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Brain and Gut Interactions in Irritable Bowel Syndrome: New Paradigms and New Understandings

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Abstract

Irritable bowel syndrome (IBS) is characterized by abdominal pain and altered bowel habits. Visceral hypersensitivity is believed to be a key underlying mechanism that causes pain. There is evidence that interactions within the brain and gut axis (BGA) that involves both, the afferent-ascending and the efferent-descending pathways as well as the somatosensory cortex, insula, amygdala, anterior cingulate cortex and hippocampus are deranged in IBS showing both the activation and inactivation. Clinical manifestations of IBS such as pain, altered gut motility and psychological dysfunction may each be explained, in part through the changes in the BGA but there is conflicting information and its precise role is not fully understood. A better understanding of the BGA may shed more knowledge regarding the pathophysiology of IBS that in turn may lead to the discovery of novel therapies for this common disorder.

Keywords

irritable bowel syndrome; brain-gut axis; cortical-evoked potentials; stress; CRF; serotonin

Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders (FGIDs) with an estimated prevalence of 10–15% in the western population (1). IBS is characterized by altered bowel habits such as constipation, diarrhea or both and accompanied by abdominal pain or discomfort (2). Psychological dysfunction is also common in IBS subjects (3) including anxiety and depression. Furthermore, several conditions such as fibromyalgia, interstitial cystitis and others frequently overlap (4).

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Conflict of Interest

Dr. Rao and Dr. Coss-Adame declare no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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Visceral hypersensitivity has been described as a hallmark of IBS (5). Over 35% of IBS subjects demonstrate some degree of hypersensitivity, with either lower pain thresholds and/or higher intensity of sensations when tested with rectal or colonic balloon distensions (6,7). Visceral hypersensitivity may also contribute to symptoms such as stool urgency, bloating and pain, making it difficult to diagnose or treat this subset of IBS patients.

The cause of visceral hypersensitivity is still unknown. However, several mechanisms have been proposed including low-grade mucosal inflammation and sensitization after injury (8). An example of this is postinfectious IBS in which both inflammation and increased intestinal permeability have been described (9). Also, altered processing of sensory information at higher central nervous system (CNS) regions has been shown through functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) in IBS subjects (10–12). These findings have provided evidence that, contrary to somatic sensations which are processed in the corresponding somatosensory homunculus area, visceral sensation is processed in the secondary somatosensory cortex (12). Thus, hypersensitivity and altered CNS processing are key features of IBS.

The interactions between the gut and the CNS are complex and a vital part of normal homeostasis and regulation of GI physiology. This is a delicately balanced and fine-tuned system that allows bidirectional relay of messages between the gut and the brain, both at rest and during provocation such as after a meal or luminal distension and controls movements, reflexes, and sensory perceptions in the gut. In this review, we discuss the relevant neuronal pathways between the gut and the brain, the recent research on visceral hypersensitivity and CNS processing of gut sensation and how bi-directional neurotransmission may be altered in IBS subjects.

BGA Neuronal Pathways

The gastrointestinal (GI) tract has a unique neuronal innervation that includes both an intrinsic neural network called the enteric nervous system (ENS) and an extrinsic neural network with connections to the central nervous system (CNS) that provides sympathetic and parasympathetic innervation. The vagus nerve and its branches provide an important connection between the brain and the gut and convey both afferent and efferent information. These networks play a crucial role in the normal regulation and homeostasis of the GI tract.

Enteric Nervous System

The ENS is an autonomic network that can self-regulate itself and can function without peripheral or CNS input (13). This network is primarily housed in two nerve plexi and an intrinsic neural network: 1) Myenteric plexus (Auerbach) is located between the longitudinal and circular muscle layers and distributed along the entire GI tract, with a special configuration in the esophagus. Its main function is to control movement of gut contents and peristalsis including for example the migrating motor complex, accommodation reflex and transit through the stomach, small bowel and colon (14). 2) Submucosal plexus (Meissner) is located in the submucosal layer and regulates secretory function and sensory-motor function (13); and 3) A third component is the Intrinsic Primary Afferent Neurons (IPANs) that are located between the myenteric and submucosal plexuses, play a key role in the response to

intraluminal stimuli and regulation of behavior especially in the absence of CNS input. These neurons are essential for the regulation of local and peripherally-mediated reflexes that occur in response to various stimuli such as serotonin- Also its activation results in motor and/or secretory responses (15).

Extrinsic network

The extrinsic nerve supply to the GI tract modulates and overrides both secretion and motor function and also establishes sensory communication between the ENS and the CNS. Extrinsic network acts in response to a broad variety of stimuli (thermal, chemical and nociceptive) and via spinal and supra-spinal reflexes, including selective somato-autonomic reflexes such as the defecation reflex and the micturition reflex (16). This system has multiple takeover points; the most important one is located in the mesenteric ganglion. The extrinsic network is also comprised of two pathways: 1) Afferent: This involves vagal and spinal nerves in which the cell bodies are located outside the gut wall and they are mostly responsible for sensory transmission. There are also primary afferents with cell bodies located inside the gut wall and they are responsible for controlling the immune function in the gut (17). 2) Efferent: This is provided by both the vagal nerve and spinal nerves. These pathways connect with both the peripheral and the CNS, and provide information that induces both secretion and peristalsis.

The CNS is a two-way traffic processor and regulator of bodily function. In the gut, afferent signaling depends on several synaptic connections that begin in the mucosa or myenteric plexus and at multiple levels, both within the spinal cord and in the supra-spinal region. These connections establish a reflex arc that begins at the peripheral level and reaches the somatosensory cortex via the midbrain, and then through the descending inhibitory pathways reaches the effector organs (Figure 1).

Ascending axis

Somatosensory information differs from one site to another within the GI tract with less specialized spatio-temporal innervation in the colon to more well-differentiated areas in the anorectum. Nerve fibers converge to form nerves that convey signals to the dorsal root ganglia (DRG) where the first relay occurs, then axons transfer these to the dorsal horn of the spinal cord from where the second relay interneurons begin. From here, information is sent via spino-thalamic and spino-reticular ascending pathways to those specific CNS nuclei where the third order of neurons are located. Subsequent information is further processed in several areas in the brain such as the cognitive, somatic, emotional and motor areas; making this axis, a very complex system whose interactions continued to be explored (18).

Descending axis

Ascending signals elicit an integrated motor response at several levels, and this information is processed distally via primitive reflexes. However, descending signals that are under voluntary control start in the anorectal motor cortex that is located at Brodmann area 4 and descend through the cortico-spinal pathway where they first synapse at the anterior horn cells in the spinal cord. From here, there are relays located in the dorsal root ganglion

(DRG) (2nd synapse) and through this they reach the intestinal wall plexi in the colon and rectum, and through a complex distribution to the anal sphincter (19) (figure 1).

Stress, BGA and hypothalamic-pituitary-adrenal axis

Communication between the brain and gut is complex and involves multiple systems including the brain cortex, hypothalamus, pituitary and adrenal glands. These structures are closely linked either by the peripheral nervous system or through neurohumoral stimuli and distinct responses have been shown in healthy subjects and IBS patients (20,21). Stress has been linked to symptom generation in IBS and is associated with an altered response or a lack of adaptability in a subset of IBS patients (22). Moreover, the inability to cope with stress is closely related to psychiatric comorbidity. Anxiety and depression are reported in 30 and 22% of IBS patients and 32% have physical and/or sexual abuse (23,24). Some IBS patients have a history of physical and/or sexual abuse that can be associated with traumatic stress (25) which may lead to peripheral sensitization and abnormal CNS pain processing. Similarly, stress induction in murine models by early maternal separation has shown alterations in the *c-fos* and 5HT concentrations at the dorsal horn of the spinal cord that may produce sensitization (26). The link for stress-induced sensitization is not well-understood. There is some evidence showing that repetitive colonic distention induces increased motor activity (27) and promotes secretion of CRF. Thus, repeated peripheral stimuli may activate stress hormones that may be involved in the pathophysiology of stress-sensitization, but merits further study. These subsets of IBS patients have increased psychological stress and higher scores for IBS severity. Interestingly, treatment directed towards the psychiatric conditions can lead to reduction in symptom severity (28).

Neuroendocrine and autonomic output from the CNS to the periphery is modulated by several structures including the periventricular nucleus, amygdala and periaqueductal gray connected to central nuclei and the pituitary gland. This circuit mediates stress response through the serotonergic and noradrenergic projections and through the release of glucocorticoids causes inhibition of the cerebral cortex and hippocampus (29). Corticotrophin plays a crucial role in regulating the response to stress. The limbic system through the amygdala is involved in the secretion of corticotropin releasing hormone (CRH), as well as the prefrontal cortex and anterior cingulate cortex (30). Together they mediate the response to psychological stress through adaptive behavior and the hypothalamic-pituitary-adrenal (HPA) axis (31).

Studies in IBS patients have shown an impaired HPA axis. In diarrhea-predominant IBS (IBS-d) there is decreased cortisol levels and response, and increased vagal activation (32). In fact, these changes may preclude the development of symptoms in postinfectious IBS and correlate with levels of anxiety and prior gastrointestinal infections (33,34). Also, there are changes in the sympathetic/parasympathetic function (35). In IBS-D, there are changes showing increased parasympathetic tone (36) and adrenergic dysfunction when compared to constipation predominant IBS (IBS-c). In turn, these changes may influence colonic motor activity and IBS subtype.

Corticotrophin releasing factor (CRF) targets extra-hypothalamic sites in the CNS that mediate behavior and autonomic responses (37). Anxiety and depression are also linked to alterations of CRF-HPA axis; in rodents, administration of CRF increases anxiety and stimulates colonic motility, secretion and hypersensitivity (38). Use of CRF antagonist attenuates stress-induced anxiety, reduces visceral hypersensitivity and gastric and colonic motility in a murine model (39, 40). In humans, CRF induces visceral hypersensitivity and increases colonic motility (41) whereas administration of CRF-antagonist ameliorates these responses (42). More recently, using fMRI Hubbard et al. have shown that an oral CRF-antagonist produces inhibitory effects on emotional arousal regions (hippocampus, hypothalamus, insula, and others) in a pain-expectation model (43). Also, qualitative changes were observed in pathways to and from the Amygdala in IBS patients but not in healthy subjects, with a greater change in patients with higher levels of anxiety. Conversely, others using a CRF-antagonist did not observe such effects (44,45). Thus, CRF antagonism may be an important target for IBS associated with stress responses including anxiety.

Emotion plays a key role in altering autonomic and endocrine function which in turn may derange the emotional circuitry. In health, peripheral stimuli travel through the afferent pathways and before reaching the higher cortical regions, they are filtered and evaluated in the neocortical and subcortical regions in order to prevent a circuit overload. When the filtering process is altered, stimuli can reach emotional areas, which in turn activate deep brain structures leading to aberrant interpretation of symptoms. Consequently non-noxious stimuli can be misinterpreted as painful or harmful. How this filtering process becomes altered in IBS patients is not known.

Gender differences in BGA

IBS is more common in women in western population (45,46) but the reasons for this gender differences is not known. Women and men differ in the behavioral responses to stress and this is linked to the primitive responses to stress; in women stress induces a protective response whereas in men it tends to be aggressive (fighting process) and both are related to the primordial survival instinct but managed differently.

Similarly gender differences have been reported in the autonomic nervous system and 5-hydroxy-tryptamine (5HT) synthesis in IBS patients. Skin conductance studies have shown that when compared to IBS women, men tend to have higher skin conductance (increased sympathetic tone) and heart rate variability (lower vagal tone) (47).

The neurotransmitter 5HT is widely distributed throughout the BGA and has been linked to the regulation or modulation of several symptoms in several subtypes of IBS (48). In one study that used positron emission tomography (PET) and a tryptophan tracer, IBS women showed greater 5HT synthesis in the right medial temporal gyrus when compared to men and healthy women. This region is critically located at the multimodal sensory association cortex which in turn may play a role in visceral pain processing (49). PET scanning following rectal stimulation by balloon inflation also showed differences among women and men. Women showed greater activation of the ventromedial prefrontal cortex, right anterior cingulate cortex and left amygdala whereas men showed alteration of the dorsolateral

prefrontal cortex, insula and dorsal pons and periaqueductal gray. These differences may be related to distinctive autonomic, cognitive and antinociceptive responses (50). Likewise, PET scan has shown differences in cortico-limbic circuitry that involves emotional arousal, pain facilitation and autonomic responses between women and men (51). Finally, some reports have shown increased cortical thickness in somatosensory and primary motor cortex and decreased bilateral subgenual ACC in female IBS patients when compared to healthy age-matched controls (52).

Therapeutic Modulation of BGA in IBS

Antidepressants have been used with some success for the treatment of IBS (53), but its mechanisms of action is poorly understood. In one interesting study, using acute tryptophan depletion (ATD) by the administration of a mixture of amino acids not-containing tryptophan in healthy women and IBS-C patients, Labus et al, showed that the emotional arousal brain circuitry is over-activated in healthy women after tryptophan depletion and these changes were similar to those observed in IBS-C patients (54). More importantly, rectal balloon distensions resulted in an increased pain perception during the ATD because of induced visceral hypersensitivity. This observation suggests that a decrease in serotonin precursors in the emotional-arousal brain areas (aACC, insula and amygdala), must play a key role in the processing of pain in the CNS (55).

In another crossover study of amitriptyline or placebo in IBS patients there was decreased activation of ACC and posterior parietal cortex during balloon distention suggesting a role for TCA in IBS (56). In another study, CNS activation was examined with fMRI after rectal balloon distension in IBS subjects, during and after administration of neurokinin-1/substance P antagonist for 3 weeks followed by a 2 week washout period. They found decreased activity of the amygdala, hippocampus and ACC and in the brain regions associated with interoception (posterior insula, anterior mid-cingulate gyrus) during active treatment (57). These studies provide evidence both for the alteration in the BGA and that it can be modulated for therapeutic purposes in IBS patients.

Imaging and BGA

CNS is involved in pain processing primarily through the primary and secondary somatosensory cortex, but several other structures play a role such as the prefrontal cortex which modulates pain-related emotions, the anterior cingulate cortex (ACC) that acts as a filter for unpleasant sensations and the amygdala, which modulates stress-nociceptive sensations.

There are significant differences between the central processing of information in IBS patients when compared to healthy subjects as revealed by neuroimaging studies, with PET (58), fMRI (59) and other techniques. Unlike somatic sensation, visceral sensation is more diffuse and mainly processed in the secondary somatosensory cortex and this could explain why visceral sensation is poorly localized (60). Spinothalamic afferents have connections to the medial thalamus which is activated consistently during brain imaging, and from here they project to the ACC and prefrontal cortex (61). Insula plays an important role in the integration of somatic and visceral information (posterior) and in the processing of

emotional stimulus (anterior), especially after nociceptive stimuli (62). Also, the homeostatic afferent network (posterior insula, midcingulate cortex and thalamus) is impaired in IBS whereas the emotional arousal network (anterior insula, ACC, hypothalamus and amygdala) is overactive (63).

ACC also has a predominant role in descending pain inhibition and recent studies have shown that IBS patients with hypersensitivity to rectal distension have reduced deactivation of this region (60). Functional studies have excellent spatial resolution for superficial layers, whereas it is somewhat limited for deeper structures such as the thalamus and brain stem. Also, this technique has poor temporal resolution, and is not specific enough to assess neuronal activity distally related to stimulus (64). Hence, further studies are needed to comprehensively understand the changes in cortical and subcortical function.

Bidirectional pathways in BGA

Another novel method of studying the BGA is by assessing the afferent pathway via cortical-evoked potentials (CEPs) and the efferent pathway by motor-evoked potentials (MEPs). CEPs have excellent temporal and spatial resolution and this is made possible by using multiple recording sites. Although there are several studies that have examined the CEPs in IBS patients, few have explored the efferent pathways using MEPs.

Most of the information on CEPs in the gut is based on applying rectal or anal stimulation with either balloon distension or electrical stimulation (65). CEP assessment is not only feasible but has been shown to be reproducible (66). However, CEPs in IBS requires further detailed study and it is necessary to establish a standard technique both, for assessing CEPs and for measurement of the CEP responses such as latency, amplitude, one peak, two peaks, etc. About 24% of IBS patients have rectal hypersensitivity and show shorter latency (CEPs), while the rest of patients either have normal (49%) or even prolonged conduction (67). Others have reported shorter latencies in IBS compared to healthy controls (68). The shorter latency observed in IBS subjects may be related to an increased recruitment of nerve terminals and/or facilitation of conduction.

Bi-directional assessment of BGA has been recently described using CEPs and MEPs in healthy humans (69). Using this approach it is possible to assess the afferent and efferent pathways in the same subject thereby providing a good temporal and spatial resolution. However, there is limited data on bidirectional assessment of BGA in IBS subjects. Preliminary reports show decreased latencies for CEPs when compared to healthy subjects (70). Also the latencies for anal and rectal MEPs after transcranial magnetic stimulation of the anorectal cortex in IBS subjects appears to be shorter when compared to healthy subjects (71). These early studies show significant perturbations in the bi-directional BGA that requires further confirmation and validation.

Conclusion

Alterations in the bi-directional signaling between the enteric nervous system and the central nervous system and consequently between the brain and the gut may play a significant role in the pathophysiology of IBS. Several mechanisms may be involved in the disruption and

impairment of the brain and gut axis (BGA) that includes altered stress response, CRF release and processing, serotonin signaling and release, inflammatory insults and deranged conduction and processing of information and. There is a need for more systematic research in the IBS subtypes, in order to better understand the changes and the potential impact of these on pathophysiology and treatment.

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Figure 1.

Bidirectional brain-gut axis. Once a stimuli is applied (yellow), afferent information travels throughout nerve. First relay occurs at dorsal root ganglia (DRG) and, second relay occurs in the spinal cord gray matter (dorsal horn). From here, a stimulus travels through either the spino-thalamic or the spino-reticular pathways. The spino-thalamic pathway relays information to the thalamus where it is processed and sent to the somato-sensory cortex, prefrontal cortex and the anterior cingulate cortex (ACC). There are connections between the ACC and the sensory vagal nucleus. The first relay of spino-reticular pathway occurs at the sensory vagal nucleus and later, information is sent to higher processing centers. Once information has been processed, an efferent response is generated. This response originates from the higher processing centers (precentral motor cortex) and is then transmitted to the motor vagal nucleus or primarily originates at the vagal motor nuclei. Then, information travels throughout the cortico-spinal pathway (efferent) and makes synapses in the spinal cord (ventral horn) and in the DRG. From here, information is sent to the efferent organ (colon-rectum) to establish synapses with both the myenteric (contractile response) and submucosal plexi (secretory response). *Reproduced from Current & Emerging Treatments - 56 – 68 with permission of Future Medicine Ltd. Adapted from Current & Emerging Treatments - 56 – 68 with permission of Future Medicine Ltd*

Table 1

Mechanisms involved in the regulation of BGA and pathogenesis of IBS

Modality	Physiology	Pathophysiologic effects
CRF-HPA axis	Stress response Release of CRF Endocrine/Autonomic	Increased motor colonic activity Increased secretion Activation of emotional arousal regions Associated to anxiety and depression
Serotonergic	Regulation of peristalsis Modulation of sensation	IBS subtypes (symptoms) Mediate Gender differences Pain processing (emotional areas)
Cortical (fMRI)	Activation/deactivation of cortical areas	Spatial resolution (mapping)
Ascending signaling (CEPs)	Activation/deactivation of cortical areas Conduction	Decreased ano-cortical and recto-cortical latency
Descending signaling (MEP)	Efferent cortico-rectal and cortico-anal conduction	Decreased cortico-rectal and cortico-anal latency