Brain Responses to Visceral and Somatic Stimuli in Irritable Bowel Syndrome: a Central Nervous System Disorder?

Lin Chang, MD

Center for Neurovisceral Sciences & Women’s Health, Department of Medicine, David Geffen School of Medicine at the University of California Los Angeles, and Veterans Affairs Greater Los Angeles Healthcare System, CURE Building 115, Room 223, 11301 Wilshire Boulevard, Los Angeles, CA 90024, USA

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder characterized by visceral hypersensitivity throughout the GI tract [1]. Most studies, however, have found normal to decreased somatic perception [2–6]. The exception is a recent study demonstrating that patients with IBS had rectal hypersensitivity and somatic hypersensitivity to thermal stimuli applied to the foot and to a lesser extent to the hand [7]. There has been considerable debate on the localization of visceral hypersensitivity (eg, peripheral versus central) in IBS, but there is evidence to support predominant central mechanisms. In recent years, an appreciation for central nervous system (CNS) modulation of visceral and somatic stimuli has occurred, particularly with the growing number of functional neuroimaging studies. Recent applications of functional brain imaging techniques of positron emission tomography (PET) and functional MRI (fMRI) have begun to more directly address the role of specific central networks in normal and altered processing of visceral and somatic related input. This article reviews the findings from functional neuroimaging studies that have evaluated central processing of visceral and somatic stimuli in healthy individuals and also provides evidence for alterations of these central networks to visceral and somatic stimuli in IBS.

E-mail address: linchang@ucla.edu

0889-8553/05/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.gtc.2005.02.003
Visceral and somatic pain perception in irritable bowel syndrome

Visceral perception

Enhanced perception of visceral stimuli has emerged as an important pathophysiologic mechanism in IBS. When abnormal motility failed to be the primary mechanism to explain the etiology of IBS, a series of studies demonstrated that patients with IBS perceive noxious and non-noxious sensations to natural stimuli (contractions) or balloon distension of the small intestine [3,8–10] and rectosigmoid colon [4,11–15] at pressures and volumes that were significantly lower than in healthy individuals. The mechanisms of visceral hypersensitivity are not understood completely, and many factors (ie, genetic, motility, inflammatory, and psychosocial factors and stress) have been proposed as contributing to alterations in enteric and afferent spinal neural function and in CNS modulation of this information, which in turn produces long-term sensitization of pathways involved in the transmission of visceral sensation.

Somatic perception

In contrast to the findings of visceral hypersensitivity, most somatic pain studies have demonstrated that patients with IBS do not exhibit generalized hypersensitivity to noxious somatic stimulation [2–6]. A recent study, however, found that patients with IBS had rectal hypersensitivity and somatic hypersensitivity to thermal stimuli applied to the foot and to a lesser extent to the hand [7].

Brain activation patterns to visceral and somatic stimuli

There is growing evidence for altered visceral sensory, affective, and motor responses found in IBS to be associated with detectable differences in regional cerebral blood flow (rCBF) using functional brain imaging. Assessment of altered perception of visceral afferent information from the digestive system generally has relied on measurements of subjective ratings of controlled visceral stimuli. Recent applications of functional brain imaging techniques of PET and fMRI have begun to more directly address the role of specific central networks in normal and altered processing of visceral and somatic-related input. Functional neuroimaging is a novel method of studying central processing and modulation of brain–gut interactions in functional bowel disorders. There have been inconsistencies in the data, however, that may be caused by several factors, including methodologic differences, small sample sizes, varying characteristics of the patient population, and lack of attention to functional neuroanatomy of brain regions such as the anterior cingulate cortex (ACC). Before discussing brain activation patterns to visceral and somatic stimuli in IBS patients, analogous findings in healthy individuals will be discussed.
Healthy individuals

In healthy subjects, the brain regions most consistently activated in visceral and somatic pain are the mid/anterior insula, subregions of the ACC, prefrontal cortex (PFC), thalamus, and in some cases pontine regions such as the dorsal pons and periaqueductal gray (PAG). Although many areas are similarly activated in response to visceral and somatic stimuli, there are also differences. Two studies compared cortical processing of nonpainful visceral (rectal) and somatic (anal) sensation [16–17]. Both studies found similar areas of cortical activation; however, anal distension was associated with a more superior activation of the primary somatosensory cortex (SI) and a lack of ACC activation in one study [16] and additional activation of the SI and motor cortex, supplementary motor area, and left cerebellum in the other [17].

Two other studies compared rCBF in healthy subjects in response to visceral distension and cutaneous heat. Strigo et al [18] found that similar brain regions were activated in response to noxious esophageal distension and cutaneous thermal stimulation applied to the upper chest. These stimuli were matched for intensity but not unpleasantness (rated as greater for the visceral than somatic stimulus). Greater activation, however, was observed in the anterior insula bilaterally and the left ventrolateral PFC in the somatic group. Greater activation was demonstrated in a relatively more rostral subregion of the ACC for esophageal distension and a more dorsal subregion for cutaneous stimulation. The second study by Dunckley et al [19] found that when visceral and somatic stimuli were matched for unpleasantness, relatively greater activation occurred in regions that encode spatial orientation (dorsolateral PFC and inferior parietal cortex) during somatic (left foot and lower back) stimulation and in regions that encode emotion/interoception (right anterior insula) during rectal distension. Interoception is the sensation of the physiological self. These studies suggest that visceral stimulation is more likely to recruit areas encoding affect and interoception, while somatic stimulation is more likely to be associated with greater activation in areas involved with spatial orientation and motor response.

Irritable bowel syndrome

Studies previously compared the relationship between the intensity of lower intestinal balloon distension and regional brain activation in healthy controls [16,20–21] and in patients with IBS [22–28]. In general, several regions that are part of a central pain processing circuitry (central pain matrix), previously described in somatic pain studies [29–30] and supported by neuroanatomical data [31] (in particular the insula and the dorsal aspects of the anterior cingulate cortex) consistently were found to be activated in response to rectosigmoid stimuli [32]. In addition, other regions (including thalamus, SI and secondary somatosensory cortex) and limbic/paralimbic
regions and structures belonging to a corticopontine pain modulation system were activated to variable degrees in different studies. Preliminary evidence suggests alterations in patients with IBS occur in the activation of regions concerned with attentional processes and response selection (dorsal ACC and anterior midcingulate cortex) and cortical regions concerned with emotional and autonomic responses to stimuli (ventromedial PFC, perigenual ACC, and infragenual cingulate cortex) and subcortical regions receiving cortical projections from the latter and afferent input from the viscera (hypothalamus, amygdala, dorsal pons) in response to actual or anticipated but undelivered colorectal distension. Some of these findings are consistent with exaggerated threat appraisal, enhanced anxiety responses and hypervigilance toward gastrointestinal sensations in IBS patients [26].

The dorsal subregion of the ACC is an area that consistently is activated to a greater degree in patients with IBS compared with controls [25–26,33]. This region is concerned with cognitive processing of sensory input, including attentional processes and response selection. Furthermore, dorsal ACC activation has been shown to correlate with the subjective unpleasantness of visceral [22] and somatic pain [34]. These observations suggest that patients with IBS may fail to use CNS downregulating mechanisms in response to incoming or anticipated visceral pain. Furthermore, they show altered activation or deactivation of brain areas involved in emotional or cognitive processing of visceral stimuli, ultimately resulting in the amplification of pain perception.

The clinical relevance of the altered activation of these brain regions is supported by the findings that normalization of these patterns by different pharmacological and nonpharmacological interventions of this pattern may be associated with a reduction in IBS symptoms. Alosetron is a selective 5-HT3 antagonist that is effective in relieving abdominal pain or discomfort and urgency and normalizing bowel habits in female patients with diarrhea-predominant IBS (IBS-D) [35]. Until recently, it was assumed that alosetron mediated its effects by means of peripheral 5HT3 receptors on enteric neurons, but recent evidence suggests that it also decreases activity in frontal and limbic structures including the amygdala, infragenual cingulate cortex, and ventromedial PFC, which are associated with improvement in IBS symptoms and emotional ratings (Fig. 1) [36,37]. There is also a case report of a woman with severe IBS with psychological distress who had resolution of activations in the region of the anterior midcingulate cortex/dorsal ACC and SI following termination of an abusive relationship, resolution of IBS symptoms, and normalization of psychological symptom scores [38]. These findings support the clinically significant contribution of centrally mediated modulation of visceral pain in IBS.

In an fMRI study comparing healthy controls and IBS patients, Verne et al [39] assessed cortical processing of visceral and somatic stimuli (ie, distensions of the rectum) with 35 and 55 mmHg pulses and immersion of the right foot into a heated water bath at 35, 45, and 47°C, respectively. IBS
patients rated the rectal and cutaneous stimuli as more intense and unpleasant than the control subjects. Despite rating the intensity of visceral and somatic stimuli similarly, the IBS patients reported significantly higher ratings of unpleasantness, fear, and anxiety for the rectal stimuli than the somatic stimuli. Compared with controls, IBS patients showed greater activation of the PFC, anterior and posterior cingulate cortices, thalamus, insula, and somatosensory cortex in response to the higher-level rectal and cutaneous stimulations. Rectal stimulation, however, was associated with activation of more areas within the PFC and thalamus. The authors concluded that these findings were more likely caused by increased ascending input to the brain rather than to altered cortical modulation of sensory information. The latter cannot be excluded completely, however, because significant activations occurred in the more rostral aspects of the
ACC and medial PFC that belong to an affective network that frequently is activated during anticipation of aversive events (rather than during the actual experience) [40] and during normal and pathological anxiety [41]. It is possible that patients with IBS show greater activation of limbic/paralimbic regions that may play a role in facilitation of perceptual responses.

There is growing evidence in the literature that IBS and fibromyalgia, the latter being a chronic condition characterized by somatic pain, are both biopsychosocial disorders that commonly overlap in the same individual [42]. These findings support the clinical impression that these two functional disorders share a common central pathophysiology [42–44]. A PET study compared rCBF in IBS and fibromyalgia patients with somatic and visceral pressure stimuli. Compared with IBS only patients, greater activation of the dorsal ACC subregion was found in patients with both IBS and fibromyalgia to a somatic stimulus compared with a visceral stimulus. Furthermore, this region was activated more greatly in IBS only patients in response to a visceral stimulus than a somatic stimulus compared with IBS patients with comorbid fibromyalgia (Fig. 2) [45]. The enhanced activation of this region in both IBS and fibromyalgia patients to visceral and somatic stimuli, respectively, suggests a similar central alteration of normal

Fig. 2. Results for the interaction of type of stimulus (visceral, somatic, and clinical group (IBS and IBS + FM). There was greater activation of the dorsal ACC in IBS patients in response to visceral distension and in the IBS + FM patients in response to somatic pressure stimuli.
attentional attribution to specific afferent information from different body regions in IBS and fibromyalgia.

Summary

In healthy subjects, the brain regions most consistently activated in visceral and somatic pain are the key regions in the central pain matrix, including the mid/anterior insula, subregions of the ACC, PFC, thalamus, and in some cases, pontine regions such as the dorsal pons and PAG. Functional neuroimaging studies have demonstrated evidence of altered regional brain activation responses during visceral and somatic stimuli in IBS that have been associated with perceptual differences. Although perceptual studies have shown increased sensitivity to rectosigmoid distension in IBS, most somatic pain studies have demonstrated normal or decreased sensitivity compared with controls; however, a recent study showed increased sensitivity to thermal heat. Altered brain responses in IBS, particularly to visceral stimuli, include activation of regions concerned with attentional processes and response selection, corticolimbic regions concerned with emotional and autonomic responses to stimuli, and subcortical regions receiving cortical projections from the latter and afferent input from the soma and viscera. Altered activations of these regions also may be present in the absence of a noxious visceral stimulus. Changes in rCBF of some of these regions have been associated with treatment response in IBS. With regard to differences in cortical processing of visceral versus somatic stimuli in IBS, there have been only two studies. Greater activations of the dorsal ACC, thalamus, and PFC have been shown with visceral stimuli compared with somatic stimuli in IBS. A plausible hypothesis for the observations from brain imaging studies is that IBS patients demonstrate a compromised activation of pain inhibition circuits including those of the cortico-pontine circuit but increased activation of limbic and paralimbic circuits that may be related to pain facilitation.

References


