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The Brain-Gut Axis in Abdominal Pain Syndromes

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Abstract

The importance of bidirectional brain-gut interactions in gastrointestinal (GI) illness is increasingly recognized, most prominently in the area of functional GI syndromes such as irritable bowel syndrome (IBS), functional dyspepsia, and functional chest pain. The brain receives a constant stream of interoceptive input from the GI tract, integrates this information with other interoceptive information from the body and with contextual information from the environment, and sends an integrated response back to various target cells within the GI tract. This system is optimized to assure homeostasis of the GI tract during physiological perturbations and to adapt GI function to the overall state of the organism. In health, the great majority of interoceptive information reaching the brain is not consciously perceived but serves primarily as input to autonomic reflex pathways. In patients with functional abdominal pain syndromes, conscious perception of interoceptive information from the GI tract, or recall of interoceptive memories of such input, can occur in the form of constant or recurrent discomfort or pain. This is often

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Enteric nervous system (ENS): Two plexus of interconnected ganglion cells sandwiched between the layers of the gut. The ENS represents the third branch of the autonomic nervous system and can regulate basic gut function without central input

Functional chest pain (FCP): Chronic midline chest pain or discomfort of presumed esophageal origin that is not of a burning quality and occurs in the absence of evidence for gastroesophageal reflux or esophageal motility disorders

IBS: irritable bowel syndrome: Chronic, recurring abdominal pain or discomfort, typically referred to the lower abdomen that is associated with defecation or a change in bowel habits; additional symptoms may include straining, urgency, bloating and abdominal distension. The diagnosis also requires the absence of detectable organic disease that may explain the symptoms

Functional dyspepsia (FD): One or more of the following symptoms, thought to originate in the gastroduodenal region) and occurring in the absence of detectable structural or organic disease: bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning

Functional abdominal pain syndrome (FAPS): Chronic continuous abdominal pain that is unrelated to physiological events (e.g., eating, defecation, menses), is not feigned, impairs daily functioning, and does not meet criteria for another functional gastrointestinal disorder

PBS/IC: painful bladder syndrome/interstitial cystitis

CRF: corticotropin-releasing factor

Emotional motor system (EMS): A parallel set of motor outputs from the brain, including the sympathetic and parasympathetic nervous system. Engagement of the EMS is associated with anxiety, anger, and stress responses

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associated with alterations in autonomic nervous system output and with emotional changes. A model is proposed that incorporates reported peripheral and central abnormalities in patients with IBS, extrapolates similar alterations in brain-gut interactions to patients with other chronic abdominal pain syndromes, and provides novel treatment targets.

Keywords

irritable bowel syndrome; functional dyspepsia; interoception

Introduction

Bidirectional brain-gut interactions play an important role in the regulation of many vital functions in health and disease. In health, brain-gut interactions are crucial in the regulation of digestive processes (including appetite and food intake), in the modulation of the gut-associated immune system, and in the coordination of the overall physical and emotional state of the organism (sleep, stress, anxiety) with activity in the gastrointestinal (GI) tract (reviewed in 1). In disease, peripheral and central alterations in brain-gut interactions are likely to underlie symptoms of chronic abdominal pain and associated GI dysfunction.

Research over the past decade has provided significant advances in the understanding of the pathophysiology of irritable bowel syndrome (IBS) (reviewed in 2) and, to a lesser degree, functional dyspepsia (FD) (reviewed in 3, 4). However, the precise mechanisms underlying symptom generation in these syndromes, or in other, less common syndromes (such as functional chest pain syndrome and functional abdominal pain syndrome) remain incompletely understood. There is an emerging consensus that the various clinical manifestations (including nongastrointestinal comorbid symptoms) of chronic abdominal pain can best be viewed as a dysregulation in the complex interplay between events occurring in the gut lumen (including enteric microbiota), the gut mucosa, the enteric nervous system (ENS), and the central nervous system (CNS), leading to alterations in sensation, motility, mood and affect, and in some circumstances immune function (5).

The Brain-Gut Axis as a Hierarchical System of Homeostatic Reflexes

As shown in Figure 1, afferent signals arising from the lumen of the gut are transmitted via various visceral afferent pathways (enteric, spinal, vagal) to the CNS (6). Homeostatic reflexes, which generate appropriate gut responses to physiological as well as pathological afferent gut signals, occur at the level of the ENS, the spinal cord, and the pontomedullary nuclei and limbic regions (7). Through such reflexes, vagal visceral afferent inputs play an important role in such diverse functions as modulation of emotion, pain, satiety, and immune response (8–10). Whereas the reflex circuits within the ENS, in principle, can regulate and synchronize all basic GI functions (motility, secretion, blood flow), coordination of gut functions with the overall homeostatic state of the organism requires continuous and close communication between the CNS and the GI tract. Descending corticolimbic influences can set the gain and responsiveness of these reflexes, impose distinct patterns of motor responses on lower circuits, and modulate visceral pain transmission (11). Such descending modulation can be triggered by cognitive or emotional influences, or in response to environmental demands, and can override local reflex function during sleep, in the context of environmental stressors, or during strong emotions such as fear and anger.

Perception of Activity within the Brain-Gut Axis

Although the great majority of homeostatic afferent inputs from the gut to the CNS are not consciously perceived in healthy subjects, there are both peripheral and central adaptive mechanisms that can enhance (and possibly reduce) perception of visceral stimuli. For example, acute tissue irritation, inflammation, and injury are typically associated with the sensitization of peripheral afferents, spinal circuits, and spino-bulbo-spinal circuits, which may result in a transient and sometimes prolonged upregulation of afferent sensitivity, as demonstrated in preclinical models (6). Similarly, various stressors have been shown to regulate visceral pain responses in animal models (12), and chronic life stressors have been associated with symptom severity in functional GI disorders (13). There are multiple mechanisms within the brain-gut axis that can tonically or phasically up- or downregulate sensitivity within visceral afferent pathways (11) and the responsiveness of homeostatic reflexes.

Functional GI Syndromes and their Relationship to other Persistent Pain Conditions

Irritable bowel syndrome (IBS), functional dyspepsia (FD), and functional chest pain of presumed esophageal origin (FCP) are characterized by chronic, recurrent symptoms of pain and discomfort. These symptoms are referred to the lower abdomen in the case of IBS, to the epigastrium and upper abdomen in FD, and to the retrosternum in FCP. In IBS and FD, pain and discomfort are associated with nonpainful symptoms (altered bowel habits, nausea and vomiting) which may be related to alterations in GI function (changes in GI transit, intestinal fluid, and electrolyte handling). Functional abdominal pain syndrome (FAPS) differs from the above syndromes in that pain is constant, or nearly so, and is unrelated to any obvious physiological events such as food intake or defecation (14). These syndromes belong to the family of functional GI disorders, which are common in both adult and pediatric populations. Unlike organic disease and in the absence of disease-specific, agreed-upon biomarkers, functional GI disorders are currently classified purely by symptom criteria.

However, five observations put into question the existence of distinct, stable, individual syndromes:

1. There is considerable overlap of among the symptoms of all abdominal pain syndromes at any given time, and transitions from one syndrome into another over time are common (15).
2. Similar symptom patterns have been reported in subsets of patients with organic disease, such as diabetic gastroparesis, celiac disease, and inflammatory bowel disease.
3. The symptoms of functional GI syndromes overlap with psychological symptoms and psychiatric syndromes, particularly anxiety, somatization, and depression.
4. There is considerable overlap of chronic GI pain syndromes with other persistent pain disorders, such as painful bladder syndrome/interstitial cystitis (PBS/IC), temporomandibular joint disorder, and fibromyalgia.
5. Subpopulations of patients with all chronic abdominal pain states (as well as the majority of other persistent pain disorders) share certain characteristics and vulnerability factors, such as stress sensitivity, female sex, a history of adverse early life events, and responsiveness to centrally targeted therapies (reviewed in 16).

Despite the benign prognosis of functional GI disorders, the health-related quality of life in these patients can be affected significantly by their symptoms, and impairment is often more pronounced than in organic disease (17).

Reported Peripheral and Central Alterations within the Brain-Gut Axis in Functional GI Syndromes

The majority of biological studies into the mechanisms underlying persistent abdominal pain states have been performed in patients with IBS, and to a lesser degree in those with a diagnosis of FD (4). In this section, we therefore focus on a review of data obtained in IBS patients.

Peripheral, Organ-Specific Abnormalities

Sensitization of primary afferent pathways—Based on preclinical studies of acute gut inflammation, it can be assumed that the acute inflammatory epithelial changes associated with infections of the GI tract are associated with peripheral and central sensitization, resulting in visceral hyperalgesia (18). In general, peripheral sensitization is transient, and response properties of primary afferents return to their normal state after complete resolution of the pre-inflammatory state. The role of sensitized primary sensory afferents in the symptoms of persistent or chronically recurrent abdominal pain states in human patient populations is not known. Evidence from mucosal biopsies in IBS patients suggests neuroplastic remodeling in the epithelium (19). Such neuroplastic changes may affect the response properties of primary afferents (including peripheral endings of spinal and vagal afferents (20). Changes in afferent nerve terminals could affect responsiveness to visceral stimuli and alter the release of neuropeptides from these terminals, resulting in neurogenic inflammation. Even though analogous information from patients is not available, it is conceivable that intermittent peripheral sensitization of primary afferent neurons may occur in subsets of patients, and may be responsible for acute, transient bouts of abdominal/pelvic pain.

Infection and microflora—A microbial etiology of persistent abdominal pain syndromes has long been suspected (including a relationship between *Helicobacter pylori* infection of the stomach and FD, and the development of IBS-like symptoms following infectious gastroenteritis). Although in the great majority of patients a causal relationship between abdominal pain and acute or chronic infections cannot be established, it remains intriguing to speculate that host-microbial interactions in vulnerable individuals during the early phase of the disorder may result in permanently altered immune or host cell responses, which then continue to play a role in the persistence of symptoms in the absence of the infectious organism.

Several studies have reported the onset of IBS-like symptoms following established bacterial or viral infections of the GI tract (21). This so-called “postinfectious IBS” (PI-IBS) occurs in ~10% of patients undergoing a documented infectious gastroenteritis, and risk factors to develop such symptom persistence are female sex, longer duration of the gastroenteritis, psychosocial stressors at the time of the infection, and psychological factors such as anxiety and depression. However, it is important to realize that the IBS-like symptoms do not typically arise in asymptomatic individuals, but rather in subjects with high somatization, that is, a history of other somatic symptoms. Thus, the “onset” of the IBS-like symptoms may in part represent an attentional shift from other somatic symptoms or reflect the generalized central pain amplification state, which produces enhanced perception of signals coming from a slowly healing mucosa. In addition to PI-IBS, other microorganism-related mechanisms have been proposed to underlie symptoms in subsets of IBS patients (22, 23).

For example, small intestine bacterial overgrowth (21) and alterations in the colonic microflora (dysbiosis) have been implicated. Given the complex interactions between the intestinal microflora and the intestinal epithelium, it is plausible to assume a possible role of the microflora in altered GI function, and even in pain perception in IBS patients (22, 24). However, a definitive causal relationship between such alterations in microflora in the intestinal tract and human IBS symptoms remains to be established.

Epithelial-immune activation—Another possible mechanism implicated in the pathophysiology of IBS is an alteration in mucosal immune/neuroimmune interactions. Reported mucosal immune changes in IBS cannot be characterized as inflammation, since generally neither leukocyte infiltration nor increased expression of mucosal inflammatory cytokines is observed. Enhanced release of neuropeptides from primary sensory nerve endings [such as substance P and calcitonin gene related peptide (CGRP)], as well as release of mast cell mediators (including serotonin, histamine, and proteases), have been implicated in the sensitization of primary afferent pathways, as well as in the release of nerve growth factor (NGF), which in turn can result in neuroplastic and morphological changes in sensory and motor innervation of the colon (19). Such neuroplastic changes may play a role in long-term symptoms long after the initial immune activation subsides.

Some IBS studies (reviewed in 21, 25) have reported small increases in the number of mucosal immune cells in the colon. Such persistent immune activation has best been demonstrated in PI-IBS, and less consistently in other sub-types (25). However, there are conflicting results concerning a relationship of the increase in immune cell numbers with an increase in plasma or mucosal pro-inflammatory cytokines, and particularly whether they play a role in symptoms. One problem is related to the relative nonspecificity of the IBS symptom-based classification compared with other chronic GI disorders, such as microscopic or lymphocytic colitis or celiac disease (26). Another possibility is that there are subsets of patients with the same symptoms, some showing evidence for mild mucosal immune activation, whereas others do not show this finding or may even show a downregulation of mucosal cytokine expression (2). The strongest argument against such a pathophysiological role of the immune system was the negative outcome of a well-designed clinical trial in patients with PI-IBS comparing prednisolone with placebo. Even though the active treatment normalized the mucosal immune activation, this was not accompanied by an improvement of IBS symptoms (27). However, it is conceivable that aberrant mucosal immune activation does occur in a distinct subset of patients, where it plays some role in symptom generation.

Mast cells—Increased mast cell numbers or density, alterations in mast cell–nerve interactions, and increased release of mast cell products from epithelial biopsies have all been reported in IBS studies (reviewed in 28–32). However, mast cell abnormalities are not specific to IBS; they have been implicated in a wide range of stress-sensitive disorders involving neuroimmune interactions, including PBS/IC, multiple sclerosis, migraine, rheumatoid arthritis, and atopic dermatitis (33, 34). Mast cells can be activated by immunoglobulins, neuropeptides, and cytokines to secrete mediators without degranulation. They can release many signaling molecules, including histamine, serotonin, corticotropin-releasing factor (CRF), and proteases. Alterations in these signaling systems have been implicated in the pathophysiology of IBS, and respective receptor antagonists (targeted at histamine, serotonin, CRF, and protease-activated receptors) have been suggested or evaluated as possible therapies (35). A particularly interesting aspect of mast cell regulation is the close interaction of mast cells with noradrenergic, cholinergic, and peptidergic nerve endings. Stress-induced de-granulation of mast cells, and increased release of mast cell products, has been reported both in preclinical and clinical studies (36–38). Persistent

alterations in the spatial and functional relationships between mast cells and nerve endings are a plausible mechanism for recurrent abdominal pain.

However, despite the strong and converging experimental evidence in IBS and other stress-sensitive disorders (including PBS/IC) for a prominent role of mast cells as a transducer between the CNS and the end organ, the clinical relationship between an increased number of mast cells and symptoms of IBS has not been established, and no high-quality clinical trial data unequivocally support a pathophysiological role. One of the reasons for the inconsistent correlation between end organ mast cell numbers/density and symptoms may be the fact that activated mast cells lose their identifiable granules once degranulation occurs, and standard histological techniques may underestimate mast cell numbers (39). Another reason may be that it is not the number or density of mucosal mast cells but their reactivity to gut and CNS stimuli that is the primary abnormality.

Epithelial permeability—There is solid evidence for increased epithelial permeability in some patients, even though a pathophysiological role of this abnormality by itself has not been demonstrated (40–42). Based on both preclinical and clinical studies, different types of increased epithelial permeability with different molecular mechanisms can be distinguished, and different underlying trigger mechanisms have been identified, including different types of stressors (43, 44) and mucosal inflammation (45). Mast cell products, such as CRF and proteases, have been implicated in mediating permeability changes in the GI tract (46) and in sensitizing pain pathways (47). Because increased mucosal permeability has also been reported in asymptomatic individuals, it is likely that this epithelial abnormality, like several other reported peripheral findings, may play a pathophysiological role only in subsets of patients and may require the presence of other factors.

Dysmotility

The concept that exaggerated and dysregulated contractile activity of the GI tract plays a role in the pathophysiology of chronic abdominal pain states has long been proposed, even though a critical review of the published literature failed to establish such a mechanism as being responsible for chronic abdominal pain in IBS or FD patients (48). However, in the case of sigmoid colonic motility, abundant clinical and anecdotal evidence implicates tonic contractile activity in the etiology of chronic pain. In a large number of patients, a contracted, tender sigmoid is palpable on physical exam, and abnormal sigmoid contractile activity has been observed radiologically, on endoscopic exam, and by manometry. It is conceivable that tonic contractions of the sigmoid colon play a role in the sensitization of visceral afferent pathways, resulting in persistent sigmoid hyperalgesia, enlarged referral areas, and abnormal reflex responses. The fact that increased sacral parasympathetic outflow to the distal colon is part of a well-characterized response of the emotional motor system (EMS) (49) implicates central mechanisms as a probable cause of these abnormal responses.

Central Mechanisms

Enhanced stress responsiveness—Whereas acute, severe, inescapable stressors are typically associated with stress-induced analgesia, other types of uncertain, unpredictable, or milder stressors can be associated with stress-induced hyperalgesia (50). There is considerable epidemiological evidence linking first symptom onset or symptom exacerbation in IBS to certain types of psychosocial stressors, and acute laboratory stressors have been shown to be associated with enhanced visceral perception (51). Based on these clinical findings, an upregulation of central stress and arousal circuits has been postulated (5). An extensive amount of preclinical and some clinical data support a role for the central (and to a certain degree the peripheral) CRF-CRF1 receptor signaling system in mediating some forms of acute and chronic stress-induced visceral hyperalgesia of the colon (32, 49).

The central CRF-CRF1 receptor signaling system involves a brain network (stress and arousal circuit) that has also been studied in human subjects using functional brain imaging techniques (52). Increased responsiveness of stress and arousal circuits is likely to contribute to the increased activity of the sympathetic nervous system observed in IBS patients (53), and may play a role in altered mast cell behavior (see above).

Central pain amplification—There are multiple mechanisms by which the CNS can modulate afferent signals from the viscera, including increased activity of endogenous pain facilitation and reduced engagement of endogenous pain inhibition. Endogenous pain modulation systems are likely to mediate the effects of affect, mood, and environmental context (e.g., stress) on pain perception (Figure 2). Three such mechanisms that may be relevant for visceral hypersensitivity are briefly reviewed below.

Neuroimmune activation in the spinal cord—Evidence from preclinical models of visceral hyperalgesia has implicated activation of glia (microglia, astrocytes) as a possible mechanism underlying the chronicity of pain following a psychological stressor or peripheral inflammation (reviewed in 54). Activation of glia can produce proinflammatory cytokines, such as tumor necrosis factor- α (TNF α), and can result in the downregulation of the glutamate transporter on astrocytes, which in turn may lead to elevated synaptic glutamate concentrations. Both effects result in an upregulation of the glutamate/*N*-methyl-D-aspartate (NMDA) receptor signaling system, thereby contributing to the development of central sensitization, and this may occur even in response to non-noxious stimuli. It remains to be determined if alterations in this spinal-neuroimmune interaction play a role in subsets of patients with persistent abdominal/pelvic pain, and if this system comes into play during stress- or inflammation-induced flares or in patients with FAPS.

Enhanced brain responses to visceral distension in IBS—In IBS patients, evidence for both increased engagement of endogenous pain facilitatory mechanisms and compromised engagement of endogenous pain inhibitory mechanisms has been reported (55; also reviewed in 52). A recent meta-analysis of published functional magnetic resonance imaging (fMRI) studies reported differences between healthy control subjects and IBS patients in the brain's response to controlled rectal balloon distension (56). Across studies, there was consistent activation in regions associated with visceral afferent processing, emotional arousal, and attention in both IBS patients and healthy control subjects. Patients showed more consistent activations in regions associated with stress and arousal circuits, compared to controls, and only patients showed activation of brain regions involved in endogenous pain modulation. Another study showed that female patients have greater engagement of the emotional arousal circuit during expectation of visceral pain than do male patients (57). Changing the emotional context of subjects resulted in greater pain ratings, and this was associated with greater brain responses to a visceral stimulus (58). These findings are consistent with the hypothesis that changes in central pain modulation systems play a prominent role in the pathophysiology of persistent abdominal pain, and that the greater prevalence of these disorders in women may in part be due to sex-related differences in the engagement of circuits related to stress and arousal, and endogenous pain modulation. The stress and arousal circuit demonstrated in human subjects using fMRI shows significant homology with the stress circuit related to the CRF-CRF1 receptor signaling system in rodents (see above).

Enhanced brain responses to expectation of visceral pain in IBS—Increased future-oriented worry and anxiety about abdominal symptoms (“anxiety sensitivity”) play a prominent role in IBS symptom severity (59). Similarly, increased attention to threat, and cognitions about pain that overestimate the likelihood of worst possible outcomes

(“catastrophizing”), have been implicated as an important mediator of symptom severity in persistent abdominal pain conditions (17). It has been suggested that alterations in prefrontal modulation of stress and arousal circuits, as well as altered engagement of endogenous pain modulation circuits, may comprise the neurobiological substrate underlying anxiety sensitivity and catastrophizing (60).

Structural brain changes in IBS—Even though FAPS by traditional definition excludes the presence of detectable structural changes, there is a growing body of evidence for structural, e.g., gray matter, abnormalities in patients with various persistent pain disorders (61), including IBS (62). IBS was associated with decreased gray matter density (GMD) in widespread areas of the brain, including medial and lateral prefrontal regions, e.g., regions involved in corticolimbic inhibition. Compared with healthy controls, *increased* GMD in IBS patients was observed in brain regions involved in the stress and arousal circuit. Analogous structural changes have been reported in other persistent pain disorders, including vulvodynia (63). The mechanism(s) underlying such structural changes remain unclear, but excitotoxicity (related to enhanced glutamate signaling) or apoptosis (related to increased cytokine release) have been implicated. Such changes could be the result of aberrant activation of glial cells (see paragraph above). It remains to be determined if patients reporting constant pain, which is no longer related to eating or defecation, may exhibit profound structural deficits in the CNS (as well as in the periphery) that cause their persistent symptoms.

Comprehensive Model of the Brain-Gut Axis in Chronic Abdominal Pain

Despite significant progress during the past two decades in the characterization of peripheral and central candidate mechanisms that may play a role in the pathophysiology of persistent abdominal pain states, it is becoming obvious that no single pathophysiological mechanism can explain symptoms in all patients. It is likely that different patterns of dysregulation in the interactions between the CNS and the respective abdominal end organ (esophagus, stomach, or intestine) are involved in different subsets of patients. Gene-environment interactions are likely to shape the vulnerability of individuals to develop chronic abdominal pain states by altering the specific components of these neuro-visceral interactions (64). While dysregulation at first onset of symptoms (typically in childhood) may be purely functional, and driven primarily by abnormal autonomic system activity, chronicity of symptoms may be associated with neuroplastic and structural changes in the brain (62), spinal cord, and gut (19). Such a developmental perspective is consistent with clinical observations that increased anxiety or painless bowel dysfunction (e.g., constipation or diarrhea) at a younger age often precedes the manifestation of a painful abdominal syndrome in adulthood.

Some plausible components of these interactions are illustrated in Figure 3. The brain receives interoceptive input from abdominal viscera and responds to these inputs in a reflexive way, taking into account contextual factors (particularly stress) and other needs of the organism. In the healthy individual, most of this interoceptive input is not consciously perceived. However, the modulation of interoceptive input and/or its perception can be altered by activity within stress and arousal circuits and by cognitive and emotional input to these circuits, which in turn can alter both the perception and the feedback to these organs via the different branches of the EMS (65).

The EMS is a set of parallel motor path-ways governing somatic, autonomic, neuroendocrine, and pain-modulatory motor responses associated with the stress response and emotional states. One of these EMS pathways, the autonomic nervous system outflow, is organ and target cell specific, such that dysregulation of a particular part of the GI tract (e.g.,

stomach versus sigmoid colon), as well as different cell types within respective viscera (e.g., mast cell, smooth muscle cell) are to be expected (66). This hardwiring principle within the brain-gut axis is most consistent with a primary role of the autonomic nervous system in the etiology of the proposed peripheral mechanisms discussed above. Whereas acute, transient changes in the autonomic nervous system output can result in acute changes in organ function (motility, secretion, blood flow, immune activity), persistent alterations can induce neuroplastic changes in specific cells within peripheral target organs. The peripheral changes reported in patients with IBS, and reviewed above, may represent such EMS-induced changes in immune (mast cell responsiveness) and neural (sensitization of primary afferents) cell populations. These changes in turn alter interoceptive feedback to the brain. In addition, “interoceptive memories” of aversive visceral states may develop over time, which may allow the brain to recall visceral experiences of discomfort and pain even in the presence of completely normal interoceptive input. Such recall may be influenced by psychosocial stress, anxiety, and mood states.

Even though scientific data are not available, one may speculate that there are different ways chronic abdominal pain syndromes can develop from dysregulation within the brain-gut axis. Longstanding transient dysregulation of homeostatic reflexes (in the periphery and/or centrally) may gradually result in neuroplastic peripheral and/or central changes, leading to permanent dysregulation and chronic pain. Alternatively, formation of maladaptive interoceptive memories may create a central mechanism by which pain and discomfort can be experienced in contexts of emotional distress, without any abnormal peripheral responses.

Relevance of the Brain-Gut Interaction Model for other Abdominal Pain Syndromes

Although this review focuses on candidate mechanisms underlying IBS, the model presented above is equally applicable to the other abdominal pain syndromes (FD and FCP), as well as to other, often comorbid pelvic pain syndromes such as PBS/IC and vulvodynia (16). For example, the findings and proposed pathophysiological mechanisms for PBS/IC are remarkably similar to those for IBS (28, 67, 68). Consistent with the involvement of both altered homeostatic reflex activity and altered perception, all these syndromes show changes in both motility and pain perception. Similarly, both mast cells and increased epithelial permeability have been implicated in several of these syndromes.

Therapeutic Approaches to Altered Brain-Gut Interactions in Functional GI Disorders

The model proposed in Figure 3 offers several general targets within the brain-gut axis in the treatment of patients with abdominal pain syndromes: centrally targeted pharmacological and nonpharmacological therapies, gut-directed therapies, and therapies aimed at modifying the enteric microbiota.

Regarding pharmacological therapies, significant progress has been made both in the identification of suitable targets within the brain-gut axis and in the early development of novel compounds with promising preclinical results (69). Compounds that target multiple sites within the brain-gut axis (such as so-matostatin receptors, opioid receptors, 5-HT₃ receptors, neurokinin receptors, and CRF₁ receptors) in chronic abdominal pain states, with symptoms involving GI function, persistent pain, and emotions, have four obvious advantages (70, 71). First, such compounds are likely to affect alterations in reflex responses involving GI motor and secretory functions, as well as abnormal perception of, and autonomic responses to, visceral stimuli. Second, they are likely to affect multiple symptoms in contrast to the current monosymptomatic therapy aimed at peripheral targets. Third,

compared with current therapies, they are more likely to reverse abnormal modulatory mechanisms rather than interfere with essential homeostatic functions, such as normal pain transmission or homeostatic reflexes. Finally, they could have a greater impact on global endpoints and health-related quality-of-life measures, owing to simultaneous treatment of non-GI-specific symptoms such as fatigue, loss of energy, and excessive worry, all of which have been identified as impairing quality of life more than than specific GI symptoms such as altered bowel habits. However, with the exception of 5-HT₃ receptor antagonists, such drugs with multiple targets within the brain-gut axis have not been found to be clinically effective, and 5-HT₃ receptor antagonists are available only within a restricted-access program because of potentially serious side effects (71, 72). Early human studies with two different CRF1 receptor antagonists did not show the beneficial effects in IBS patients that had been expected on the basis of extensive preclinical studies (73, 74). Similarly, efforts to develop effective IBS treatments targeting mucosal mast cells have not shown the effects expected on the basis of the strong construct validity of this mechanism (reviewed above). On the other side, several compounds specifically targeted at stimulating secretion or motility of the intestine have been shown to be effective in reducing overall symptoms, including small beneficial effects on abdominal pain (reviewed in 75). For example, two drugs aimed at modulating different epithelial chloride channels in the intestinal epithelium have been shown to positively affect symptoms in patients with IBS and constipation (76). Compounds targeting colonic 5-HT₄ receptors (tegaserod, prucalopride), which are able to accelerate colonic transit, have been found to be effective in patients with IBS and constipation, even though tegaserod (76, 77) has been withdrawn from the market due to side effects, and prucalopride is only available outside the United States. There is also evidence supporting the concept that modulating the intestinal flora with a nonabsorbable antibiotic (78) or probiotics (79) may have beneficial effects on some IBS symptoms. With all these compounds aimed at specific aspects of gut function, it remains to be determined if the observed small reduction in abdominal pain is a direct effect on visceral pain pathways, or if it is secondary to the relief the patients get from improvement of their bowel habits, the resultant reduction in symptom-related anxiety, and reduction in anxiety-related pain amplification.

Regarding nonpharmacological therapies, cognitive behavioral therapy and hypnosis have been shown to be effective in several high-quality clinical trials (80), even though the validity of the control groups in these studies has been questioned. Based on the increasing understanding of ineffective cortico-limbic-pontine pain modulation mechanisms in patients with chronic abdominal pain (16, 81), one may speculate that these approaches are able to reestablish appropriate functioning by enhancing prefrontal inhibitory control mechanisms over hyperactive stress and arousal circuits, and by altering maladaptive interoceptive memories.

Summary and Conclusions

Considerable progress has been made in the understanding of peripheral and central components of the brain-gut axis. The traditional emphasis of incompatible disease models (either peripheral or central) has given way to a more comprehensive understanding of a bidirectional network with multiple functional and structural alterations. Chronic abdominal pain syndromes are almost certainly developmental disorders, which nearly always first manifest in some form early in life, and the expression of which may vary throughout life (15). The initial manifestation is often different from the later adult symptom presentation; for example, adult IBS may be preceded by childhood anxiety or painless constipation, and childhood IBS may transform into adult FD or FAPS. The fact that symptoms in the same patient may be referred to different regions of the GI tract (from esophagus to rectum) at different times argues against a primary role of organ-specific peripheral changes. These

syndromes are also likely to be heterogeneous, with different subpopulations showing distinct patterns of abnormalities and requiring different types of therapeutic approaches.

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Summary Points

1. The brain-gut axis consists of a hierarchy of reflex loops that assure homeostatic control of GI function. Conscious perception of activity within these reflexes is minimal in health, with the exception of situations that require a specific action (food intake, defecation).
2. Alterations in the gain of these homeostatic reflexes can be associated with alterations in intestinal secretions, motility, blood flow, and afferent sensitivity. Such changes can lead to symptoms of chronic abdominal pain and discomfort and alterations in bowel habits.
3. Different patterns of abdominal pain and discomfort have been classified into individual syndromes based on predominant symptoms. There is currently insufficient biological and epidemiological evidence to support this strict categorical classification.
4. Distinct peripheral and central biological dysregulations have been identified in patients with chronic abdominal pain, which can be seen as part of a larger dysregulation within the brain-gut axis.
5. A developmental view of chronic abdominal pain syndromes has to take into account the possible role of autonomic dysregulation of target cells within the gut, followed by development of neuroplastic changes in both the gut and the CNS. In some patients, the recall of interoceptive memories of past experiences of pain and discomfort may be sufficient to trigger clinical symptoms.

Future Issues

1. There is a need to replace the current symptom-based classification of abdominal pain syndromes with a neurobiological one, taking into account the close interrelationship between central and peripheral components of the brain-gut axis, the developmental aspects of development of chronic abdominal pain, and the likely subsets of patients with distinct patterns of biological changes.
2. There is a need to determine the genetic architecture of abdominal pain syndromes, and the role of environmental factors interacting with gene polymorphisms. This will make it possible to determine the relative role of autonomic nervous system dysregulation and alterations in interoceptive processing.
3. The development of more effective treatments will require identification of those alterations within the brain-gut axis that are correlated with subjective symptoms, and differentiate them from the larger group of alterations that are secondary effects of brain-gut alterations.

Figure 1.

Hierarchical organization of homeostatic reflex systems within the brain-gut axis. (a) Homeostatic afferents that report the physiological condition of the GI tract terminate in lamina I of the dorsal horn (corresponding vagal afferent pathways are not shown). The ascending projections of these neurons provide the basis for autonomic reflex arcs at different levels of the brain-gut axis (enteric nervous system reflexes not shown). Limbic, paralimbic, and prefrontal centers provide modulatory influences on the gain of these reflexes. The interoceptive input into these reflexes is generally not consciously perceived except in situations that require an action (e.g., pain) or in pathological conditions. Modified with permission from Reference 82. (b) Cortical modulation of homeostatic afferent input to the central nervous system. Prefrontal regions modulate activity in limbic and paralimbic regions, subregions of the anterior cingulate cortex, and hypothalamus, which in turn regulate activity of descending inhibitory and facilitatory descending pathways through the periaqueductal gray and pontomedullary nuclei. Activity in these corticolimbic pontine networks mediates the effect of cognitions and emotions on the perception of homeostatic feelings, including visceral pain and discomfort. Abbreviations: ANS, autonomic nervous system; dlPFC, dorsolateral PFC; orbFC, orbitofrontal cortex; PAG, periaqueductal gray; RVM, rostromedial medulla; RVLM, rostromedial medulla; VMM, ventromedial medulla; A6, locus coeruleus; Ins, insula; Hypoth, hypothalamus; Amy, amygdala; ACC, anterior cingulate cortex.

Figure 2.

Multiple systems and brain networks involved in endogenous pain modulation (adapted with permission from Reference 16). For details, see text.

Figure 3.

Bidirectional brain-visceral interactions. Interoceptive input is encoded by a network of transducers in the gut and conveyed to the brain via vagal and spinal afferents, immune mediators, and endocrine signals. Signals from the intestinal microflora may also be transduced into interoceptive signals at the host-microbial interface. At the brain level, this interoceptive information is integrated with information about contextual factors, and appropriate responses reach the gut via the two branches of the autonomic nervous system and the hypothalamic pituitary axis (HPA). Prolonged dysregulation of these interactions may result in central and peripheral neuroplastic changes. Abbreviations: ACTH, adrenocorticotrophic hormone; SNS, sympathetic nervous system; PSNS, parasympathetic nervous system; ICC, interstitial cell of Cajal; ECC, enterochromaffin cell. For details, see text. Modified from Reference 83 with permission.