Applied Principles of Neurogastroenterology: Physiology/Motility Sensation

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Many of the symptoms prominent in the functional gastrointestinal disorders (FGIDs) are consistent with dysfunction of the sensory and/or motor apparatus of the digestive tract. Assessment of these phenomena in man can be undertaken by using a wide variety of invasive and noninvasive techniques, some well established and others requiring further validation. By using such techniques, alterations in both sensory and motor function have been reported in the FGIDs; various combinations of such dysfunction occur in different regions of the digestive tract in the FGIDs. Our understanding of the origins of this gut sensorimotor dysfunction is gradually increasing. Thus, inflammatory, immunologic, and other processes, as well as psychosocial factors such as stress, can alter the normal patterns of sensitivity and motility through alterations in local reflex activity or via altered neural processing along the brain-gut axis. In this context, a potential role of genetic factors, early-life influences, enteric flora, dietary components, and autonomic dysfunction also should be considered in the disease model. A firm relationship between sensorimotor dysfunction and the production of symptoms, however, has been difficult to show, and so the clinical relevance of the former requires continuing exploration. Based on the conceptual framework established to date, a number of recommendations for further progress can be made.

The digestive tract is fitted with a complex wiring system that modulates its response to the internal and external environment. The 2 aspects of gut physiology most relevant to the functional gastrointestinal disorders (FGIDs) are sensation and motility. In health, physiological stimuli from the gut induce motor reflexes, but these remain largely unperceived, with the exception of those related to ingestion and excretion. Visceral afferent pathways, however, also serve as an "alarm" system to induce conscious perception when appropriate. Gut motility, encompassing myoelectrical activity, phasic contractions, tone, compliance, accommodation, and transit, is regulated by reflex mechanisms and is intimately related to gut sensitivity. In the FGIDs, sustained and inappropriate gut hypersensitivity, as well as gut dysmotility, are well documented. These sensory-motor dysfunctions seem related to alterations in neural processing in the brain-gut axis and in visceral reflex pathways. Their underlying causes and their relevance to symptom generation are the subject of ongoing research. The aim of this article is to summarize the key principles of applied neurogastroenterology as they relate to the FGIDs.

Basic Concepts

Sensation

Although *sensation* refers to a conscious experience, the term *sensitivity*, when applied to the gastrointestinal tract, has been used to refer both to conscious perception of gut stimuli and to afferent input within gastrointestinal sensory pathways, whether related to perception or to reflex responses. For the purpose of this review, the term *sensitivity* is restricted to the processes leading to conscious perception.

Unlike other tissues in the body, the viscera are unique in that each organ is innervated by 2 sets of nerves, vagal and splanchnic spinal nerves or pelvic and splanchnic spinal nerves. Both systems participate in the reflex control of gut function, but their involvement in sensation differs.[1] Discomfort and pain from the gastrointestinal tract are conveyed to the central nervous system (CNS) principally by spinal afferents. Activation of

Abbreviations used in this paper: CNS, central nervous system; ENS, enteric nervous system; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; IBS, irritable bowel syndrome.

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vagal afferents is not considered to give rise to sensations perceived as pain; their activation may, however, modulate spinal visceral (and somatic) pain. From second-order neurons in the spinal dorsal horn, which receive direct input from spinal visceral afferent fibers, visceral sensory information is conveyed to supraspinal sites and finally to cortical areas in which conscious perceptions arise. Perception pathways can be activated in healthy subjects by mechanical distention of the gut, but the final conscious perception is modulated by various interacting factors. For instance, intestinal nutrients, especially fat, enhance such perception.[2,3]

In addition to mechanosensitive structures and polymodal endings, the viscera are innervated by a group of mechanically insensitive afferent fibers. Normally, these endings in the viscera are unresponsive ("silent") to mechanical stimulation, but, after organ insult, acquire spontaneous activity and mechanosensitivity and contribute significant input to the CNS. Increases in neuron excitability both peripherally and in the spinal cord lead to visceral hypersensitivity, a characteristic feature of the FGIDs. Neurons in supraspinal sites also exhibit increases in excitability, particularly in brain areas associated with descending modulation of spinal sensory transmission.[1] These modulatory circuits can be influenced in turn by cognitive, affective, and stressful influences, as well as by expectation and prior experience.

Motility

The major functions of human digestive tract motility are to accomplish propulsion along the gut, to mix gut contents with digestive secretions and expose them to the absorptive surface, to facilitate temporary storage in certain regions of the gut, to prevent retrograde movement of contents from one region to another, and to dispose of residues. Motility is controlled by reflexes, both central and peripheral, as well as by descending modulation from the brain-gut axis. Communication between various regions of the gut is facilitated by the transmission of myogenic and neurogenic signals longitudinally along the gut.[4] Gastrointestinal contractions may be classified on the basis of their duration; contractions may be of short duration (phasic contractions) or may be more sustained (tone). Tone is clearly recognized in organs with reservoir function, such as the proximal stomach (accommodation response to a meal) and the colon (response to feeding), as well as in sphincter regions. Compliance refers to the capability of a region of the gut to adapt to its content; it is expressed as the ratio of the change in volume to the change in pressure and is obtained from the pressure-volume curve. Compliance reflects the contribution of several factors, including the capacity (diameter) of the organ, the resistance of surrounding organs, the elastic properties of the gut wall, and its muscular activity. Wall tension, related to compliance, describes the force acting on the gut wall and results from the interaction between intraluminal content and the elasticity of the wall. Gut sensation is influenced by tonic or phasic contractions, and several observations suggest that this is mediated in part by an effect on wall tension; assessment of wall tension is therefore important in the interpretation of results of tests assessing perception of visceral stimuli.

Transit refers to the time taken for intraluminal contents to traverse a specified region of the gastrointestinal tract. It reflects the combined effects of the various phenomena outlined earlier. Most measurements of transit are based on detecting intraluminal movements of an extrinsic marker labelling the luminal content. Transit depends on many factors, such as the physical (eg, solid, liquid, and gas) and chemical (eg, pH, osmolality, and nutrient composition) nature of both gut contents and the administered marker. Measurement of transit is influenced by the state of gut motility at the time of marker administration (eg, fasted vs fed motility) and any preparation of the gut (eg, cleansing of the colon).

In the context of the FGIDs, gastrointestinal dysmotility can develop through dysfunction of the control mechanisms at any level from the gut to the CNS. For example, inflammatory, immune, infiltrative, degenerative, or other processes may directly affect the muscle and/or other elements of the enteric nervous system, whereas psychosocial stressors can induce profound alterations in motility. Because patients with FGID tend to have a greater gastrointestinal motor response to stressful conditions than do healthy subjects, psychosocial stressors are particularly relevant to the symptomatic manifestations of the FGIDs.

Evaluation of Digestive Tract Sensorimotor Function

The presence of altered visceral sensitivity and/or enteric dysmotility is usually evaluated by measuring responses to test stimuli applied to the gut under various physiological and nonphysiological experimental conditions. This form of provocative testing involves 3 key components: stimulation type and technique, measurement of the responses, and modulatory factors that may affect the responses (Figure 1). Physiological stimuli, such as orally or intraluminally administered nutrients, can be used to study reflex motor responses, but supraphysiological stimuli, such as gut distention or overloading with nutrients, are required to activate sensory path-

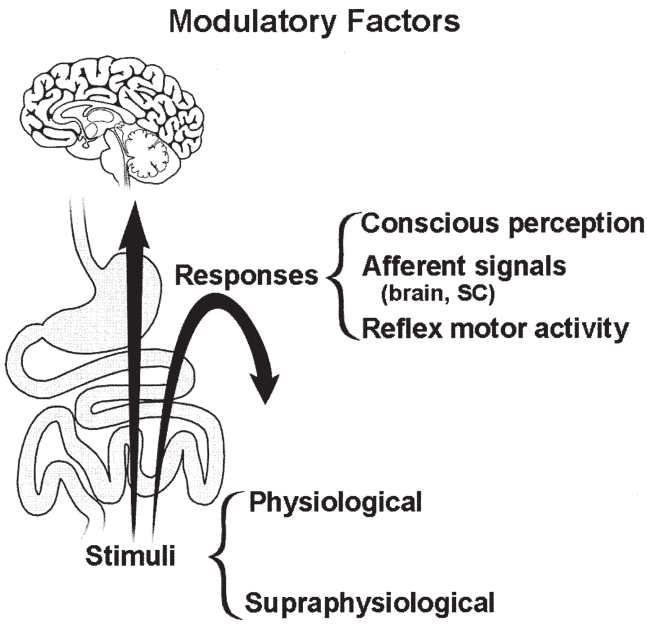

Figure 1. Provocative testing schema for the evaluation of gut sensation and motility in the functional gastrointestinal disorders. SC, spinal cord.

ways and induce perception. Various paradigms can be used to blind the stimuli and make them less predictable.[5]

A range of responses to gut stimulation can be measured, including conscious perception, afferent signalling within the brain and spinal cord, gut motor activity, and autonomic responses. Assessment of conscious perception includes the quality, intensity, and affective dimensions, as well as the location and referral of the perceived sensations. A rating scale such as a visual analog scale or threshold detection paradigms (ie, the magnitude of stimulus required to reach a certain level of perception, such as discomfort or pain) can be used. Detection of afferent signals within the brain can be achieved using a variety of techniques, including cortical-evoked potentials, magnetoencephalography, positron-emission tomography, functional magnetic resonance imaging, and single-photon–emission computed tomography.[6] Similarly, a variety of recording techniques can be used to measure digestive tract motor activity during basal conditions and in response to stimuli; the latter also enables testing of specific enteric reflexes (Table 1). In the absence of a widely accepted and convenient test of visceral autonomic integrity, autonomic responses to visceral stimuli are usually measured with tests of primarily cardiac autonomic innervation, such as heart rate variability;[7] it is not known, however, whether this measurement is representative of other autonomic responses to gut stimuli. Finally, different types of responses can be evaluated simultaneously and correlated (eg, conscious perception and motor or autonomic reflexes).

Many factors, both local and extraintestinal, can modify the previously described responses to stimuli and require attention in the testing of sensorimotor function. For example, anticipatory knowledge increases perception of gut distention,[8] whereas anxiety and fear of impending pain can trigger brain activation patterns similar to those evoked by actual rectal stimulation.[9]

Table 1. Measurement of Gastrointestinal Motor Responses

Recording techniques	Main applications
I. Transit	
Radio-opaque markers and x-ray[a]	Gastric emptying, colonic transit
Hydrogen breath tests[a]	Orocecal transit
Scintigraphy[a]	Esophageal transit
	Gastric emptying
	Small bowel and colonic transit
	Bile flow
	Dynamics of defecation
Labelled C-substrate breath tests[a]	Gastric emptying
	Orocecal transit
Magnetic resonance imaging	Gastric emptying
Pharmacologic markers	
Acetaminophen	Gastric emptying of liquids
Sulfasalazine	Orocecal transit time
Intraluminal impedance monitoring	Esophageal transit
II. Reflux	
X-ray[a]	Gastroesophageal reflux
Scintigraphy	
pH monitoring[a]	
Bilirubin absorbance monitoring	
Intraluminal impedance monitoring	
III. Wall motion	
Ultrasonography	Antropyloric contractions
	Gastric areas and volume
	Gallbladder volume
Scintigraphy	Antral contractions
Magnetic resonance imaging	Antral contractions
SPECT	Gastric accommodation
IV. Intraluminal pressure	
Water-perfused manometry[a]	Phasic contractions and sphincter
Solid-state transducers	Tone at all levels of the digestive tract
V. Myoelectrical activity	
Electrogastrography	Gastric surface electrical activity
Intraluminal electromyography	Gastric, small intestinal, and colonic electrical activity
Needle electromyography	Anal sphincter and pelvic floor muscle activity
VI. Tone, compliance & wall tension	
Barostat	Tone and compliance at all levels of the GI tract

[a]Most widely available techniques. Modified and reprinted with permission.[75]

Some tests are designed specifically to evaluate these modulatory mechanisms.[10]

Sensorimotor Dysfunction and Symptoms in the FGID

Hypersensitivity to distention affecting various regions of the gastrointestinal tract has been a consistent finding in many FGIDs; there appears to be some specificity for individual FGIDs, at least with respect to the organ considered most relevant in the pathophysiology of the disorder.[11] Likewise, abnormal motor responses to gut stimuli have frequently been documented in the FGIDs. Sensory and motor dysfunctions may interact to produce symptoms, the specific clinical syndrome depending on the pathways, and territories affected, but these aspects require further study.

In functional dyspepsia (FD), gastric hypersensitivity, delayed gastric emptying, and impaired accommodation of the proximal stomach have been well documented, but the prevalence of these abnormalities (around 50%) depends on the population studied. Impaired gastric accommodation has been shown to not necessarily be associated with gastric hypersensitivity, delayed gastric emptying, or the presence of *Helicobacter pylori*;[12] in this latter study, the symptom of early satiety was independently associated with impaired accommodation. In a scintigraphic study[13] of the intragastric distribution of a meal, early satiety was correlated with early redistribution of liquids to the antrum, whereas the symptom of fullness was correlated with late proximal gastric retention. The reproducibility of hypersensitivity appears to be greatest with fundic distention in patients with postprandial symptoms and with antral distention in pain-predominant FD patients, whereas nutrients exaggerate the gastric hypersensitivity.[14] Normally, antral filling elicits a reflex relaxation of the proximal stomach that contributes to meal accommodation. Accommodation is then further modulated by enterogastric reflexes depending on the load and composition of intestinal chyme. Impaired gastrogastric and enterogastric reflexes in dyspepsia[14] may result in a defective relaxation of the proximal, but not the distal stomach, with consequent alteration in the intragastric distribution of contents and antral overload. Evidence for a relationship between symptom subgroups and different pathophysiologic and psychopathologic mechanisms continues to increase,[15] although this aspect remains controversial[16–18] and is likely influenced by studies of different patient populations. Gastric hyporeflexia may be a factor in the reduced tolerance of FD patients to intragastric volume increase, thereby contributing to the generation of clinical symptoms in the absence of major motor dysfunction.[14]

In irritable bowel syndrome (IBS), hypersensitivity to rectal or sigmoid balloon distention can be shown in 50% to 70% of patients. As well, at least half of patients perceive the stimuli over wider referral areas than healthy subjects, and the proportion of patients reported as hypersensitive thus depends, among other factors, on whether such abnormal viscerosomatic referral is included. In IBS patients without concomitant FD, rectal hypersensitivity appears to be present in isolation, whereas if FD is also present, gastric, as well as rectal, hypersensitivity is often demonstrable.[11] Cerebral responses to rectal balloon distention appear to be abnormal in IBS, supporting the concept of visceral hypersensitivity. Although there is diversity in the literature, the largest brain-imaging studies suggest that IBS patients show augmented activation in the dorsal portion of the anterior cingulate cortex, in association with increased subjective pain reports to the stimuli.[9,19,20] These data do not necessarily indicate a cerebral etiology for visceral hypersensitivity; they could in fact reflect a normal cerebral response to a heightened incoming sensory signal. However, brain areas important in descending pain inhibition, namely the perigenual anterior cingulate cortex and the periaqueductal gray region of the brainstem, appear to be underactive in IBS,[9,21] and further studies are required.

Both rectal and small bowel hypersensitivity in IBS have been associated with motor hyperreactivity in response to gut stimuli.[22,23] Alterations in the colonic motor[24,25] and sensory[26] response to feeding have been documented. A temporal correlation between high-amplitude propagating contractions and abdominal pain episodes has been observed in the ileocecal region[27] and sigmoid colon[25] in IBS patients. However, these high-amplitude contractions were also observed in the absence of pain in IBS patients and did not differ manometrically from those associated with pain. Moreover, only a proportion of the IBS patients in these studies showed such contractions. The colorectal tonic reflex, namely the normal increase in rectal tone in response to distention of the descending colon, has been reported to be attenuated in IBS patients.[28]

Recent studies evaluating intestinal gas dynamics further substantiate the role of combined sensory and motor disturbances in symptom production. Gas-transit studies have revealed that patients with bloating exhibit impaired reflex control of gut handling of contents.[29,30] Segmental pooling, either of gas or alternatively of solid/liquid components, may induce the sensation of bloating, particularly in patients with hypersensitivity. Further-

more, altered viscerosomatic reflexes may contribute to abdominal wall protrusion and objective distention, even without major intra-abdominal volume increment.

Putative Origins of Sensorimotor Dysfunction

Several potential causes of the sensorimotor dysfunction in the FGID have been identified. The most important of these are discussed briefly.

Genetic and Early-Life Factors

There is now a body of evidence that documents various genetic alterations in both FD[31] and IBS.[32] The importance of early-life experiences and social learning in the etiopathogenesis of the FGIDs is also increasingly recognized. These 2 areas are reviewed in accompanying articles. Also of note in IBS are reported alterations in the synthesis, uptake, and turnover of secreted serotonin in the gut mucosa.[33,34] Given the role of mucosal serotonin in intestinal motility and possibly sensation, it is conceivable that such alterations contribute to sensorimotor dysfunction in IBS, but further work is required.

Enteric Inflammation and Immune Activation

The entity of postinfectious IBS is well recognized, with a prevalence of up to 30% after an acute episode of bacterial gastroenteritis.[35–39] Significant risk factors for the development of this condition include female sex; a prolonged or severe acute initial illness; and higher scores for anxiety, depression, somatization, and neurosis.[35] Histologic features include increased numbers of mucosal chronic inflammatory cells, enteroendocrine cells, and intraepithelial lymphocytes.[36–39] Even in IBS patients without a history of prior infection, an increase in intraepithelial lymphocytes and CD25+ cells in the lamina propria has been documented,[40] whereas in patients with severe IBS, low-grade infiltration of lymphocytes has been shown in the myenteric plexus.[41] In some of these latter patients, there was an associated increase in intraepithelial lymphocytes, evidence of neuronal degeneration, longitudinal muscle hypertrophy, and abnormalities in the number and size of interstitial cells of Cajal. Physiological dysfunction of the gut documented in postinfectious IBS includes altered rectal sensorimotor activity, altered colonic transit, and altered small bowel permeability.[36,37]

Prior infection may also explain the increase in terminal ileal and colonic mucosal mast cells documented in IBS.[39,42–44] The close proximity of mast cells with enteric nerves in IBS has been related to symptoms,[44] perhaps via tryptase activation of specific protease-activated receptors on sensory nerves and the development of visceral hypersensitivity. These findings support the possible involvement of a neuroimmune axis in the pathophysiology of IBS.[43,44] Indeed some studies indicate that IBS patients may have a relative deficiency of anti-inflammatory cytokines[34] and/or increased expression of the proinflammatory cytokines.[45] In FD, an increase in mucosal mast cells also has been documented,[46] and a likely infectious antecedent to the development of impaired fundic accommodation identified in some patients.[47]

It should be acknowledged that some studies reporting an association between IBS and immune activation would not be designated as IBS based on current criteria because they involve the description of pathologic findings indicative of other diagnoses, for example, inflammatory bowel disease, celiac disease, or microscopic colitis. Although these reports reflect the nonspecificity of symptoms of intestinal origin, they also provide avenues for the exploration of the mechanisms whereby inflammation, of any grade, may induce symptoms. However, it must also be stressed that evidence of immune activation has been provided by studies of patients who do not appear to have an alternative diagnosis and who truly appear to suffer from IBS.

Alterations in Enteric Flora

Bacteria commensal to the gut can influence enteric motor activity, can modulate the host immune system development and function, and can enhance epithelial barrier function. It is thus feasible that chronic alterations of the enteric flora may play a role in the development of the FGIDs, particularly IBS, and there is limited evidence that counts of colonic bacteria[48] and the fermentative activity of enteric flora[49] are different in IBS when compared with health. More recently, increased bacterial colonization (overgrowth) of the small intestine in IBS has been suggested[50] and associated with a lower-than-normal frequency of small intestinal–migrating motor complexes. However, these data, based on lactulose breath testing, have been seriously questioned,[51] and studies in larger populations of IBS are required. An association between antibiotic use and IBS[52] has been reported; it is conceivable that antibiotics, by disrupting the normal flora, may facilitate the enteric effects of potentially immunogenic or pathogenic bacteria. Preliminary data suggest that IBS patients may respond symptomatically to manipulation of the flora through the use of probiotic bacterial preparations,[53] but further work is required before definitive conclusions can be reached.

Dietary Components

Patients with both FD and IBS commonly report a postprandial exacerbation of their symptoms and assume that this close temporal relationship implies either an allergy or an intolerance to specific food items or constituents.[54] This relationship between eating and symptoms remains poorly understood. Exaggerated sensorimotor effects of certain nutrients, especially fat, have been reported in both FD[14] and IBS[2,29] and could explain symptom provocation without invoking either allergy or intolerance. The incomplete absorption in the small intestine of substances such as fructose and sorbitol has been proposed as one dietary factor provoking symptoms in IBS,[55] but there is little clinical evidence to incriminate firmly other specific foods or chemical substances in the pathogenesis of IBS.[54] Furthermore, trials of elimination diets have provided conflicting and generally disappointing results,[56] although a recent study reported some success with elimination diets based on the results of testing for immunoglobulin G (but not immunoglobulin E) antibodies to foods.[57] The increased intestinal permeability in some IBS patients,[39] however, does raise the possibility that food and other antigens may gain more ready access than usual to the mucosal compartment of the gut, enabling overly prolonged stimulation of the musosal immune system and the enteric nervous system (ENS). In this regard, it is of interest that patients with celiac disease can fulfil symptom criteria for IBS.[58]

Psychosocial Stress and Other Cognitive Factors

For both FD and IBS, it appears that severe chronic life stress threat (arising from relationship difficulties, divorce, lawsuits, business failures, housing difficulties, forced redundancies, and so on), together with the prolonged and effortful coping associated with the stressor, has significant and consistent effects on symptom onset and exacerbation over time.[59] In this context, it is relevant that psychological stress and other cognitive aspects can also be related to sensorimotor dysfunction in FGID patients.[60] For example, in IBS, the severity of psychosocial disturbance parallels the degree of small bowel motor and/or sensory dysfunction,[23] whereas exposure to psychological stress provokes rectal hypersensitivity.[61] Hypervigilance is another factor that influences symptom reporting by IBS patients during rectal distention testing.[21] In FD, cognitive factors have been implicated in both symptom induction[62] and sensorimotor dysfunction.[63]

The physiological effects on the gut of chronic stress are receiving greater attention. In the rat, chronic psychological stress impairs mucosal defences against luminal bacteria, and intestinal permeability is increased during stress via a cholinergic mechanism that requires the presence of mucosal mast cells.[64] Other potential mediators of stress-induced gastrointestinal sensorimotor responses include norepinephrine and corticotropin releasing factor (CRF). Two CRF receptors have been identified; CRF-1 mediates stress-induced increases in colonic contractility, whereas CRF-2 mediates stress-induced gastric hypomotility and surgical ileus.[65] Human data suggests that IBS patients are particularly sensitive to CRF effects on colonic motility,[66] and infusion of CRF increases rectal sensitivity in healthy volunteers.[67] It is conceivable that either heightened release of CRF or heightened effects of CRF contributes to FGID pathophysiology.

Autonomic Dysfunction

In FD, it has been proposed that abnormal proximal gastric accommodation may be caused by an underlying vagal defect.[68] On the other hand, studies of vection-induced nausea and gastric dysrhythmias[69] have raised the possibility of central neurohumoral dysfunction in the pathogenesis of FD. In IBS, constipation-predominant patients may exhibit vagal dysfunction,[70] whereas diarrhea-predominant patients may exhibit sympathetic adrenergic dysfunction[70] or a postprandial decrease in cardiovagal tone.[71] Other reports in IBS have documented increased sympathetic activity at rest and impaired suppression of parasympathetic activity during orthostatic stress[72] and an autonomic hyperresponsiveness to visceral stimuli that is independent of acutely perceived gut symptoms and not associated with HPA activation.[73] It remains unclear, however, whether the autonomic alterations in the FGIDs are a primary phenomenon or merely reflect the bidirectional interactions of CNS-ENS dysregulation.

A Disease Model

Although some of the factors outlined earlier, such as genetic makeup and early-life experiences, may be regarded as predisposing factors to sensorimotor dysfunction and the FGIDs, others such as the enteric inflammation and psychosocial stress documented in IBS may be regarded as trigger factors. A theoretical disease model for the CNS-ENS dysregulation observed in IBS patients, based on the biopsychosocial model,[74] is depicted in Figure 2; a similar schema can be proposed for other FGIDs. It should be noted, however, that in some instances the precise role of a given factor, that is whether a predisposing, triggering, or modifying influence, remains unclear.

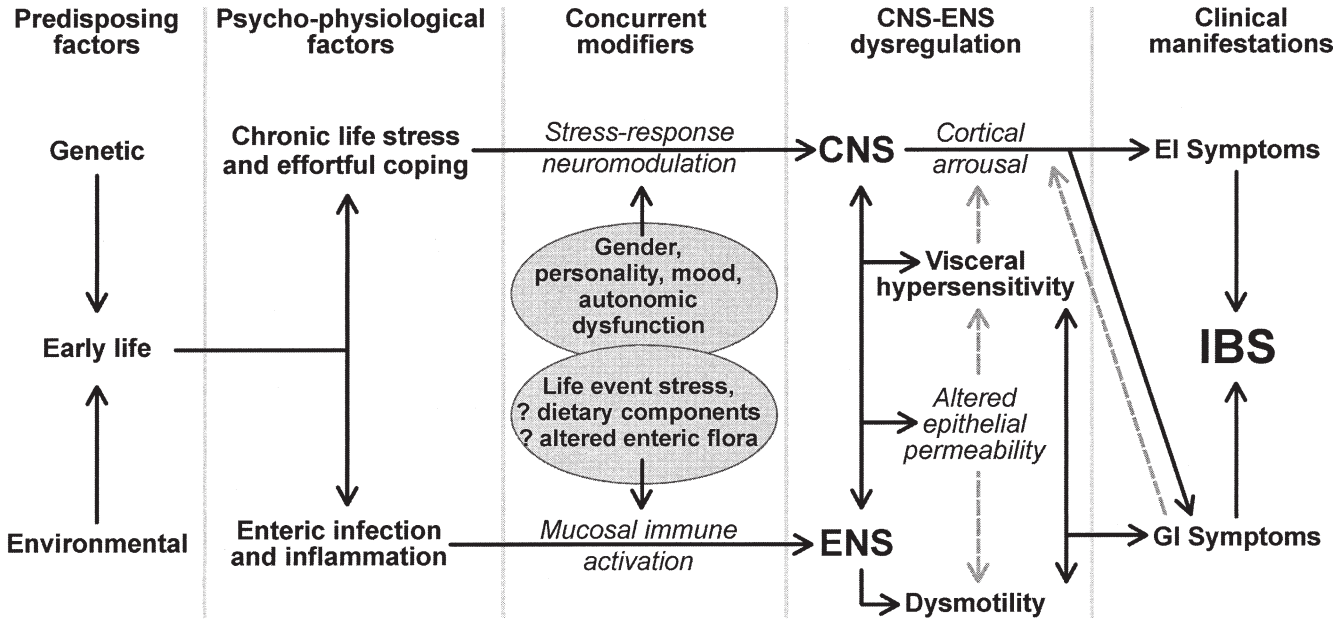

Figure 2. Schematic disease model of the putative importance of chronic life stress and enteric infection/inflammation and their potential interactions with both early life factors and concurrent modifying factors, in the genesis of the CNS-ENS dysregulation present in irritable bowel syndrome. GI, gastrointestinal; EI, extraintestinal. Modified and reprinted with permission.[59]

Recommendations for Further Progress

The concepts of sensory and reflex dysfunction leading to visceral hypersensitivity and enteric dysmotility have provided a conceptual framework for plausible mechanisms of symptom production in the FGIDs. Advances in a range of areas are of crucial importance, however, to further clarify the clinical relevance of this sensorimotor dysfunction. Three such areas are as follows:

1. A greater understanding of the basic origins of gut perception: the key question in comparing animal and human research data is what is important for the encoding of information that ultimately determines the sensation consciously perceived. No data currently are available in this area, but increasingly sophisticated brain-imaging techniques, as well as spinal recording techniques, are required to probe the interactions between cognitive factors and luminal causes of ENS activation in the modulation of cerebral activation patterns. Sensory testing, including evoked brain or spinal cord responses, could in the future be used to categorize FGID patients to determine appropriate therapeutics.
2. More detailed information about the interactions between both the afferent fiber sensory endings in the gut and the ENS, and their local environments, such as the presence of low-grade inflammation, different luminal contents, hormonal fluctuations, and so on: although the study of an inflammatory basis to IBS is in its infancy, this concept provides a tangible basis for constructing novel animal models enabling investigation of luminal factors, including the enteric flora and dietary constituents, that initiate and/or perpetuate gut sensorimotor dysfunction via immune activation. Important data on genetic predisposing factors and the dietary regulation of gene expression, including the effects of different probiotics, are awaited with great interest.
3. More precise delineation of the relationships between sensorimotor dysfunction, individual symptoms, and individual FGIDs: conceivably, the clinical manifestations in FGID patients depend on the specific sensory and/or reflex pathways and territories affected. Improved symptom criteria, together with quantitative data relating to physiological dysfunction (eg, hypersensitivity, dysmotility, and reflex dysfunction), to mucosal inflammation/immune/endocrine activation and to autonomic dysfunction, and in the future to molecular risk factors, should enable better categorization of patient subgroups using techniques such as cluster analysis. More sophisticated techniques to assess compliance, wall tension, and accommodation and to assess more precisely the flow of luminal content and gas and the effects of dietary constituents on sensorimotor function are required. In this regard, the development of minimally or noninvasive tech-

niques of investigation, which can function as true surrogate markers of sensorimotor dysfunction and which can be repeated in patients after various therapeutic maneuvers, is essential.

References

1. Bielefeldt K, Gebhart GF. Visceral pain—Basic mechanisms. In: Koltzenburg M, McMahon S, eds. Textbook of pain. 5th ed. New York: Churchill-Livingstone. 2005:721–726.
2. Evans PR, Kellow JE. Physiological modulation of jejunal sensitivity in health and in the irritable bowel syndrome. Am J Gastroenterol 1998;93:2191–2196.
3. Accarino AM, Azpiroz F, Malagelada J-R. Modification of small bowel mechanosensitivity by intestinal fat. Gut 2001;48:690–695.
4. Sarna SK. Myoelectrical and contractile activities of the gastrointestinal tract. In: Schuster MM, Crowell MD, Koch KL, eds. Schuster atlas of gastrointestinal motility in health and disease. 2nd ed. Hamilton: BC Decker Inc, 2002:1–18.
5. Whitehead WE, Delvaux M. Standardization of procedures for testing smooth muscle tone and sensory thresholds in the gastrointestinal tract. Dig Dis Sci 1997;42:223–241.
6. Aziz Q, Thompson DG. Brain-gut axis in health and disease. Gastroenterology 1998;114:559–578.
7. Tougas G. The autonomic nervous system in functional bowel disorders. Gut 2000;47:iv78–iv81.
8. Accarino AM, Azpiroz F, Malagelada J-R. Attention and distraction effects on gut perception. Gastroenterology 1997;113:415–422.
9. Naliboff BD, Derbyshire SWG, Munakata J, et al. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. Psychosom Med 2001;63:365–375.
10. Azpiroz F. Gastrointestinal perception: pathophysiological implications. Neurogastroenterol Motil 2002;14:1–11.
11. Bouin M, Lupien F, Riberdy M. et al. Intolerance to visceral distention in functional dyspepsia or irritable bowel syndrome: an organ-specific defect or a pan-intestinal dysregulation? Neurogastroenterol Motil 2004;16:311–314.
12. Tack J, Piessevaux H, Coulie B, et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998;115:1346–1352.
13. Piessevaux H, Tack H, Walrand S, et al. Intragastric distribution of a standardized meal in health and functional dyspepsia; correlation with specific symptoms. Neurogastroenterol Motil 2002;124:903–910.
14. Caldarella MP, Azpiroz F, Malagelada J-R. Antro-fundic dysfunctions in functional dyspepsia. Gastroenterology 2003;124:1220–1229.
15. Fischler B, Tack J, de Gucht V, et al. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. Gastroenterology 2003;124:903–910.
16. Boeckxstaens GE, Hirsch DP, Kuiken SD, et al. The proximal stomach and postprandial symptoms in functional dyspeptics. Am J Gastroenterol 2002;97:40–48.
17. Bredenoord AJ, Chial HJ, Camilleri M, et al. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. Clin Gastroenterol Hepatol 2003;1:264–272.
18. Delgado-Aros S, Camilleri M, Cremonini F, et al. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. Gastroenterology 2004;127:1685–1694.
19. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and non-painful rectal distention. Gastroenterology 2000;118:842–848.
20. Verne G, Himes N, Robinson M, et al. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. Pain 2003;103:99–110.
21. Silverman DHS, Munakata JA, Ennes H, et al. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology 1997;112:64–72.
22. Whitehead WE, Holtkotter B, Enck P, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990;98:1187–1192.
23. Evans PR, Bennett EJ, Bak Y-T, et al. Jejunal sensorimotor dysfunction in irritable bowel syndrome—Clinical and psychosocial features. Gastroenterology 1996;110:393–404.
24. Snape WJ, Carlson GM, Cohen S. Colonic myoelectric activity in the irritable bowel syndrome. Gastroenterology 1976;70:326–330.
25. Clemens CH, Samsom M, Roelofs JM, et al. Association between pain episodes and high amplitude propagated pressure waves in patients with irritable bowel syndrome. Am J Gastroenterol 2003;98:1838–1843.
26. Simren M, Abrahamsson H, Bjornsson ES. An exaggerated sensory component of the gastrocolonic response in patients with irritable bowel syndrome. Gut 2001;48:20–27.
27. Kellow JE, Phillips SF, Miller LJ, et al. Dysmotility of the small intestine in irritable bowel syndrome. Gut 1988;29:1236–1243.
28. Ng C, Danta M, Kellow J, et al. Attenuation of the colorectal tonic reflex in female patients with irritable bowel syndrome. Am J Physiol 2005;289:G489–G494.
29. Serra J, Salvioli B, Azpiroz F, et al. Lipid-induced intestinal gas retention in the irritable bowel syndrome. Gastroenterology 2002;123:700–706.
30. Passos MC, Tremolaterra F, Serra J, et al. Impaired reflex control of intestinal gas transit in patients with abdominal bloating. Gut 2005;54:344–348.
31. Holtmann G, Siffert W, Haag S, et al. G-protein B3 825 CC genotype is associated with unexplained (functional) dyspepsia. Gastroenterology 2004;126:971–979.
32. Gonsalkorale WM, Perrey C, Pravica V, et al. Interleukin 10 genotypes in irritable bowel syndrome; evidence for an inflammatory component. Gut 2003;52:91–93.
33. Coates MD, Mahoney CR, Linden DR, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology 2004;126:1657–1664.
34. Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. Clin Gastroenterol Hepatol 2005;3:349–357.
35. Neal KR, Hebdon J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome. Br Med J 1997;314:779–782.
36. Gwee K-A, Leong Y-L, Graham C, et al. The role of psychological and biological factors in post-infective gut dysfunction. Gut 1999;44:400–406.
37. Spiller RC, Jenkins D, Thornley, JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;47:804–811.
38. Parry SD, Stansfield R, Jelley D, et al. Does bacterial gastroenteritis predispose people to functional gastrointestinal disorders? A prospective, community-based, case control study. Am J Gastroenterol 2003;98:1970–1975.

39. Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. Am J Gastroenterol 2003;98:1578–1583.
40. Chadwick VS, Chen W, Shu D, et al. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology 2002;122:1778–1783.
41. Tornblom H, Lindberg G, Nyberg B, et al. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 2002;123:1972–1979.
42. O'Sullivan M, Clayton N, Breslin NP, et al. Increased mast cells in the irritable bowel syndrome. Neurogastroenterol Motil 2000;12:449–457.
43. Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. Gut 2004;53:1096–1101.
44. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693–702.
45. Gwee K-A, Collins SM, Read NW, et al. Increased rectal mucosal expression of interleukin 1B in recently acquired post-infectious irritable bowel syndrome. Gut 2003;52:523–526.
46. Collins JS, Hamilton PW, Watt PC, et al. Quantitative histological study of mucosal inflammatory cell densities in endoscopic duodenal biopsy specimens from dyspeptic patients using computer-linked image analysis. Gut 1990;31:858–861.
47. Tack J, Demedts I, Dehondt G, et al. Clinical and pathophysiological characterisitics of acute-onset functional dyspepsia. Gastroenterology 2002;122:1738–1747.
48. Madden JA, Hunter JO. A review of the role of the gut microflora in irritable bowel syndrome and the effects of probiotics. Br J Nutr 2002;88(Suppl 1):S67–S72.
49. King TS, Elia M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. Lancet 1998;352:1187–1189.
50. Pimentel M, Chow E, Lin H. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2003;98:412–419.
51. Hasler W. Lactulose breath testing, bacterial overgrowth, and IBS: just a lot of hot air? Gastroenterology 2003;125:1898–1900.
52. Maxwell PR, Rink E, Kumar D, Mendall MA. Antibiotics increase functional abdominal symptoms. Am J Gastroenterol 2002;97:104–108.
53. O'Mahony L, McCarthy, J, Kelly P, et al. A randomized, placebo-controlled, double-blind comparison of the probiotic bacteria lactobacillus and bifidobacterium in irritable bowel syndrome (IBS): symptom responses and relationship to cytokine profiles. Gastroenterology 2005;128:541–551.
54. Locke GR, Zinsmeister AR, Talley NJ, et al. Risk factors for irritable bowel syndrome: role of analgesics and food sensitivities. Am J Gastroenterol 2000;95:157–165.
55. Choi YK, Johlin FC, Summers RW, et al. Fructose intolerance: an under-recognized problem. Am J Gastroenterol 2003;98:1348–1353.
56. Burden S. Dietary treatment of irritable bowel syndrome: current evidence and guidelines for future practice. J Hum Nutr Diet 2001;14:231–241.
57. Atkinson W, Sheldon TA, Shaath N, et al. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomized controlled trial. Gut 2004;53:1459–1464.
58. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. Eur J Gastroenterol Hepatol 2003;15:407–413.
59. Bennett EJ, Kellow JE. Relations between chronic stress and bowel symptoms. In: Camilleri M, Spiller RC, eds. Irritable bowel syndrome: diagnosis and treatment. Edinburgh, Saunders, 2002:27–36.
60. Whitehead, WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. Gastroenterology 1998;115:1263–1271.
61. Murray CDR, Flynn J, Ratcliffe L, et al. Effect of acute physical and psychological stress on gut autonomic innervation in irritable bowel syndrome. Gastroenterology 2004;127:1695–1703.
62. Feinle-Bisset C, Meier B, Fried M, et al. Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia. Gut 2003;52:1414–1418.
63. Haug TT, Svebak S, Hausken T, et al. Low vagal activity as mediating mechanism for the relationship between personality factors and gastric symptoms in functional dyspepsia. Psychosom Med 1994;56:181–186.
64. Santos J, Yang PC, Soderholm JD, et al. Role of mast cells in chronic stress induced colonic epithelial barrier dysfunction in the rat. Gut 2001;48:630–636.
65. Tache Y, Martinez V, Million M, et al. Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. Am J Physiol 2001;280:G173–G177.
66. Fukudo S, Suzuki J. Colonic motility, autonomic function, and gastrointestinal hormones under psychological stress on IBS. Tohoku J Exp Med 1987;151:373–385.
67. Lembo T, Plourde V, Shui Z, et al. Effects of the corticotrophin-releasing factor (CRF) on rectal afferent nerves in humans. Neurogastroenterol Motil 1996;8:9–19.
68. Troncon LE, Thompson DG, Ahuwalia NK, et al. Relations between upper abdominal symptoms and gastric distention abnormalities in dysmotility like functional dyspepsia and after vagotomy. Gut 1995;37:17–22.
69. Kim MS, Chey WD, Owyang C, et al. Role of plasma vasopressin as a mediator of nausea and gastric slow wave dysrhythmias in motion sickness. Am J Physiol 1997;35:G853–G862.
70. Aggarwal A, Cutts TF, Abell TL, et al. Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system abnormalities. Gastroenterology 1996;110:393–404.
71. Elsenbruch S, Orr W. Diarrhea- and constipation-predominant IBS patients differ in postprandial autonomic and cortisol responses. Am J Gastroenterol 2001;96:460–466.
72. Adeyemi EO, Desai KD, Towsey M, Ghista D. Characterisation of autonomic dysfunction in patients with the irritable bowel syndrome by means of heart rate variability studies. Am J Gastroenterol 1999;94:816–823.
73. Elsenbruch S, Holtmann G, Oezcan D, et al. Are there alterations of neuroendocrine and cellular immune responses to nutrients in women with irritable bowel syndrome? Am J Gastroenterol 2004;99:703–710.
74. Drossman DA. Gastrointestinal illness and the biopsychosocial model. Psychosomat Med 1998;60:258–267.
75. Rome II: the functional gastrointestinal disorders. Drossman DA, ed. 2nd ed. McLean, VA: Degnon Associates, Inc, 2000. http://www.romecriteria.org.

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