among the neurotransmitters implicated as inhibitory neurotransmitters at neuromuscular junctions in the digestive tract.

Inhibitory motor neurons

Enteric inhibitory motor neurons have central importance in consideration of ENS neuropathy because their loss is manifest as profound pathologic changes in contractile behavior of the intestinal musculature. The pathologic changes in motor behavior associated with degeneration of inhibitory motor neurons reflect the specialized physiology of the musculature. The gastrointestinal musculature is a self-excitable electrical syncytium consisting of interstitial cells of Cajal (ICCs) that function as pacemakers for the gastric musculature and the intestinal circular muscle coat. The term "electrical syncytium" infers that action potentials and pacemaker potentials spread by way of gap junctions from smooth muscle fiber to muscle fiber in three dimensions. The action potentials trigger contractions as they spread through the bulk of the musculature. The ICCs are a non-neural pacemaker system of electrical slow waves that are electrically coupled to the musculature and account for the self-excitable characteristics of the muscle[9-13]. The electrical slow waves, in this construct, are an extrinsic factor to which the circular muscle responds. Consideration of these

functional aspects of the musculature raises the question of why the circular muscle fails to respond with action potentials and contractions to each and every pacemaker cycle and why action potentials and contractions do not spread in the syncytium throughout the entire length of intestine whenever they occur at any point along the bowel. The answer is that the circular muscle in a segment of bowel can only respond to invading electrical slow waves from ICCs when the inhibitory motor neurons in the ENS of that segment are inactivated by input from the control circuits formed by interneurons (Figure 1). Likewise, action potentials and associated contractions can propagate only into regions of musculature where the inhibitory motor neurons are inactivated. Therefore, activity of inhibitory motor neurons determines when the omnipresent slow waves initiate a contraction, as well as the distance and direction of propagation once the contraction has begun.

Some of the inhibitory motor neurons to the circular muscle fire continuously and continuously release inhibitory neurotransmitters at their junctions with the muscle. This results in ongoing inhibition of contractile activity. Action potentials and contractions of the muscle are permitted only when the active inhibitory neurons are inactivated by input from the interneuronal control circuitry[14,15]. The behavior of inhibitory motor neurons to smooth muscle sphincters (e.g. lower esophageal and internal anal sphincters) is opposite to that of the intestinal circular muscle coat. Inhibitory motor neurons to the sphincters are normally silent and are switched to firing mode with timing appropriate for coordinated opening of the sphincter with physiological events in adjacent regions. When inhibitory motor neurons fire, they release inhibitory neurotransmitters that relax ongoing muscle contraction in the sphincteric muscle and prevent excitation-contraction in the musculature on either side of the sphincter from spreading into and closing the sphincter.

In non-sphincteric circular muscle, the activity state of the inhibitory innervation determines the length of a contracting segment by controlling the distance of spread of action potentials within the three-dimensional electrical geometry of the smooth muscle syncytium. Contraction can occur in segments in which ongoing inhibition is inactivated while adjacent segments with continuing inhibitory input cannot contract. The boundaries of the contracted segment reflect the transition zone from inactive to active inhibitory motor neurons. The directional sequence in which the inhibitory motor neurons are inactivated establishes the direction of propagation of the contraction. Normally, inhibition is progressively inactivated in the aboral direction, resulting in contractile activity that propagates in the aboral direction. During emesis, the inhibitory motor neurons must be inactivated in a reverse sequence to account for small intestinal propulsion that travels toward the stomach. In general, any treatment or condition that ablates the intrinsic inhibitory neurons results in spastic contractile behavior of the intestinal circular muscle coat.

Several conditions associated with ablation of enteric inhibitory neurons are associated with conversion from a hypoactive contractile condition of the circular muscle to a hyperactive contractile state. Observations of this nature, usually made by manometric recording methods *in vivo*, reinforces the evidence that a subset of the pool of inhibitory motor neurons is tonically active, and that blockade or ablation of these neurons releases the circular muscle from the inhibitory influence[14-16]. The behavior of the muscle in these cases is tonic contracture and recurring disorganized phasic contractile activity that is non-propulsive.

Disinhibitory motor disease

The inhibitory neuromuscular relations in the intestine predict that spasticity and "achalasia" (i.e. failure to relax) will accompany any condition where inhibitory motor neurons are rendered inactive or destroyed. Without ENS inhibitory neural control, the self-excitable smooth muscle contracts continuously and behaves as an obstruction. This occurs because the muscle responds to each and every ICC-generated electrical slow wave with contractions that propagate in all directions without any control of amplitude or distance of propagation. Contractions spreading in the uncontrolled syncytium collide randomly resulting in chaotic-ineffective behavior in the affected intestinal segment in ways which are reminiscent of fibrillation in the myocardium.

Loss or malfunction of inhibitory motor neurons is the pathophysiological starting point for disinhibitory motor disease, which includes several forms of chronic intestinal pseudoobstruction and sphincteric achalasia. Neuropathic degeneration of the ENS includes loss of the pool of inhibitory motor neurons along with the interneuronal pool and is a progressive disease that in its early stages may be manifest as symptoms that could be interpreted as a functional gastrointestinal disorder (e.g. IBS).

Intestinal pseudoobstruction is a pathophysiological state with symptoms that resemble those of a mechanical obstruction to forward propulsion, but without the presence of a mechanical obstruction. Chronic intestinal pseudoobstruction can be myopathic or neuropathic. The neuropathic form of chronic intestinal pseudoobstruction is a form of disinhibitory motor disease linked with neuropathic degeneration in the ENS. Failure of propulsive motility in the affected length of bowel reflects loss of the neural microcircuits that program and control the repertoire of motility patterns required for the necessary functions of that region of bowel. Pseudoobstruction occurs mainly because contractile behavior of the circular muscle is hyperactive, but disorganized in the denervated regions[17,18]. Hyperactivity determined by manometric recording methods is a diagnostic sign of the neuropathic form of chronic small bowel pseudoobstruction. The hyperactive and disorganized contractile behavior reflects the absence of inhibitory nervous input to the muscles, which are autogenic when released from the braking action of the inhibitory motor neurons of the ENS. Chronic pseudoobstruction is therefore symptomatic of the advanced stage of a progressive enteric neuropathy. Retrospective review suggests that IBS-like symptoms in a subgroup of patients can be an expression of early stages of the neuropathy[19-21].

Degenerative non-inflammatory and inflammatory ENS neuropathies are two kinds of disinhibitory motor

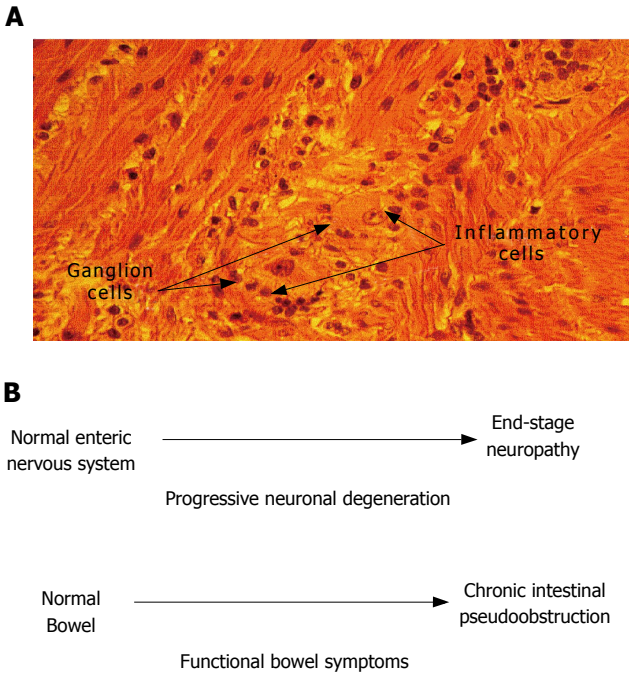

Figure 2 Enteric neuropathy underlies the pathophysiology in a subset of patients with functional gastrointestinal disorders. **A**: Idiopathic myenteric ganglionitis. Histology of the myenteric plexus in a full-thickness small intestinal biopsy taken during exploratory laparotomy for intestinal obstruction. A diagnosis of neuropathic pseudoobstruction was made on the basis of neuronal degeneration associated with an inflammatory infiltrate localized to the myenteric plexus. The patient had a multiple year history of complaints suggestive of IBS. Histological section and patient history courtesy of Dr. Claudio Fiocchi, The Cleveland Clinic, Cleveland, Ohio; **B**: Enteric neuronal degeneration and associated symptoms progress in parallel (e.g. symptoms of IBS). Most individuals start postnatal life with a normal ENS and normally functioning bowel. Neuronal degeneration mediated by autoimmune attack directed to the ENS (e.g. paraneoplastic syndrome, Chagas disease, idiopathic inflammatory neuropathy) can progress to a stage where ENS function is lost. Functional bowel symptoms appear and worsen as neurons are progressively lost from the ENS microcircuits required for integrated function of the whole organ. Chronic intestinal pseudoobstruction of the neuropathic form occurs when the loss of neurons progresses to a stage where the neuronal circuits for propulsive motility are no longer functional.

disorders that culminate in pseudoobstruction. Non-inflammatory neuropathies are classified as familial or sporadic[22]. In the former, the neuropathological findings include a marked reduction in the number of neurons in both myenteric and submucosal plexuses, and the presence of round, eosinophilic intranuclear inclusions in roughly 30% of the residual neurons. Histochemical and ultrastructural evaluations reveal the inclusions not to be viral particles, but rather proteinaceous material forming filaments that is are in some ways reminiscent of Alzheimer's disease in the brain[23,24]. Members of two families have been described with intestinal pseudoobstruction associated with the autosomal dominant form of ENS neuropathy[25,26]. The numbers of enteric neurons in these patients were decreased with no alterations found in the CNS or parts of the autonomic nervous system outside the gut.

Degenerative inflammatory ENS neuropathies are characterized by a dense inflammatory infiltrate confined to enteric ganglia. Paraneoplastic syndrome, Chagas disease and idiopathic degenerative disease are recognizable forms of pseudoobstruction related to inflammatory neuropathies.

Paraneoplastic syndrome is a form of pseudoobstruction where commonality of antigens between some forms of cancer cells (e.g. small-cell carcinoma of the lungs) and enteric neurons leads to autoimmune attack, which results in loss of neurons[27,28]. Most of the patients with symptoms of pseudoobstruction in combination with small-cell lung carcinoma express immunoglobulin-G autoantibodies that react with neurons in their ENS[29]. These antibodies react with molecules expressed on the nuclear membranes of neurons (e.g. Hu and Ri proteins) and with cytoplasmic Yo protein of Purkinje cells in the cerebellum[30,31]. Immunostaining with sera from paraneoplastic patients shows a characteristic pattern of staining in enteric neurons[30]. The detection of anti-enteric neuronal antibodies in the patient's serum establishes the specific diagnosis. The circulating antibodies damage the neurons by inducing apoptosis[32].

The association of enteric neuronal loss and symptoms of pseudo-obstruction in Chagas disease also reflects autoimmune attack on the neurons with accompanying symptoms that mimic the situation in sphincteric achalasia and paraneoplastic syndrome. *Trypanosoma cruzi*, the blood-borne parasite that causes Chagas disease, has antigenic epitopes similar to enteric neuronal antigens[33]. This antigenic commonality activates the immune system to assault the ENS coincident with its attack on the parasite.

Idiopathic inflammatory degenerative ENS neuropathy occurs unrelated to neoplasms, infectious conditions or other known diseases[32,34-38]. Patients have been described with early complaints of symptoms similar to IBS that progressively worsened and were later diagnosed as idiopathic degenerative inflammatory neuropathy based on full-thickness biopsies taken during exploratory laparotomy, which revealed chronic intestinal pseudoobstruction[20,35-38]. Each of these patients had inflammatory infiltrates localized to ganglia of the myenteric plexus. Sera from these patients contain antibodies against enteric neurons that are similar to those found in secondary inflammatory neuropathies (i.e. anti-Hu), but with different immunolabeling patterns characterized by prominent cytoplasmic rather than nuclear staining.

Recognition of the brain-like functions of the ENS leads to a conclusion that early neuropathic changes are expected to be manifest as symptoms that worsen with progressive neuronal loss. In diagnostic intestinal motility studies (e.g. manometry), degenerative loss of enteric neurons is reflected by hypermotility and spasticity[17] because inhibitory motor neurons are included in the missing neuronal population.

The observations in patients with autoimmune attack on the ENS suggest that early stages of an enteric neuropathy might be expressed as IBS-like symptoms. Early symptoms in these patients can be lower esophageal sphincter achalasia, which reflects loss of inhibitory innervation of the sphincter, and postprandial cramping abdominal pain and diarrhea. The disease in these individuals appears to progress from IBS-like symptoms to symptoms of chronic intestinal pseudoobstruction in parallel with progressive loss of neurons from their ENS (Figure 2).

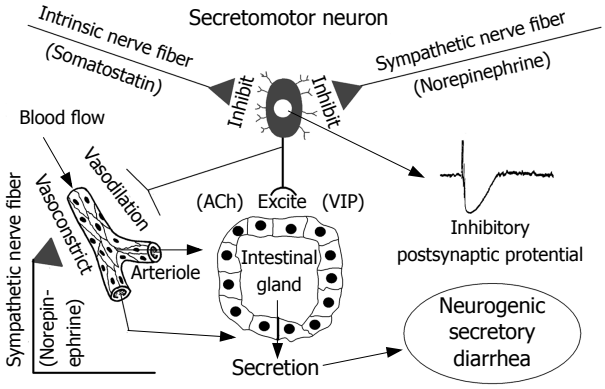

Figure 3 Intestinal secretory glands (i.e. crypts of Lieberkühn and Brunner's glands) are innervated by secretomotor neurons in the ENS. Neurotransmitters (e.g. ACh and VIP), which evoke secretion, are released at the neuro-epithelial junctions when secretomotor neurons fire. Axon collaterals to blood vessels simultaneously dilate submucosal vessels to increase blood flow in support of stimulated secretion. Noradrenergic input from the sympathetic nervous system and somatostatinergic input from intrinsic ENS neurons suppress firing of secretomotor neurons and thereby inhibit secretion. Factors that cause hyperactivity of secretomotor neurons enhance secretion and lead to neurogenic secretory diarrhea. In inflammatory states (e.g. ulcerative colitis and Crohn's disease) the release of inflammatory mediators elevates activity of secretomotor neurons leading to diarrhea. Certain pathogens and enterotoxins (e.g. cholera toxin and Clostridium difficille toxin A) activate secretomotor neurons to produce a diarrheal state. In food allergies, presence of sensitizing food antigens (e.g. shellfish, tree nuts) triggers mast cell degranulation and releases mediators such as histamine, serotonin and prostaglandins, all of which activate secretomotor neurons to evoke diarrhea. When secretomotor neurons are hypoactive, secretion is reduced, the liquidity of the intestinal contents is reduced and a state of constipation can follow. Activating opioid or somatostatinergic receptors (e.g. by opioid analgesics or octreotide) on secretomotor neurons inhibits their excitability and suppresses secretion.

NEUROGENIC SECRETION: DIARRHEA AND CONSTIPATION

Disordered defecation in IBS is related directly to the physiology of enteric secretomotor neurons. Secretomotor neurons are excitatory motor neurons in the submucosal plexus of the ENS, which innervate and stimulate secretion from the intestinal crypts of Lieberkühn, Brunner's glands and goblet cells (Figure 3).

Secretomotor neurons

Secretomotor neurons are uniaxonal with characteristic shapes described as Dogiel Type I and electrophysiological behavior like S-type enteric neurons[39-41]. When they fire, they release acetylcholine and vasoactive intestinal polypeptide at their junctions with the secretory epithelium. Collateral projections from the secretomotor axons innervate submucosal arterioles (Figure 3). Collateral innervation of the blood vessels links secretomotor activity in the glands to submucosal blood flow[42]. Active firing of secretomotor neurons releases acetylcholine simultaneously at neuroepithelial and neurovascular junctions. Acetylcholine acts at the blood vessels level to release nitric oxide from the endothelium, which in turn dilates the vessels and increases blood flow[42].

Secretomotor neurons have receptors that receive excitatory and inhibitory synaptic input from other neurons in the integrative circuitry of the ENS and from sympathetic postganglionic neurons (Figure 3)[43-45]. Secretomotor neuronal excitability is greatly influenced also by paracrine chemical messages from nonneural cell types in the mucosa and submucosa (e.g. enterochromaffin cells, mast cells and other kinds of immune/inflammatory cells). Activation of the excitatory receptors on secretomotor neurons stimulates the neurons to fire and release their transmitters at the junctions with the secretory glands and regional blood vessels. The overall result of secretomotor neuronal firing is stimulation of the secretion of H_2O, NaCl, bicarbonate and mucus from the intestinal glands into the intestinal lumen[46,47].

Inhibitory input to secretomotor neurons

Inhibitory inputs from other neurons hyperpolarize the membrane potential of secretomotor neurons and this decreases the probability of firing (Figure 3). The physiological effect of inhibiting secretomotor firing is suppression of mucosal secretion. Postganglionic neurons of the sympathetic nervous system are an important source of inhibitory input to the secretomotor neurons. Norepinephrine released from sympathetic nerve terminals in the submucosal plexus acts at alpha2 noradrenergic receptors to inhibit firing of the secretomotor neurons. Inhibition of secretomotor firing reduces the release of excitatory neurotransmitters at the junctions with the secretory epithelium. The end result is reduced secretion of water and electrolytes. Suppression of secretion in this manner is part of the mechanism involved in sympathetic nervous shut-down of gut function in homeostatic states where blood is shunted from the splanchnic to systemic circulation.

Neurogenic secretory diarrhea and neurogenic constipation

Knowledge of the neurobiology of submucosal secretomotor neurons is necessary for understanding the pathophysiology of secretory diarrhea, as well as constipation. In general, secretomotor hyperactivity is associated with neurogenic secretory diarrhea; hypoactivity is associated with decreased secretion and a constipated state. Suppression of secretomotor firing by antidiarrheal agents (e.g. opiates, clonidine and somatostatin analogs) is manifest as harder-drier stools. Stimulation by chemical mediators, such as vasoactive intestinal peptide (VIP), serotonin and histamine, is manifest as more liquid stools.

Watery diarrhea may be caused by several different pathophysiological events. For example, secretomotor neurons may be overly stimulated by circulating VIP released from VIPomas, excessive serotonin release from mucosal enterochromaffin cells or histamine release from inflammatory/immune cells in the mucosa/submucosa[48]. Release of histamine or other inflammatory mediators associated with diarrhea not only stimulates the firing of secretomotor neurons, but also simultaneously acts at presynaptic inhibitory receptors to suppress the release of norepinephrine from the postganglionic sympathetic axons that provide inhibitory input to secretomotor neurons[44,48]. Two pathological factors are therefore involved in the production of neurogenic secretory diarrhea. One is over

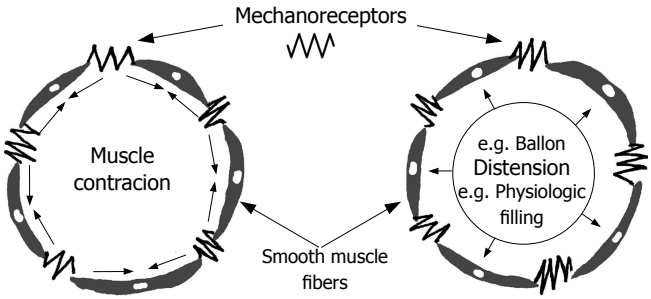

Figure 4 Mechanoreceptors are connected "in-series" with the long axes of the smooth muscle fibers that form the intestinal circular muscle layer. Either contraction of the muscle or distension of the intestinal wall "stretches" the receptors and evokes firing of impulses in the sensory afferent fibers connected to the receptor. Firing frequency of the receptor increases in direct relation to the amount of "stretch" or, in some receptors, the rate at which the length changes. Mechanosensory information generated in this manner is transmitted by spinal afferents to the spinal cord or vagal nerve afferents to the dorsal vagal motor complex in the brain stem.

stimulation of secretomotor neuronal firing and the other is presynaptic suppression of norepinephrine release from sympathetic postganglionic neurons. Presynaptic suppression of norepinephrine removes the sympathetic braking action from the neurons (Figure 3).

Excitatory Input to secretomotor neurons

Secretomotor neurons have excitatory receptors for several neurotransmitters, which include acetylcholine, VIP, substance *P* and serotonin[49]. One of the serotonergic receptors belongs to the 5-HT_3 receptor subtype[50].Efficacy of blockade of 5-HT_3 receptors by a 5-HT_3 antagonist in the treatment of diarrhea in the diarrhea-predominant population of women with IBS[51,52] suggests that hyperstimulation of secretomotor neurons by serotonin is a significant factor in this form of IBS. Observations that IBS symptoms of cramping abdominal pain, diarrhea and fecal urgency are commonly exacerbated in the postprandial state[7,53] and evidence for elevated postprandial release of serotonin[54,55] suggests that overactive release of serotonin from the enterochromaffin cell population might underlie the diarrheal symptoms of IBS. This is reinforced by suggestions of elevated numbers of serotonin-containing enterochromaffin cells and also mast cells in the mucosa of IBS patients[56-58].

ABDOMINAL PAIN AND DISCOMFORT

Primary causes of abdominal pain of digestive tract origin are distension and excessively strong muscular contractions. Stimuli, such as pinching and burning of the mucosa applied *via* fistulae, do not evoke pain. Hypersensitivity of the sensory mechanoreceptors for stretch (distension) and contractile force are implicated as pain factors in IBS. Hypersensitivity to distension is present in a substantial subset of IBS patients[59-62]. Filling of a balloon placed in the recto-sigmoid region evokes sensations of discomfort and pain at lower distending volumes for IBS patents than for normal subjects. Hypersensitivity of this nature to distension is not restricted to the distal bowel. Patients, who are diagnosed with functional dyspepsia, also experience more discomfort and pain at lower distending volumes in the stomach than normal subjects[63,64] and hypersensitivity to distension is present in the esophagus of patients with non-cardiac chest pain[65].

IBS patients experience the same kind of hypersensitivity to electrical stimulation applied to the lining of the recto-sigmoid region as they do during balloon distension in the recto-sigmoid[66]. This hypersensitivity to direct electrical stimulation of the intramural sensory innervation implicates abnormal sensory neurophysiology rather than mechanical factors (e.g. wall tension and compliance) as underlying the decreased sensory thresholds present in IBS patients. Identification of the sensory defect in IBS continues as an area of active investigation and is yet to be elucidated convincingly. The lower sensory threshold in IBS might reflect: (1) sensitization of intramural mechanoreceptors; (2) sensitization of neurotransmission at synapses in the spinal cord; (3) abnormal processing of the sensory information when it reaches the brain; (4) combinations of each of these possibilities.

Peripheral neuropathological factors

Mechanosensitive primary sensory afferents in the walls of the specialized organs of the digestive tract detect and signal contraction and distension of the musculature. The mechano-sensing structures at the afferent terminals behave as if they are attached "in-series" with the long axes of the smooth muscle fibers (Figure 4). This arrangement accounts for activation of the sensors by either muscle contraction or distension. The cell bodies of the neurons that give rise to intestinal afferents are located in vagal nodose ganglia and dorsal root spinal ganglia. Mechanosensitive information is transmitted along spinal afferents to the spinal cord by way of dorsal root ganglia and along vagal sensory afferents to the brain stem by way of the nodose ganglia and synaptic relays in the nucleus tractus solitarius.

Vagal and spinal afferent fibers are predominantly unmyelinated C-fibers or thinly myelinated A δ -fibers each of which transmits different modalities of sensory information at low conduction velocity. In general, vagal afferents transmit sensory information on the nature and composition of the luminal contents, the presence or absence of motility and on contractile tension in the musculature. Spinal afferents transmit mechanosensitive information and pathophysiological information related to potentially noxious mechanical or chemical stimuli arising through tissue injury, ischemia or inflammation. Sensations of pain and discomfort of digestive tract origin reflect transmission in spinal afferents and information processing in the spinal cord and brain. Sensory information transmitted by the vagus nerves appears not to reach the level of conscious sensation because patients with high spinal cord transections and intact vagal pathways experience little or no sensations of digestive tract origin. On the other hand, conscious perception of sensations from the digestive tract remains following a surgical vagotomy. This presumably reflects transmission over spinal afferents to the spinal cord and onward to conscious centers in the brain.

The barrage of mechanosensory information, which is

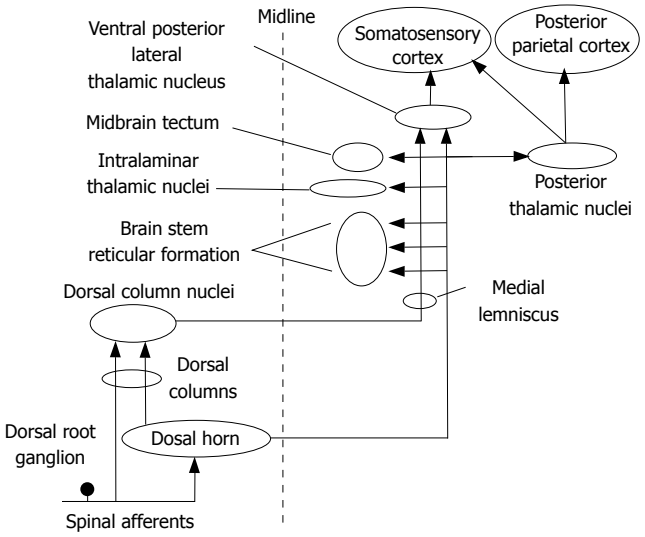

Figure 5 Visceral nociceptive information is transmitted along multiple ascending spinal pathways to multiple processing centers in the brain. Projection pathways in the dorsal spinal columns transmit information from tactile receptors in the skin and visceral pain from nociceptors in the bowel.

transmitted from the small and large intestine to the CNS is generated by three kinds of sensory afferents known as low-threshold, high-threshold and silent afferents[67]. Low-threshold afferents, which code small changes in wall tension, are thought to transmit the minute-to-minute information required for functional autonomic negative-feedback control during contractile events. High-threshold afferents require stronger changes in wall tension, which might be produced by distension of the lumen or strong contraction of the musculature, in order to be activated. The high-threshold afferents are postulated to be responsible for the range of sensations from mild to severe pain that are associated with excessive distension or exceptionally strong muscle contraction. Silent afferents cannot be activated by distension when the bowel is in its normal state. They take on pathophysiological significance by becoming active and highly sensitive to stimuli during inflammatory states[68,69].

Postinfectious IBS

A significant percentage of patients develop IBS-like symptoms following an acute bout of infectious enteritis[70-73]. Hypochondriasis and adverse life events during the infectious episode are reported to double the risk for development of postinfective IBS[70]. Nevertheless, the question of whether the association between acute infectious enteritis and IBS reflects low-level inflammation (e.g. microscopic enteritis) and chronic exposure of the neural and glial elements of the ENS to elevated levels of serotonin, histamine or other inflammatory mediators remains to be fully resolved.

Serotonin receptors on sensory afferents

Application of exogenous 5-HT evokes increased firing in extrinsic afferents and this is mediated by 5-HT_3 receptors that can be blocked by selective 5-HT_3 receptor antagonists (e.g. alosetron)[74,75]. Intramural terminals of both spinal and vagal sensory nerves express 5-HT_3 receptors. Reported efficacy of alosetron in the treatment of abdominal pain and discomfort in the diarrhea-predominant form of IBS in women suggests that these symptoms might reflect over-active endogenous release and elevated levels of 5-HT[51,76].

Persistence of 5-HT at its receptors, due to a defective serotonin transporter, is a second possibility for hyperstimulation of intramural serotoninergic receptors. Active uptake mediated by the serotonin transporter, which is expressed by enteric neurons and mucosal epithelial cells, restricts accumulation and action of 5-HT at its receptors following its release[77]. Down regulation of both transporter mRNA expression and expression of immunoreactivity for the serotonin transporter were reported to be present in mucosal biopsies taken from the large intestine of IBS patients[78]. Watery stools and enhanced propulsive motility occurred in mice with a deletion in the serotonin transporter gene and the mice were reported to sometimes alternated between diarrhea and constipation in a way reminiscent of the subset of IBS patients that are classified as "alternators"[79].

Receptors for inflammatory mediators on sensory afferents

Aside from the 5-HT_3, receptors for bradykinin, ATP, adenosine, prostaglandins, leukotrienes, histamine and mast cell proteases are expressed on spinal sensory nerve terminals[67,80]. Any one of these mast cell or ischemia-related mediators has potential for elevating the sensitivity of intestinal sensory nerves, especially in the disordered conditions of inflammation or ischemia. This suspicion is reinforced by findings that a reduced threshold for painful responses to balloon distension in the large bowel is associated with degranulation of mast cells in animal models. Treatment with mast cell stabilizing drugs prevents lowering of the pain threshold, which occurs during mucosal inflammation in the animal models[81], and suggests that mast cell stabilization might turn out to be an efficacious treatment in human IBS[82,83].

Central neuropathological factors

Much of the evidence suggests altered peripheral sensory transduction as the underlying factor for the exaggerated sensitivity to distension found in IBS patients[84]. In this scenario, mechanosensitive primary afferents in the gut wall become hypersensitive to mechanical stimuli and as a result transmit at elevated frequencies of firing that is interpreted in the CNS as nociceptive information. In an alternative scenario, normally functioning mechanoreceptors transmit accurate information, which is then misinterpreted in processing circuits in the spinal cord and/or brain to evoke conscious perceptions of disordered sensations from the gut.

Ascending sensory pathways in the spinal cord

Ascending spinal pathways involved in the transmission of nociceptive signals from the digestive tract are the spinothalamic, spinohypothalamic, spinosolitary, spinoreticular, and spinoparabrachial tracts (Figure 5). Visceral pain information is also transmitted to higher

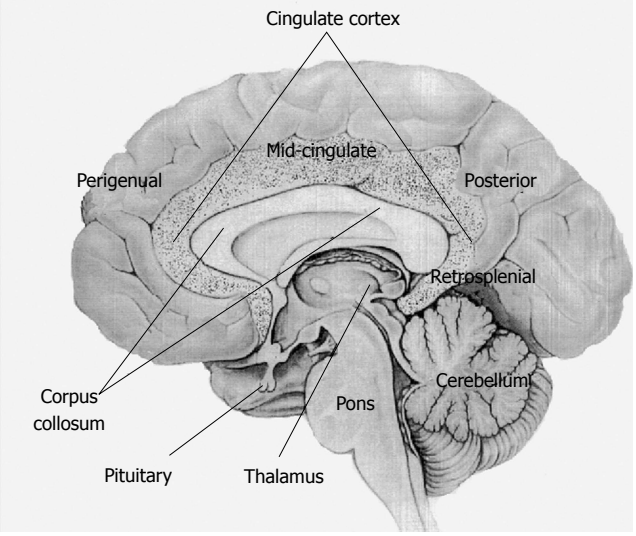

Figure 6 Conscious perception of visceral sensations emerge from the cingulate region of the cerebral cortex. Medial view of the brain showing organization of the cingulate cortex. Perigenual, midcingulate, posterior and retrosplenial are important structural and functional regions of the cingulate cortex with the following properties: (1) Perigenual anterior cingulate cortex surrounds the rostral portion of the cingulate cortex and is primarily involved in affect with a subsector devoted to visceromotor control *via* projections to the cranial parasympathetic and spinal sympathetic divisions of the autonomic nervous system. (2) Midcingulate cortex is involved in response selection and motivation and has a skeletomotor control subsector with neurons that project directly to the spinal cord. (3) Retrosplenial cingulate cortex is associated with memory recall. (4) Posterior cingulate cortex overlays the entire surface of the cingulate gyrus and has a caudomedial subsector that overlaps with the retrosplenial cingulate cortex. The retrosplenial cingulate cortex and posterior cingulate cortex are both involved in memory and activation of the caudomedial sector of the posterior cingulate cortex during memory of emotional events (e.g. emotional events associated with affect and gut function) provide an important framework for assessment of visceral function and disorder in brain imaging studies.

processing centers in the brain *via* pathways in the dorsal spinal columns[85,86-90]. Spinal afferents, which transmit nociceptive information, connect synaptically with second order neurons in the dorsal column nuclei (i.e. nucleus gracilis and nucleus cuneatus). Second order neurons in the spinal dorsal horn also provide input to the dorsal column nuclei (Figure 5). The pain signals are transmitted upward *via* the ipsilateral dorsal column nuclei to the contralateral ventroposterolateral nucleus of the thalamus[85,90-92]. Dorsal column transmission is now considered to be more important than the spinothalamic and spinoreticular tracts in visceral nociceptive transmission.

A midline myelotomy, which severs axons in the human dorsal columns, attenuates otherwise intractable visceral pain[87,90]. Stimulation of the dorsal columns in patients with severe IBS evokes an immediate increase in the intensity of their abdominal pain[93]. These observations in humans are consistent with experimental results in animals. Severing the axons of the dorsal columns in rats or monkeys reduces the neuronal responses to colorectal distension in the ventral posterolateral nucleus of the thalamus and of neurons in the dorsal column nuclei, particularly in the nucleus gracilis[86,88].

Sensory processing in the cerebral cortex

Methods of brain imaging offer another investigative modality for addressing questions related to abnormal processing of sensory information in the cerebral cortex of IBS patients[84,94-96]. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are now commonly used to study information processing in the higher brain centers that underlie an individual's experience of conscious sensations.

Results from imaging studies suggest that unlike somatic sensation, which has a main homuncular representation in the primary somatosensory cortex, visceral sensation is mainly represented in the secondary somatosensory cortex[96,97]. Differences in processing in these specialized regions might account for the vagueness of an individual's ability to localize visceral sensation in relation to somatic sensation. Beyond the sensory cortices, fMRI and PET images show representation of both somatic and visceral sensation to be similar in the limbic and paralimbic regions of the cortex (e.g. anterior insular, anterior and posterior cingulate, prefrontal and orbitofrontal cortices[94,95]. These areas are known to be involved in the individual's motivational and emotional mood states and in the cognitive components of visceral sensations.

Gender differences, reminiscent of those found in IBS, are seen in the cortical representation when a balloon is distended in the recto-sigmoid region in healthy subjects[98]. Activation in the sensory/motor and parieto-occipital areas does not differ between genders. On the other hand, more extensive activation appears in the anterior cingulate and prefrontal cortices in females than in males. The volume of evoked cortical activity in females is greater than in males for perception levels in the range from the urge to defecate to sensations of fullness, mild discomfort and pain. Significance of these gender differences is unclear; nevertheless, they are reminiscent of the greater perceptual responses reported in female patients with functional gastrointestinal disorders (e.g. IBS)[99].

In healthy subjects, painful sensations evoked by distension of a balloon in the recto-sigmoid region or the anticipation of a potentially painful distension are associated with increased blood flow in the anterior cingulate cortex (Figure 6). In IBS patients, activation of the anterior cingulate cortex was reported not to occur in response to painful distension or the anticipation of painful distension[94,100]. On the other hand, an fMRI study found that patients with IBS showed enhanced activation of the mid-cingulate cortex in response to rectal distension[101]. Selective activation of the pre-frontal cortex appeared to take place coincident with decreased activation of the anterior cingulate cortex in another study[94]. Attention is focused on the cingulate cortex because it is generally thought to be an integrative center for both emotional experience and specific representation for pain that might account for the linkage between pain and emotional state. This cortical region is formed around the rostrum of the corpus callosum and has projections into the motor regions of the cortex (Figure 6). The "affective" areas of the cingulate cortex have extensive connections with the amygdala and periaqueductal gray matter and with autonomic nuclei in the brain stem[102]. This connectivity integrates autonomic and endocrine functions and recall of

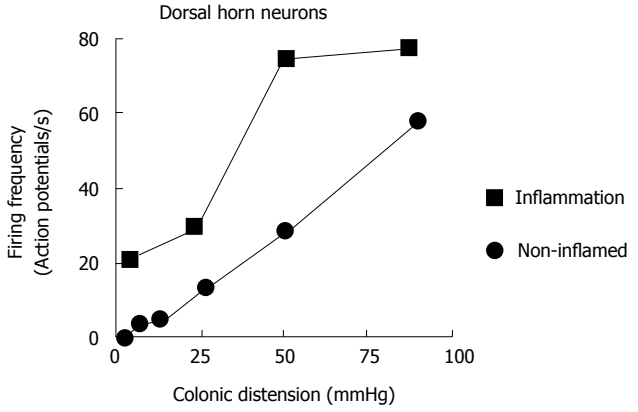

Figure 7 Firing frequency of neurons in the dorsal horns of the spinal cord in response to distension of the colon is increased during experimentally induced inflammation of the colon in rats. Increased sensitivity is reflected by a decreased firing threshold and increased gain (increased slope) of the relation of firing frequency to degree of distension. Data extracted from Cervero and Laird[177].

emotional experiences. Cognition is believed to reside in the caudal portion of the anterior cingulate cortex where the microcircuits are delegated to premotor functions and processing of nociceptive information.

The functional neuroanatomy of the cingulate cortex offers an explanation for the well documented association of psychosocial disturbances (e.g. negative life events) with more severe cases of IBS[99]. Rectal distension in persons with histories of severe sexual and/or physical abuse has been reported to selectively activate the perigenual region of the anterior cingulate cortex (Figure 6). One case report described a middle-aged female whose low pain threshold for rectal distension and diarrhea-predominant IBS improved after she was extricated from an abusive psycho-social situation. Brain imaging with fMRI in this individual showed activation of the mid-cingulate cortex during rectal distension prior to treatment and resolution of activation associated with improvement in the patient's psycho-social situation[103].

Sensory processing in the spinal cord

Nociceptive afferents, which do not project to dorsal column nuclei, terminate in the dorsal horn of the spinal cord. They form synapses with second order nociceptive neurons that are located mainly in laminae Ⅰ & Ⅱ. Most of the neurons in laminae Ⅰ & Ⅱ receive direct synaptic input from A-delta and nonmyelinated C-fibers. Large numbers of neurons in lamina Ⅰ respond exclusively to noxious stimulation and project the information to higher brain centers (Figure 5).

Central sensitization ("wind-up")

Elevated excitability in nociceptive dorsal horn neurons underlies spinally mediated hyperalgesia, which is termed central sensitization to distinguish it from sensitization that occurs at nociceptive terminals in the periphery. In conditions of severe tissue injury and persistent injury, nociceptive C fibers fire repetitively and the excitability of the second order neurons in the dorsal horn increases progressively in response to the elevated synaptic input. This effect is sometimes called "wind-up" and reflects the synaptic release of glutamate from the incoming C-fibers and activation of N-methyl-D-aspartate (NMDA)-type glutamate receptors expressed by the second order neurons. These long-lasting changes in the excitability of dorsal horn neurons are like a memory imprint of the nociceptive input. Accumulating evidence suggests that the spinal wind-up phenomenon may be operational and be an underlying factor in the intestinal hypersensitivity associated with IBS.

One piece of the suggestive evidence for wind-up hypersensitivity is the finding that second order neurons in the dorsal horn show induction of the early gene c-fos in response to noxious balloon distension of the colon in rats[104]. Changes in gene expression in this case are expected to underlie postsynaptic excitability changes in the second order nociceptive neurons. A related phenomenon occurs in the rat spinal cord where excitability of second order nociceptive neurons become sensitized to distension-evoked input following inflammation of the colon produced by application of acid to the mucosa (Figure 7). The same phenomenon is evident in dorsal column nuclei where firing of second order neurons to colo-rectal distension becomes sensitized following inflammation of the colon evoked by application of mustard oil to the mucosa[105]. These effects of inflammation are characterized by a decrease in threshold and an increase in firing rate of the neurons in the dorsal horn and dorsal column nuclei in response to distension of the large intestine. This is believed to reflect central sensitization secondary to peripheral sensitization and elevated firing of sensory nerve terminals in the inflamed intestinal wall.

In a study, which is reminiscent of the connection between sexual and physical abuse in early childhood and IBS in adult humans, Al-Chaer *et al*[106] reported that central sensitization may also be induced in animal models in the absence of inflammation. Neonatal rats in this study were subjected daily to noxious colo-rectal distension or intracolonic injection of mustard oil beginning 8 d postpartum and lasting for 21 d. When tested in adulthood, the rats that were "abused" as neonates were hypersensitive to colo-rectal distension as reflected by a lower threshold and elevated intensity of reflex responses indicative of abdominal pain. Single-unit electrophysiological recording from dorsal horn neurons in the lumbar and sacral regions of the spinal cord of the adult animals found significantly higher background firing frequencies in the animals that were "abused" as neonates and enhanced firing frequencies in response to colo-rectal distension when compared with non-abused controls. Histological examination found no evidence of an inflammatory state in the large intestine in either the adult "abused" animals or their controls in these studies.

Limited evidence for central sensitization to distension of the large bowel has been obtained for humans, who meet diagnostic criteria for IBS[61]. In IBS patients, repetitive inflation of a balloon in the sigmoid colon, to noxious levels of stimulation, alters the processing of afferent information entering the spinal cord from the rectum. Altered central processing appears to be present in IBS patients and not in normal subjects. The

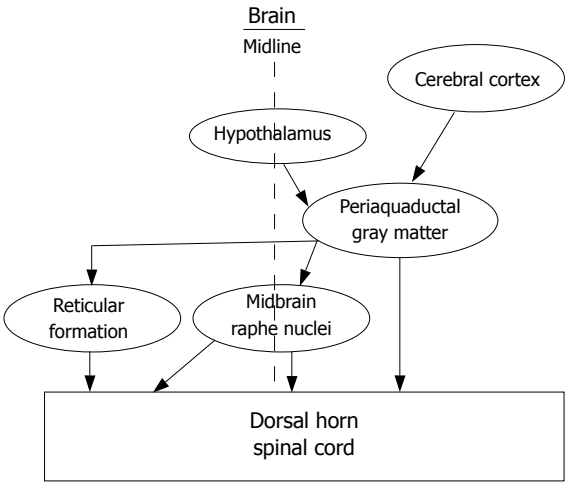

Figure 8 Multiple descending pathways from integrative centers in the brain project to the dorsal horn of the spinal cord where they release neurotransmitters that modulate the transmission of nociceptive signals after entry into the spinal cord.

altered central processing in human IBS is reflected by development of hyperalgesia in response to rectal distension and spontaneously developing hyperalgesia over an extended period of time in the recto-sigmoid region in the absence of any further application of the repetitive distension protocol.

Descending spinal modulatory pathways

Processing of incoming nociceptive signals in the spinal cord is subject to descending modulatory influences from supraspinal structures in the brain (e.g. periaqueductal gray, nucleus raphe magnus, nuclei reticularis gigantocellularis, and the ventrobasal complex of the thalamus) (Figure 8). The descending modulatory activity can be either inhibitory, facilitatory or both depending on the context of the visceral stimulus or the intensity of the descending neural activity. The descending pathways, which originate in the brainstem and higher centers, influence the processing of nociceptive signals from the bowel within the microcircuitry of the dorsal horn of the spinal cord. These descending pathways release serotonin and noradrenalin and to a lesser extent dopamine as neurotransmitters at their synapses in the spinal cord.

Descending modulation of visceral nociceptive processing at the spinal cord level is ongoing and includes both inhibitory and facilitative influences on synaptic transmission in the dorsal horn microcircuits. Experimental data, which correlate behavioral responses and neuronal electrical and synaptic behavior, suggest that activity in descending modulatory pathways influences neuronal activity at the spinal cord level and the behavior of individuals experiencing acute and persistent pain[107]. The descending modulation includes facilitative and inhibitory influences both of which can alter the sensing of pain of gut origin.

Electrical stimulation or chemical activation (i.e. intracerebral injection of neurotransmitters or blocking drugs) of several different supraspinal centers modulates the neuronal and behavioral responses to visceral stimuli. For example, nociceptive responses to intraperitoneal injection of hypertonic saline in rats are attenuated by electrical stimulation in the periaqueductal gray matter[108]. Chemically-induced activation of neuronal cell bodies in the rostro-ventral medulla also attenuates responses to visceral stimulation[109,110]. Electrical stimulation or microinjection of glutamate into the periaqueductal gray matter, nucleus raphe magnus or the nuclei reticularis gigantocellularis suppresses spinal dorsal horn neuronal responses to visceral afferent fiber stimulation and to noxious colo-rectal distention[111-113]. The descending inhibition from the rostro-ventral medulla travels along pathways in the dorsolateral spinal cord[114]. Electrical stimulation of the ventrobasal complex of the thalamus suppresses the responses of dorsal horn neurons to colorectal distension in normal rats[115].

Sensory visceral input to the dorsal horn is also subject to descending facilitative modulation. Descending facilitation might enhance conscious perception of the bowel in the absence of any noxious stimulation and could possibly explain the hypersensitivity often reported to be present in IBS. Several lines of evidence support the presence of tonic descending facilitative influences in animals. In cats, reversible blockade of descending pathways by cervical cooling suppresses the responses of a subset of visceral neurons to stimulation of the splanchnic nerves[116]. Zhuo and Gebhart[114] investigated the effects of electrical or chemical stimulation in the rostro-ventral medulla on reflex contractions of the abdominal musculature of the rat in response to noxious colo-rectal distension. Reflex contraction of the abdominal musculature in response to colorectal distension in this kind of study is regarded as a measurable perimeter for assessment of severity of visceral pain in this rat model. When applied at 22 different sites in the rostro-ventral medulla, electrical stimulation facilitated the reflex responses to noxious distension at low stimulus intensities of 5, 10, and 25 μA and suppressed the reflex responses at stimulus intensities greater than 50 μA. Electrical stimulation at all intensities tested (5-200 μA) in other sites in the rostro-ventral medulla only inhibited or only facilitated reflex responses to noxious colorectal distention. Microinjection of glutamate into the rostro-ventral medulla mimics the findings for electrical stimulation. Reversible spinal blockade by injection of lidocaine or irreversible transection of spinal funiculi revealed that descending facilitatory influences from the rostro-ventral medulla were transmitted in the ventrolateral/ventral funiculus and descending inhibitory influences were carried by the dorsolateral funiculi. Descending modulation, whether inhibitory or facilitative, is linked to a reflex response to noxious stimulation; neither electrical stimulation nor glutamate injection alters contractile behavior of the abdominal musculature in the absence of colorectal distension.

Intestinal motility and abdominal pain

Strong contractions of the intestinal circular muscle coat during intestinal power propulsion (Figure 9) underlie the sensation of cramping abdominal pain[21,117]. Power

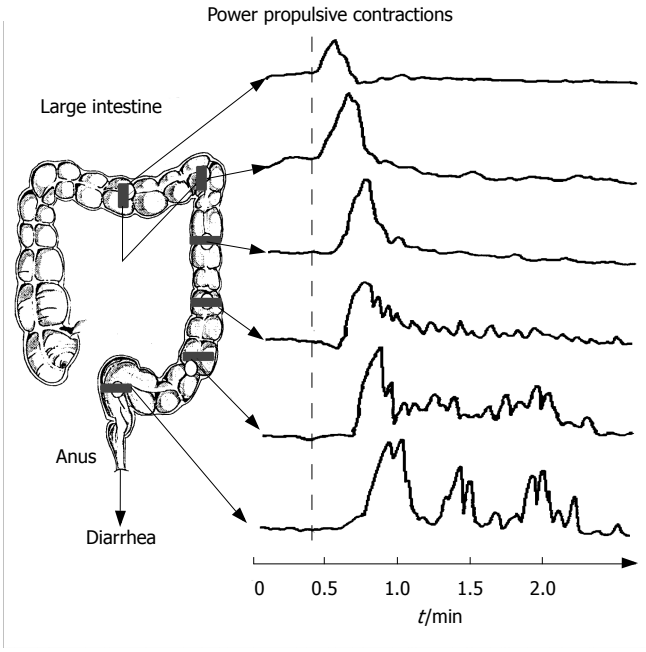

Figure 9 Power propulsion is a protective response to the presence of food allergens or other threatening agents in the intestinal lumen. It is an ENS programmed motility pattern that can be recorded with sensors (e.g. force transducers) as strong, long lasting contractions of the circular muscle that propagate rapidly for extended distances along the intestine. Power propulsion quickly strips the lumen clean as it travels along extended lengths of intestine. Abdominal cramping, urgency, diarrhea and threat of incontinence are associated with this motor program. Application of irritants to the mucosa, the introduction of luminal parasites, enterotoxins from pathogenic bacteria, allergic reactions and exposure to ionizing radiation each can trigger the propulsive motor program.

propulsion, which is one of the patterns of motility stored in the program library of the ENS, occurs more frequently in IBS patients than in normal subjects and the circular muscle contractions are significantly stronger than normal in IBS patients[53]. Postprandial power propulsion is more prevalent in the colon of IBS patients than in normal individuals and power propulsion in the colon is often associated with their diarrhea[48].

Power propulsion in the large intestine generally starts in the proximal colon and strips the lumen clean as it travels rapidly toward the recto-sigmoid region (Figure 9). In diarrheal states, 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. Relaxation of the internal anal sphincter and conscious need for contraction of the external sphincter and puborectalis muscle occur at this time coincident with the sensation of urgency and concern about incontinence. The sensation of urgency is derived from mechanosensory information transmitted to the CNS along spinal afferents from the recto-sigmoid region and pelvic floor musculature.

The pain and discomfort in IBS patients during the powerful contractions of power propulsion may be explained in three ways, either separately or in combination. One explanation is for the exceptionally powerful circular muscle contractions to activate high-threshold mechanoreceptors that transmit the information centrally where it is processed and projected to consciousness as the perception of pain and discomfort. A second is for the mechanoreceptors to become sensitized in the IBS patients (e.g. by inflammatory mediators or other paracrine signals) and send erroneously coded information to processing centers in the spinal cord and brain. A third explanation is for accurately coded sensory information carried by spinal afferents to be mis-interpreted as it is decoded in the spinal cord and central processing centers of the brain.

PSYCHOGENIC STRESS

Psychological stress and negative life experiences are recognized as exacerbating psychosocial factors in IBS[5,99,100,103,118]. Stress often exacerbates symptoms of cramping abdominal pain, diarrhea and urgency in IBS patients. These stress-exacerbated symptoms in IBS are similar, if not identical, to the abdominal pain, diarrhea and urgency associated with enteric allergic responses, infectious enteritis, radiation-induced enteritis and noxious mucosal irritation (e.g. senna laxatives). Recent advances in the basic science of brain-to-gut and immune cells-to-ENS signaling have introduced fresh insight into mechanisms underlying the effects of psychological stress on the intestinal tract.

Neuro-immunophysiological paradigm for IBS-Like symptoms

The human enteric immune system is developed at birth and is colonized by populations of immune/inflammatory cells that will change continuously in response to luminal conditions and pathophysiological states throughout the individual's lifetime. The enteric immune system is positioned to provide security at one of the most contaminated borders between the interior of the body and the outside world. It deals continuously with dietary antigens, parasites, bacteria, viruses, and toxins as they appear in the warm-dark-moist-anaerobic environment of the intestinal lumen. The system is continuously challenged because physical and chemical barriers at the epithelial interface never exclude the large antigenic load in its entirety. Furthermore, stress in the form of threatening environmental conditions in animal models or handling of the gut during laparotomy in humans opens the barrier[119-121].

Immuno-neural crosstalk

Insight into how chemical communication between the mucosal immune system and the ENS takes place is derived from electrophysiological recording in enteric neurons in intestinal preparations from animal models after sensitization to foreign antigens[122-124]. Signals from enteric immune/inflammatory cells activate 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. The signaling mechanism is chemical in nature (i.e. paracrine) and incorporates specialized sensing functions of intestinal mast cells for foreign antigens together with the capacity of the ENS for intelligent interpretation of antigen-evoked mast cell signals[16,48,125]. Immuno-neural integration starts with immune detection and progresses sequentially

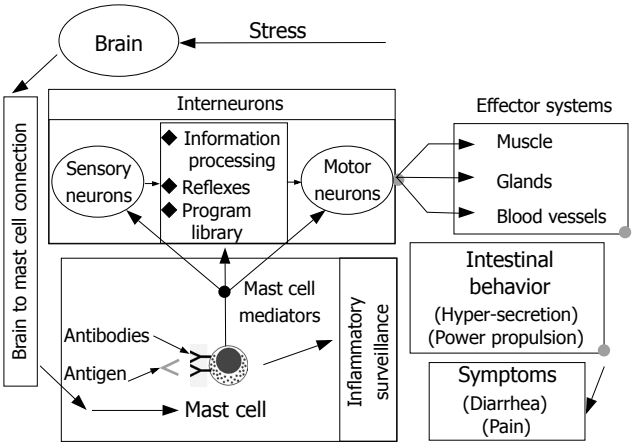

Figure 10 Heuristic model for brain-gut interaction in response to stress. The ENS is a minibrain located in close apposition to the gastrointestinal effectors it controls. Enteric mast cells are positioned to detect foreign antigens and signal their presence to the ENS. When, stimulated mast cells release several paracrine mediators simultaneously. Some of the mediators signal the ENS while others act as attractant factors for polymorphonuclear leukocytes responsible for acute inflammatory responses. The ENS responds to the mast cell signal by initiating 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 result from operation of the defense program. Neural inputs to enteric mast cells from the brain 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 this brain-to-mast cell connection.

with 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 (i.e. power propulsion, see Figure 9) that effectively clears the threat from the intestinal lumen. IBS-like symptoms of cramping lower abdominal pain, fecal urgency and watery diarrhea reflect operation of the immuno-neural defense program.

Sources of immuno-neural signals

Lymphoid and myeloid cells colonize the gastrointestinal tract in numbers that continuously fluctuate with changing luminal conditions and pathophysiological states[126]. Cell types including polymorphonuclear leukocytes, lymphocytes, macrophages, dendrocytes and mast cells are present in continuously varying numbers in the intestinal mucosa, lamina propria and smooth muscle and are potential sources of immuno-neural signals. Each of these cell types can be situated in close histoanatomical association with the neuronal elements of the ENS, vagal nerve fibers and spinal sensory nerves[56,58,127-130].

Signaling from the cells of the enteric immune/inflammatory system to the ENS establishes a first line of defense against foreign invasion at the vulnerable interface of a single epithelial cell barrier between the body and the outside environment. In inflammatory states, close histoanatomical proximity of elevated numbers of lymphocytes and polymorphonuclear leukocytes to enteric nerve elements suggests that inflammatory mediators released by these cells might access and influence the ENS. Electrophysiological studies in enteric neurons confirm that inflammatory mediators released in paracrine fashion alter electrical and synaptic behavior of enteric neurons[122-124].

Enteric mast cells

All kinds of immune/inflammatory cells are putative sources of paracrine signals to the ENS. Most is known, however, about signaling between enteric mast cells and the neural elements of the ENS. Enteric mast cells are packed with granules that are sites of storage for a broad mix of preformed chemical mediators. Antigens stimulate the mast cells to release the mediators, which then diffuse into the extracellular space inside the ENS. Enteric mast cells express high affinity receptors for IgE antibodies or other immunoglobulins on their surfaces. A deluge of multiple 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 10).

Infections with nematode parasites stimulate proliferation of intestinal mast cells in animal models[127,131]. These nematode-infected models and food allergic models have been valuable for studies of mast cell involvement in enteric immuno-neural communication. In the sensitization models, a second exposure to antigen isolated from the infectious agent (e.g. intestinal nematode) or to a food antigen results in predictable protective integration of intestinal motor and secretory behavior[119,132-135]. Recognition of the antigen by antibodies bound to the sensitized mast cells triggers degranulation and release of the mast cell's mediators. Once released, the mediators become paracrine signals to the ENS, which responds by suspending operation of other programs in its library and running a defense program designed to eliminate the antigen from the lumen. Copious secretion and increased blood flow followed by orthograde power propulsion of the luminal contents are the behavioral components of the program. Abundant evidence supports a hypothesis that mast cells are equipped and strategically placed to recognize foreign agents that threaten whole body integrity and to signal the ENS to program a defensive response, which expels the threat. The immuno-neural defensive program in the lower half of the intestinal tract is reminiscent of the emetic program, which provides a similar defense for the upper gastrointestinal tract.

Mast cell function in immuno-neural communication is an immune counterpart of sensory detection and information coding in sensory neurophysiology. In sensory physiology, sensory neurons are genetically programed to express detection mechanisms for specific stimuli (e.g. touch, temperature or light), which 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 of specific antibodies by the immune system. Detection specificity for foreign antigens is acquired and reinforced throughout life due to formation of new antibodies that bind to and occupy 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 brain and spinal cord. 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 and the brain-gut connection

Aside from their sensing function, enteric mast cells provide a connection node between the CNS and ENS. This is a brain-gut interaction in which central psychological status can be linked to irritable states of the digestive tract by way of mast cell degranulation and release of mediators. Mast cell degranulation evoked by psychological stress activates the ENS "defense program" to produce the same symptoms of diarrhea and abdominal distress as antigen-evoked degranulation. Evidence for a brain-mast cell connection appears in reports of Pavlovian conditioning of enteric mast cell degranulation[136]. Release of mast cell proteases into the systemic circulation and intestinal lumen is a marker for degranulation of enteric mucosal mast cells. Release of proteases into the circulation occurs as a conditioned response in laboratory animals to either light or auditory stimuli after pairing with antigenic sensitization[136]. In humans release of mast cell proteases into the lumen of the small intestine occurs as a conditioned response to stress[137], which like the animal studies, reflects a brain to enteric mast cell connection. Central nervous influence on mast cells in the upper gastrointestinal tract is suggested by close histological association between vagal afferents and enteric mast cells[130] and by elevated expression of histamine in intestinal mast cells in response to vagal nerve stimulation[128]. Electrical stimulation of spinal afferents in nerve trunks in the small intestinal mesentery likewise stimulates release of histamine from enteric mast cells, which is mediated by the action of substance *P* at the neurokinin-1 receptor subtype expressed by the mast cells[138].

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 the evidence in support of a CNS to mast cell connection[139]. Intracerebroventricular injection of TRH in the rat brain 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[140]. Like the effects of central TRH on gastric mucosal pathology, intracerebroventricular injection of corticotropin releasing factor mimics large intestinal responses to stress. Injection of a corticotropin releasing factor receptor antagonist or pretreatment with mast cell stabilizing drugs suppresses stress-evoked responses in the lower gastrointestinal tract[141]. The brain-mast cell connection is significant 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 or input from the brain during stress.

Mast cell degranulation releases mediators that sensitize "silent" nociceptors in the large intestine[67]. In animals, degranulation of enteric mast cells results in a reduced threshold for pain responses to intestinal distension and this is prevented by treatment with mast cell stabilizing drugs[81]. Receptors for mast cell mediators are expressed on the terminals of vagal and spinal sensory afferent neurons[142-144]. Actions of mast cell mediators to sensitize sensory nerves is reminiscent of the characteristic hypersensitivity to intestinal distension found in a subset of patients with IBS[60,61,64]. Colonic mucosal biopsies from patients with IBS reportedly contain elevated numbers of mast cells and this raises the question of whether the hypersensitivity to distension reflects sensitization of intramural endings of spinal mechanosensitive nerves by the release of mediators from these pools of mast cells[57,58].

Degranulating mast cells release mediators to signal the ENS that degranulation has taken place and at the same time attract immune/inflammatory cells into the intestinal wall from the mesenteric circulation. Placement of purified *Clostridium difficile* toxin-A into intestinal loops stimulates influx of acute inflammatory cells coincident with activation of the ENS "defense program". Activation of the defensive program becomes evident as copious mucosal secretion and power propulsion. Blockade of enteric nerves by tetrodotoxin, treatment with tachykinin NK-1 receptor antagonists or mast cell stabilizing drugs prevents the acute inflammatory response to the toxin[145-148]. Responses to *C. difficile* toxin-A do not occur in mast cell deficient mice[149].

Substance *P* is a recognized mediator in the chain of events leading to toxin-A-induced mast cell degranulation and release of chemoattractant factors for inflammatory cells from the circulation[150,151]. The neuropeptide is expressed by enteric neurons and spinal sensory afferent neurons. It is a putative neurotransmitter in the ENS and for intramural axonal reflexes mediated by spinal sensory afferents. Substance *P* is a secretagogue for histamine and cytokine release from mast cells[138,150,151]. The excitatory action of *C. difficile* toxin-A on enteric neurons is expected to releases neuronal substance *P*, which in turn acts to degranulate mast cells in the neighborhood where it is released.

Exposure of enteric myenteric and submucosal neurons to *C. difficile* toxin-A depolarizes the membrane potential and elevates 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[152]. Suppression of noradrenergic neurotransmission removes sympathetic braking action from secretomotor neurons and this facilitates stimulation of secretion (Figure 3). Together with toxin-A evoked excitation of secretomotor neurons, this is undoubtedly an underlying factor in the diarrhea associated with antibiotic-related overgrowth of *C. difficile* in the large intestine.

Mast cell signal substances

Several mast cell-derived mediators have neuropharmacological actions on electrical and synaptic behavior of neurons in the ENS. Some important mediators known

to act at their receptors on neural elements in the ENS are: (1) Histamine; (2) Interleukin-6; (3) Leukotrienes; (4) 5-hydroxytryptamine; (5) Platelet activating factor; (6) Mast cell proteases; (7) Adenosine; (8) Interleukin-1β; (9) Prostaglandins.

Histamine

Histamine is not synthesized by enteric neurons and is not considered to be a neurotransmitter in the ENS[153]. Mast cells and neutrophils are sources of histamine in the intestine. Knowledge of histaminergic actions on ENS neurons comes from results obtained from electrophysiological and immunohistochemical studies on single enteric neurons in animals. 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[154,155]. Unlike the intestine, enteric neurons in the guinea-pig stomach do not express histamine receptors and do not respond to experimental applications of histamine[124].

Histamine has three significant 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 H_2 receptors[154,155]. The second is at fast excitatory nicotinic synapses, where it acts at presynaptic inhibitory histamine H_3 receptors to suppress cholinergic synaptic transmission[45,156,157]. The third action is to prevent inhibition by the sympathetic innervation of the intestine of secretomotor-evoked mucosal secretion (Figure 3). 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 provide inhibitory input to secretomotor neurons[45].

Mast cells in colonic mucosal biopsies from patients with diarrhea-predominant IBS release more histamine than normal subjects[58]. Elevated release and flooding of histamine onto the neural networks, which control the secretomotor innervation of the intestinal secretory glands in this subset of IBS patients, might enhance intestinal secretion leading to secretory diarrheal symptoms like those associated with infectious agents and food allergies. Histaminergic receptor antagonists have been used effectively in the past to treat watery diarrhea symptoms associated with mastocytosis and microscopic colitis[158]. The H_2 receptor antagonist cimetidine has been used effectively in the treatment of pediatric diarrhea and diarrhea associated with short-bowel syndrome in patients with Crohn's disease[159]. And finally, mast cell stabilizing drugs, which act to suppress histamine release, are efficacious in the treatment of diarrhea-predominant IBS[83].

Serotonin

5-Hydroxytryptamine is another preformed mediator that is known to be released during degranulation of enteric mast cells and mucosal enterochromaffin cells to form a neuromodulatory overlay on the ENS in animal models and humans. Two receptors mediate the excitatory actions of serotonin at the cell bodies of guinea-pig enteric neurons. One of the receptors, which was initially identified as a 5-HT_{1P} receptor, is a metabotropic receptor activation of which evokes long-lasting excitatory responses in enteric neurons[160-162]. What was initially reported as serotonergic slow synaptic excitation, mediated by the 5-HT_{1P} receptor, is now known to be blocked by a 5-HT_7 antagonist, SB 269970, and mimicked by application of a 5-HT_7 agonist, 5-carboxamidotryptamine[163]. Liu and Gershon[164] presented results, which suggested that the 5-HT_{1P} receptor is a dimer of a 5-HT_{1B} receptor and a dopamine D_2 receptor. Both receptors are expressed by enteric neurons.

The response to stimulation of the elusive 5-HT_{1P} receptors, like stimulation of histamine H_2 receptors, evokes long-lasting excitatory responses in the time range of minutes in ENS neurons. The second receptor, identified as a 5-HT_3 receptor, is an ionotropic receptor directly coupled to non-selective cation channels[165]. Binding of 5-HT to the 5-HT_3 receptor evokes "fast" depolarizing responses that quickly desensitize and occur in the millisecond time range like those evoked by nicotinic receptor stimulation. Expression of two kinds of serotonergic receptors with different mechanisms of postreceptor signal transduction differs from the situation for histamine where only a single metabotropic receptor subtype is expressed by the neuronal cell body.

Histamine and 5-HT both act at presynaptic inhibitory receptors on cholinergic axons to suppress fast neurotransmission at nicotinic synapses in the enteric neural networks[156,166]. Presynaptic inhibition by both neuromodulators is mediated by a different receptor subtype than the one that evokes excitatory responses in the neuronal cell bodies. Identification of the presynaptic inhibitory 5-HT receptor is equivocal; the evidence suggests that it might be a 5-HT_1 receptor[167,168]. In addition to presynaptic inhibitory action at enteric neuronal synapses, histamine and 5-HT each act presynaptically to suppress the release of norepinephrine from sympathetic postganglionic fibers in the ENS[45,169].

Serotonin and functional disorders

Infusion of 5-HT either intravenously or into the intestinal lumen evokes copious secretion of H_2O, electrolytes and mucus from the intestinal secretory glands[45,170]. The stimulatory action of 5-HT underlies its action as a diarrheagenic agent and its involvement in diarrheagenic syndromes in humans[171]. Efficacy of blockade of the 5-HT_3 serotonergic receptor subtype by the selective 5-HT_3 receptor antagonist, alosetron, in the treatment of diarrhea and abdominal pain in the diarrhea-predominant population of women with IBS[52,76] suggests that enhanced stimulation of neural elements in the ENS by 5-HT might be a pathophysiological factor in this form of IBS.

The IBS symptoms of cramping abdominal pain, diarrhea and fecal urgency are exacerbated in the postprandial state[6,7]. Elevated appearance of 5-HT in the hepatic portal circulation in the postprandial state reflects stimulated release from mucosal enterochromaffin cells[54]. The normal postprandial release of 5-HT is reported to be augmented in IBS patients[55] and this

contributes to the suspicion that overactive release of serotonin might be an underlying factor in the symptoms of IBS in diarrhea-predominant patients. This suspicion is reinforced by findings of elevated numbers of mast cells and enterochromaffin cells, both of which contain 5-HT, in colonic mucosal biopsies from IBS patients[57,58].

Reports that a significant proportion of IBS patients develop IBS-like symptoms following an acute bout of infectious enteritis are reminiscent of the basic research findings for the actions of inflammatory mediators, including histamine and serotonin, in the ENS. Gwee *et al*[70] reported that 23 percent of patients, who experienced an acute bout of gastroenteritis, progressed to IBS-like symptoms within 3 mo. Hypochondriasis and adverse life events are reported to double the risk for development of postinfective IBS and may account for the increased proportion of women who develop the syndrome[73]. Nevertheless, the question of whether the association between acute infectious enteritis and IBS reflects low-level inflammation (e.g. microscopic enteritis) and chronic exposure of the neural and glial elements of the ENS to elevated levels of serotonin, histamine or other inflammatory mediators remains to be fully resolved.

Exposure to 5-HT evokes increased firing in sensory nerves that leave the intestine and make synaptic connections in the spinal cord[74]. This excitatory action on intestinal sensory nerves is mediated by the 5-HT_3 receptor subtype and is blocked by selective 5-HT_3 receptor antagonists (e.g. alosetron)[75]. Intramural terminals of both spinal and vagal sensory nerves express 5-HT_3 receptors. Reported efficacy of the 5-HT_3 receptor blocking drug, alosetron, in the treatment of abdominal pain and discomfort in the diarrhea-predominant form of IBS in women[52,76] suggests that the pain and discomfort, like the diarrhea and fecal urgency, reflect disordered endogenous release of 5-HT and its action at the 5-HT_3 receptors present on sensory terminals in the intestinal wall.

Receptors on sensory nerve terminals

Aside from 5-HT_3 receptors, the sensory nerve terminals in the intestine express receptors for several other putative signal substances, including inflammatory mediators. Functional receptors for bradykinin, ATP, adenosine, prostaglandins, leukotrienes and mast cell proteases are expressed on spinal sensory nerve terminals[80]. Intramural pooling of any one of these mediators has potential for increasing the sensitivity of intestinal sensory nerves, especially in conditions of inflammation or ischemia.

Mediators, released by mast cells, are known to sensitize nociceptors in the large intestine[68]. Mast cell degranulation in animal models, results in a reduced threshold for pain responses to balloon distension in the large bowel. Treatment with mast cell stabilizing drugs prevents lowering of the pain threshold during mucosal inflammation in animal models[81]. The results obtained from animals leads to the unresolved question of whether the association between an acute bout of infectious enteritis and the follow-up IBS symptoms of abdominal pain and elevated sensitivity to distension reflects chronic sensitization of intestinal sensory nerves as they function in an environment with low-level inflammation.

Brain-to-mast cell connection: Implications for functional disorders

A brain-to-mast cell connection is currently the most plausible mechanism for explanation of the well-known relationship between stress and IBS-like bowel symptoms. Sympathetic nervous activation is not a plausible explanation! Activation of the sympathetic nervous system accounts for elevations of blood pressure and heart rate in the stressed individual, but cannot explain the symptoms of cramping lower abdominal, watery diarrhea and fecal urgency. Advances in understanding of the sympathetic interface with the ENS ruled-out sympathetic involvement because sympathetic activation inhibits secretomotor neurons and thereby suppresses the neurogenic secretion that is necessary for generation of loose stools (Figure 3)[172]. 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.

A brain-to-mast cell connection implies a mechanism that links central psycho-emotional status to irritable states of the digestive tract. 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 expected to occur irrespective of the mode of stimulation of the mast cells (Figure 10). Degranulation and release of mediators evoked by neural input to the mast cells will have the same effect of triggering a program of secretion and power propulsion as degranulation triggered by antigen detection. This most likely explains the similarity of bowel symptoms between those associated with noxious insults in the lumen and those associated with psychogenic stress in susceptible individuals.

The immuno-neurophysiological evidence reinforces the hypothesis that moment-to-moment behavior of the gut, whether normal or pathological, is determined primarily by integrative functions of the ENS. The enteric minibrain processes input signals derived from immune/inflammatory cells (e.g. mast cells), sensory receptors and the CNS. Enteric mast cells utilize 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, the mast cells signal its presence to the enteric minibrain. The minibrain 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. The immuno-neurophysiology in this respect is suggestive of mechanisms with susceptibility to malfunctions that could result in symptoms resembling diarrhea-predominant IBS.

A lingering issue for the enteric neuro-imunophysiological paradigm is the question of the functional significance of

the brain-mast cell connection. What were the selective pressures that led to evolution of central signaling to mast cells in the gut? A hypothesis emerges from the fact that the barrier between an extremely "dirty" luminal environment and the interior of the body is a single epithelial cell layer. Probability of a break in the barrier is higher during physical stress and the potential for trauma (e.g. "predacious attack, fright and flight"). Stress factors are known to increase the permeability of the barrier in animals[173]. The potential for threats to breach the mucosal barrier suggests a need for immune surveillance at a dangerous interface in the body. Increased immune surveillance would include an influx of acute inflammatory cells into the intestinal lamina propria and mucosa.

The brain has evolved to program homeostatic adjustments to environmental stressors and the emotional stress associated with negative life events. These adjustments include cardiovascular, hormonal and metabolic changes and probably the targeting of inflammatory cells into the gut from the systemic circulation. The only apparent mechanism available to the brain for selective targeting of inflammatory surveillance to the gut is to transmit nervous signals that degranulate enteric mast cells and release chemoattractant factors to "call-in" inflammatory cells from the circulating blood (Figure 10).

Studies of colitis in a non-human primate (cotton-top tamarin) implicate two co-existing factors as being necessary for the initiation and progression of inflammatory bowel disease (i.e. ulcerative colitis) in this model. One of the factors is environmental stress and the other is the large intestinal microflora[126,174,175]. Colitis was not found in cotton-top tamarins living in a natural "stress-free" environment and with the normal microflora present in the large intestine. Movement of colitis-free tamarins out of their natural environment and into a stressful environment leads to an acute inflammatory response in the large intestine only if the feces are present. Studies, in which the fecal stream was diverted from loops of large intestine, found that colonoscopic and histological features of colitis disappeared from the loops and progressed in the colon in the same animal. These changes occurred while the tamarins in the study remained in a colitis-inducing environment. Results of a preliminary study, in which putative neural input to colonic mast cells was suppressed by dosing cotton-top tamarins with a non-peptide neurokinin-1 receptor antagonist, showed suppression of the inflammatory response in cotton-top tamarins held in a colitis-inducing (i.e. stressful) environment[176,177].

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