

Brain-Gut Interaction in Irritable Bowel Syndrome: New Findings of a Multicomponent Disease Model

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Abstract

Knowledge on the pathophysiology of irritable bowel syndrome has evolved, beginning with disturbances in motility to visceral hypersensitivity, and ultimately to alterations in brain-gut bi-directional communication, where neurotransmitters such as serotonin play a key role. Recently, a multicomponent disease model that integrates all these alterations was proposed. This model is divided into physiological, cognitive, emotional and behavioral components that explain the gastrointestinal as well as the constitutional symptoms. In recent years there has been an explosion of research together with new developments in pharmacological treatments for IBS that support each component of this model. This review presents recent data in favor of these alterations in IBS.

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Irritable bowel syndrome together with functional dyspepsia and non-cardiac chest pain encompass the three most common functional bowel disorders. Functional as opposed to organic syndromes are defined as those presenting pain and/or discomfort unexplained by structural abnormalities detectable with currently available diagnostic modalities [1]. In the absence of a reliable biological marker, the diagnosis of IBS, as with other functional bowel disorders, is based on recently revised symptom criteria known as the Rome II criteria [2]. These emphasize a “positive diagnosis,” meaning the presence of the symptoms rather than exhaustive tests to exclude other diseases. Although the accuracy and pathophysiologic significance have yet to be reported, the Rome criteria constitute probably the most reasonable approach for clinical diagnosis and research purposes.

Since the 1950s our knowledge has evolved in the attempt to explain IBS – from alterations in bowel motility to visceral hyperalgesia, and from alterations in brain-gut interactions to neuroendocrine abnormalities where 5-hydroxytryptamine has been the focus of recent attention as a mediator of gut motility

and visceral sensitivity. An emerging approach proposed by Mayer [1] integrates all these concepts in a more comprehensive disease model that includes physiological alterations within the central nervous system. These may manifest as alterations in the central processing or modulation of visceral information, altered autonomic input to the gut, and altered neuroendocrine response to stress. Additionally, cognitive factors such as inappropriate coping styles, illness behavior and inappropriate concepts about disease may influence healthcare utilization and may play a role in turning a subject with IBS symptoms from being a non-patient to a healthcare-seeking patient. Emotional factors such as anxiety and depression, and behavioral factors such as stressful or traumatic life events contribute to symptom generation and exacerbation. This model is able to explain symptoms of pain or discomfort caused by enhanced visceral sensitivity, alterations in bowel habit by autonomic dysregulation, and other constitutional symptoms such as alterations in appetite, libido, sleep and energy [1,3]. This review presents recent data supporting these alterations in IBS.

Physiological factors

Visceral hypersensitivity

In 1973 Ritchie [4] was the first to provide evidence for the concept of visceral hypersensitivity in IBS. Patients and controls were evaluated for their pain thresholds in response to progressive distension of a balloon placed in the sigmoid colon. At the same volume of distension, the patients reported higher pain scores compared to the controls. This finding has been reproduced by further studies. With the introduction of the barostat, a computerized distension device, the distension procedures have been standardized. Physiological studies indicate the presence of visceral hypersensitivity as the most consistent abnormality in chronic abdominal pain syndromes such as IBS.

Two concepts of visceral hypersensitivity have been introduced – hyperalgesia and allodynia. Normal visceral sensations are experienced at lower intraluminal volumes suggesting hyperalgesia, and pain or discomfort is experienced at volumes usually producing normal internal sensations, a finding referred to as allodynia [5]. At least four mechanisms have been proposed to explain visceral hypersensitivity: a) increased end-organ sensitivity, b) spinal hyperexcitability with activation of nitric

IBS = irritable bowel syndrome

oxide and other neurotransmitters, c) long-term hyperalgesia due to the development of neuroplasticity in response to chronic visceral stimulation, and d) alterations in endogenous modulation at cortical and brainstem levels of the nociception [5].

Aside from hypersensitivity, at least a second perceptual alteration can be distinguished – hypervigilance. It refers to a greater propensity to label negatively expected aversive sensations [6]. Hypervigilance may explain other extraintestinal symptoms in IBS and the co-occurrence of other syndromes such as fibromyalgia, and may determine whether predominant symptom expression involves the musculoskeletal system, gastrointestinal system or both. Fibromyalgia occurs in up to 65% of patients with IBS, and functional bowel symptoms occur in 65–70% of patients with fibromyalgia [7].

● **Pain pathways.** To understand these perceptual alterations we should state that there is a continual bi-directional communication between brain and gut. Bowel pain inputs are transmitted through three orders of neurons. The first carries information from the viscera through the thoracolumbar sympathetic nervous system and synapses in the dorsal horn of the spinal cord. Neuropeptides or excitatory amino acids released from primary afferents interact with receptors such as substance P and calcitonin gene-related peptides, and Ca enters through N-Methyl-D-Aspartate receptors resulting in nitric oxide synthetase. Nitric oxide is then released and diffuses to the presynaptic terminal, producing a positive feedback and hypersensitivity by facilitating neurotransmitter release [8]. The second order then crosses the midline of the spinal cord and ascends via the spinothalamic tract to synapse with the thalamus, and via the spinoreticular tract to synapse with the reticular formation. The third ascends from the spinothalamic system to the somatosensory cortex and from the spinoreticular tract to the limbic system (including the anterior cingulate) and prefrontal cortices. The first order provides the sensory-discriminative component, whereas the second provides the motivational-affective and evaluative component [8].

One of several endogenous neural systems that modulate peripheral sensory input is the descending endorphin-mediated analgesia. It descends from the cortex and hypothalamus to the peri-aqueductal gray area in the midbrain, then traverses and synapses in the nucleus raphe magnus in the medulla, ending at the dorsal horn of the spinal cord where it increases or decreases the afferent information arising from the first order neurons. This system may be facilitated by mediators such as serotonin (5-HT) and norepinephrine [8].

Viscerosomatic perception abnormalities

● **Altered rectal-sigmoid perception.** Altered rectal perception has been proposed as a biological marker of IBS. It is found in the form of lowered thresholds for aversive sensations, increased intensity of sensations, or altered viscerosomatic referral [9]. Using the barostat, hypersensitivity was found only for aversive

sensations in response to rapid phasic distension but not to slow ramp distension [9]. Two subgroups of patients with predominant IBS constipation have been identified on the basis of responses to different types of rectal distension: those who have lost the natural call to stool (no urge), and those who experience a constant sensation of incomplete evacuation (urge) [10]. Both groups were hypersensitive to an ascending series of phasic rectal distensions distinguishing patients from controls. Furthermore, the no-urge group was hyposensitive to a slow gradual distension of the rectum. The first finding is consistent with hypervigilance towards aversive visceral stimulation elicited by predictable increasing phasic distensions of the rectum [6]. The second finding may result from an increase in central pain-inhibitory mechanisms, or alternatively from a failure to activate central attentional systems in response to physiological rectal filling [10]. Using a double-balloon catheter and barostat-driven distensions in the rectum and sigmoid colon, Munakata and co-workers [11] reported that after repetitive rapid phasic distensions (30 seconds, 60 mmHg) in the sigmoid colon, there was a significant reduction in rectal perception thresholds in IBS patients but not in control subjects. A failure in central pain-modulating systems was suggested as the pathophysiological basis.

Finally, the perceptual responses to visceral aversive stimuli in IBS are altered with the co-existence of fibromyalgia. Rectal perception thresholds are significantly lower in patients with IBS than in normal subjects and those with both IBS + fibromyalgia, whereas after sigmoid conditioning patients with IBS + fibromyalgia developed rectal hypersensitivity similar to IBS alone [12].

● **Somatic hypoalgesia.** Hypersensitivity is specific to the bowel, since IBS patients have somatic hypoalgesia [7]. This hypoalgesia seems to be specific to mechanical but not thermal pain, while hypervigilance to thermal but not somatic pain has been reported in IBS, suggesting that the processing of thermal and mechanical pain is differentially modulated in IBS [13]. Conversely, patients with both IBS + fibromyalgia have somatic hyperalgesia [7]. Modality-specific alterations in descending pain-modulation systems may explain the distinct somatic and visceral perceptual responses in IBS patients.

Viscerosensory symptoms

Abdominal pain is thought to be the hallmark of IBS, although in the currently revised Rome II diagnostic criteria [2] “discomfort” was added to “pain” to broaden symptom description. In a recent study in a tertiary referral population of IBS patients, only a third of the patients reported that their most bothersome viscerosensory symptom was abdominal pain, from the four group cluster of abdominal pain, bloating-type discomfort, sensation of incomplete evacuation, and extra-abdominal (chest pain or pressure and nausea). Yet, although pain predominance did not correlate with the severity of gastrointestinal or psychological symptoms, there was a significant correlation with the development of rectal hyper-

5-HT = 5-hydroxytryptamine

algia in response to sigmoid-conditioning stimulus [14]. Moreover, the “pain/discomfort associated with a change in consistency of stools” criterion has been associated with lower rectal discomfort thresholds in IBS patients [15]. More recently, sigmoid sensitivity has been shown to strongly correlate to IBS symptom severity compared to rectal sensitivity, which is poorly correlated [16].

The above supports the use of discomfort as a hallmark in the definition of IBS and may have implications for responses seen in subsets of patients, depending on predominant symptoms.

Brain alterations

Using positron emission tomography scanning, a functional imaging technique to evaluate regional brain activity, it has been shown that in response to anticipation or actual rectal distension, IBS patients activate the left prefrontal cortex, an area related to increased alertness or vigilance. In contrast, healthy controls activate the anterior cingulate cortex, a site of pain modulation [17]. Subsequent studies have confirmed that IBS patients show less activation of the ventral subregion of the anterior cingulate cortex, the perigenual area (an affective subdivision), but higher activity of a more dorsal region, the mid-cingulate (a cognitive division) [18]. Also, IBS patients show additional activation of the premotor cortex after repetitive sigmoid stimulation that may reflect activation of supraspinal visceromotor reflexes and support alterations in bowel motility [19]. Functional magnetic resonance imaging has also revealed differences in brain activation between controls and IBS patients [20]. These findings clearly suggest a brain dysfunction in IBS patients, which may lead to hypervigilance, increased perception and a failure in pain modulation.

Earlier it was stated that the co-existence of fibromyalgia alters the perceptual responses to visceral and somatic stimuli in IBS. This has also been confirmed with PET studies: the attention-related brain regions are activated during acute rectal discomfort or its anticipation in IBS, but when both IBS and fibromyalgia co-exist, this region is activated during somatic pain [21].

Autonomic and neuroendocrine dysfunction

Autonomic alterations have also been described in IBS. Visceral afferent stimulation results in activation on the hypothalamus pituitary adrenal axis and autonomic nervous system, involving the release of neurotransmitters and hormones such as corticotropin-releasing factor which may play a role in the modulation of emotions. It was recently demonstrated that compared with normals, IBS patients have an increased vagal response to rectal distension, decreased vagal response to sigmoid distension, a blunted adrenocorticotrophic hormone response and lower plasma cortisol levels, suggesting an alteration in central control mechanisms involved in autonomic and neuroendocrine response to visceral stimulation [22].

One of the most important neurotransmitters within the enteric and autonomic system that has been associated with IBS is 5-HT. In the human body, 95% of serotonin is packed in the enterochromaffin cells and neurons of the gastrointestinal tract and 5% in the central nervous system. At least 14 subtypes of the 5-HT receptor have been identified with most actions in the gastrointestinal tract mediated by 5-HT₁, 5-HT₃ and 5-HT₄ receptors that elicit a variety of effects. In response to mechanical or chemical stimuli, 5-HT is secreted from the enterochromaffin cells of the mucosa and stimulates intrinsic and/or extrinsic sensory neurons. Intrinsic neurons (enteric) activated by 5-HT_{1p} and 5-HT₄ initiate peristaltic and secretory reflexes. Extrinsic sensory neurons are activated by 5-HT₃ and initiate sensations such as nausea, bloating and pain. 5-HT₃ receptors have also been identified in many structures of the central pain-processing networks, in particular the amygdala and the prefrontal cortex, the same areas involved in autonomic responses to sensory events. The antagonist effect of 5-HT₃ increases sensory thresholds to balloon distension of the rectum and slows colonic transit in humans, evidence that may provide a mechanism to explain the therapeutic effects of 5-HT₃ antagonists in pain modulation [23].

Sleep disturbances

Recent studies have suggested that patients with functional gastrointestinal disorders, in particular those with functional dyspepsia, may suffer from poor sleep and that IBS symptoms correlate with the quality of the previous night's sleep [24]. An increase in the percentage and duration of rapid eye movement, a sleep phase characterized by arousal, increased cardiovascular sympathetic activity and increased parasympathetic outflow to the colon, has been reported in IBS [25]. In fibromyalgia, an intrusion of alpharhythm into slow wave sleep (stage 4), which has been associated with a non-restorative sleep pattern, has been reported and may well be responsible for a decrease in stage 4 seen in patients with both IBS + fibromyalgia [26]. Ascending serotonergic, cholinergic and noradrenergic arousal systems involved in the mediation of the currently accepted disease model for functional bowel disorders, which includes alterations of central autonomic regulations, visceral sensitivity and alterations in the neuroendocrine response to stress, may also play a role in the mediation of sleep alterations [3,24].

Different bowel habits

Traditionally, IBS patients have been sub-classified based on bowel habit predominance into those having constipation (IBS-C) and diarrhea (IBS-D) predominance. In many patients the bowel habit may alternate between the two patterns. This arbitrary classification preceded the newly revised Rome II criteria [2]. Converging evidence suggests that the different patterns may be related to alterations in central nervous system responses to a variety of physical and psychosocial stressors. This altered CNS response includes variable alterations in autonomic and perceptual responses and constitutional function systems, manifested as a wide variety of symptoms. Accord-

PET = positron emission tomography

ingly, altered autonomic outflow presents as alterations in bowel habits, altered perceptual responses manifest as viscerosensory and somatosensory symptoms, and constitutional functions.

We recently reported that patients with “hard/lumpy” stools, a criterion for constipation, had lower rectal thresholds to mechanical distension than those with normal stools; likewise, patients with the diarrhea-supporting criterion “loose/watery” stools had higher thresholds than those with normal stools [15]. We also found that in IBS patients without fibromyalgia, those in the IBS-C group, as compared to the IBS-D group, showed a greater prevalence of a wide range of symptoms related to the upper and lower abdomen and to musculoskeletal and constitutional functions such as early satiety, fullness, upper abdominal bloating, higher severity ratings for lower gastrointestinal bloating, neck/shoulders and back/hip pain, sleep impairment, loss of appetite and decreased sexual function [27].

Effect of food

Most patients with IBS report that food exacerbates their symptoms. Food intake could result in symptoms via excessive activation of mechanoreceptors due to increased intraluminal volumes or increased motor activity, such as a prolonged gastrocolonic response, increased gas production resulting in intestinal distension, interaction of food components with chemoreceptors in the mucosa, and triggering of true allergic responses [5]. We have shown that gastrocolonic response in IBS patients induced an increase in rectal tone and a reduction in rectal compliance in IBS-D patients as well as a decrease in rectal perception threshold in this subgroup [28]. These findings could explain the postprandial urgency reported by IBS-D patients. Furthermore, a variety of food components, including glucose, amino acids and fatty acids, interact via the release of chemical substances such as cholecystokinin. Cholecystokinin-mediated activation of vagal chemoreceptors plays a role in the regulation of gastric and intestinal motility, and activation of mechanoreceptive vagal afferents may play a role in modulation of visceral perception [5].

Capsaicin, the pungent ingredient of peppers, has been well characterized as a selective stimulant of unmyelinated C-fiber sensory afferent neurons, such as the peripheral terminals of spinal and vagal afferents. Approximately 80% of C-fiber afferent neurons are polymodal “silent” nociceptors activated by noxious thermal, mechanical or chemical stimuli. Capsaicin stimulation results in many physiological effects such as blood flow alteration, smooth muscle contractility, and the release of many neuropeptides including substance P, known to mediate pain [5]. We have shown that 1 g of guajillo chili pepper (0.112% of capsaicin) with each meal for 7 days in patients with IBS significantly decreased the rectal pain threshold to an ascending series of mechanical distensions (tolerance threshold) [29]. It appears that the development of mechanosensitivity of a population of “silent” C fibers in response to chemical irritants is related to changes in the signal transduction mechanism of peripheral nerve terminals [5].

Gender differences

Women are more likely than men to report IBS symptoms. In the U.S. Householder Survey [30], IBS was present in 14.5% of women but in only 7.7% of men. Similarly, in Mexico, in a small study on subjects aged 17–22 years, IBS was present in 29.7% of women and 6.6% of men [31]. Within clinical populations the proportion of women seen ranges from 75 to 80%; however, these differences are reversed in India [30,32], which is probably due to differences in access to medical care. Female patients report higher levels of a variety of intestinal and non-intestinal sensory symptoms despite similar levels of IBS severity, abdominal pain, psychological symptoms and illness impact [33]. In up to 40%, worsening of symptoms is seen during the menstrual cycle [33], although no differences in plasma estradiol and progesterone levels between women with and without IBS symptoms have been demonstrated. While variations related to menstrual cycle have been shown, there seems to be no differences in relation to postmenopausal stage. Lower pain thresholds have been reported in female patients, as well as in animals. Also, gender differences in the central response to visceral pain and anticipation of pain evaluated with brain PET have been reported in IBS. In contrast to females, male patients during rectal stimulation showed activation of the insula, a brain region involved in autonomic control and antinociception. Moreover, compared with female patients, male IBS patients appear to have increased sympathetic outflow to heart and skin, differences that were not observed in control subjects. Finally, gender differences in therapeutic responses to 5-HT₃ receptor antagonists are consistent with differences in the modulation of pain-processing networks by serotonergic mechanisms [34].

Cognitive factors

Inappropriate coping styles, illness behavior and inappropriate concepts about disease, nutrition and medications are common in IBS patients. These factors may determine the response and ability to cope with stressors and may influence healthcare utilization and clinical outcomes.

It is generally assumed that patients seen in primary care settings have less severe symptoms and less psychological compromise than those seen in tertiary referral centers [30]. Recruitment by advertisement is extensively used in clinical trials. Similarly, the characteristics of IBS patients responding to such advertisements may differ from those attending a specialty clinic. In a prospective study surveying 657 IBS patients – 52% recruited from a functional bowel disorders clinic and 48% from advertisement for clinic trials – the clinic population reported more prevalent and severe abdominal pain, higher psychological symptom scores, higher number of medical visits, and lower quality of life [35]. However, when visceral perception studies were conducted, both groups demonstrated evidence of hypersensitivity to rectal distension before and after sigmoid stimulation, and there were no differences based on recruitment source [35]. From these results it can be concluded

that the recruitment method affects the clinical characteristics of IBS subjects but it does not appear to influence the enhanced perception of rectal distension.

Emotional factors

Affective factors such as depression and anxiety are present in 40–60% of patients with IBS seeking healthcare [1,30]; yet the influence of psychological factors on the presentation of viscerosensory symptoms and visceral perception is poorly understood. To address this question [36], the Symptom Checklist-90R (depression, anxiety, hostility, somatization) was applied to 653 IBS patients, and rectal discomfort thresholds were evaluated in a subset of 39 by a non-biased tracking protocol during phasic rectal balloon distensions, before and after sigmoid stimulation using a second balloon. In this large sample, psychological symptom severity was not associated with overall gastrointestinal symptom severity, chronicity or demographic variables of age and gender. Bowel pattern was significantly different between the group with a normal hostility score and the group with an elevated score, as the prevalence of both normal and elevated hostility was higher among patients with alternating bowel habit compared to those with a predominant habit of constipation or diarrhea. Furthermore, the group with an elevated somatization score reported a greater frequency of viscerosensory symptoms than the group with normal range somatization. Finally, patients with elevated hostility scores had higher thresholds both at baseline and after sigmoid distension [36]. Based on these results one may speculate that psychological factors may modulate the expression of symptom generation and visceral perception in IBS.

Behavioral factors

Role of stress

Most patients report that stressful life events exacerbate or are associated with the first onset of symptoms, yet the underlying mechanism remains unknown. It has been proposed that early life events and the subsequent long-lasting alterations in stress responsiveness are important predisposing factors in visceral hyperalgesia and allodynia. In the high pressure repetitive stimulation of the sigmoid colon paradigm discussed earlier, there was a significant reduction in rectal perception thresholds in IBS patients but not in control subjects [11]. While a role for a failure in central pain-modulating systems was suggested as the pathophysiological basis for this rectal sensitization in response to sigmoid stimulation [11], this paradigm by itself is a stressful event that may have contributed to the development of rectal hyperalgesia. In an animal model in rats, long Evans dams and their male pups were randomly assigned to either no handling and no separation, or to 180 minutes daily maternal separation from postnatal day 2 to 14 [37]. At 3 months the visceromotor response to colorectal distension was quantified by recording electromyographic activity from the external oblique musculature. Baseline response to graded phasic distension was similar in both groups. Following acute one hour water-avoidance stress, there was a significant increase in

the magnitude of the visceromotor response at all intensities in the rats separated for 180 but not in the no-handling rats [37]. These findings provide an animal model that mimics key features of IBS and support a role for early life events in stress responsiveness that predispose to the development of visceral hyperalgesia. In a recent study [38] in patients with erosive esophagitis and non-erosive reflux disease, the time to initial perception, intensity rating and acid sensitivity were determined after baseline acid perfusion and after repeated perfusion during crossover randomization to stress (dichotic listening) or control condition (nature music). During stress both groups demonstrated shorter lag time to initial symptom perception compared to baseline, and higher intensity acid perfusion sensitivity scores. This study demonstrates that acute laboratory stress exacerbates gastroesophageal reflux disease symptoms by reducing perception thresholds [38]. Studies to evaluate the effect of stress in perception thresholds in IBS patients are underway.

Enteric infections and inflammation

Trigger factors in the form of physical stressors include gastroenteric infections, inflammation, and/or tissue irritation. Some patients with IBS report the onset of their abdominal symptoms following an acute episode of gastroenteritis, called “post-infectious IBS,” and up to one-third of patients develop IBS-like symptoms following a gastroenteric infection [1,39]. However, recent prospective studies found that patients who developed IBS symptoms after an acute gastroenteritis had higher scores for anxiety, depression, somatization and neurotic traits at the time of their infection before developing IBS than those patients who later returned to normal bowel function [39]. Also, patients who develop IBS symptoms have been found to have a greater number of chronic inflammatory cells in the rectal mucosa than patients who become asymptomatic [39]. In a subset of IBS patients, enhanced visceral sensitivity following a transient inflammatory process in the gut has been postulated as an etiological mechanism. Transient mucosal inflammation may induce neuroplastic changes of visceral afferent pathways that may outlast the original tissue injury [5]. These observations shed light on the complex interactions between psychological and biological factors in the development of IBS symptoms.

Chang and colleagues [40] compared perceptual responses to rectosigmoid distension in IBS patients and in patients with ulcerative colitis and mild inflammation of the rectosigmoid, in order to determine if chronic low grade inflammation limited to the mucosa might be a plausible explanation for rectosigmoid hypersensitivity reported in both IBS and UC patients. In this study, although UC activity index scores negatively correlated with perception thresholds for discomfort, rectal perception was attenuated in UC but enhanced in IBS both before and after noxious sigmoid conditioning stimulus [40]. These findings are

UC = ulcerative colitis

consistent with an adaptive response of the central nervous system to the presence of chronic visceral injury. It is suggested that low grade mucosal inflammation alone is unlikely to be responsible for symptoms in functional bowel disorders, and once again a failure in the activation of central antinociceptive mechanisms may be implicated.

Conclusions

Recent research on IBS supports alterations in physiological factors, including sensory perception abnormalities, altered autonomic input to the gut, and neuroendocrine response to stress. It is evident that hypervigilance, failure in brain modulation systems, and neurotransmitters such as serotonin play an important role in these abnormalities. In addition, cognitive, emotional and behavioral factors may interact with physiological factors, such that the integration of these multiple components integrate to promote gender and bowel habit differences, the development of visceral hyperalgesia and, finally, symptom generation.

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