The brain-gut interaction: the conversation and the implications

Abstract
Bi-directional interactions between the gut and the brain play a role in health and disease. It is involved in glucose homeostasis, satiety and obesity, functional gastrointestinal disorders and possibly in inflammatory disorders such as inflammatory bowel disease. Data is starting to elucidate the conversation between the mini brain, enteric nervous system (ENS) and the central nervous system. Various factors play a role in the conversation including sensory output via afferents, neurotransmitters and the gut microbiota.

Introduction
Do you sometimes have a gut feeling? Having a gut wrenching experience? If we look superficially at the gut, it is a pretty simple structure, a long tube with one hole at each end, and two side branches, the biliary and pancreatic ducts. Its purpose is intake, digestion, absorption, nutrient extraction and excretion. However, it is smarter and more complex than that. The gut is the only organ that contains an intrinsic nervous system with an ability to mediate reflexes in the complete absence of input from the brain or spinal cord; it really does have a mind of its own.

Bi-directional brain-gut interactions play an important role in the regulation of many vital functions in health and disease. In health, it plays a role in the regulation of digestive processes (including appetite and food intake) and in the gut immune system. In disease, it causes altered brain-gut interactions which may underlie the symptom generation in functional gastrointestinal tract disorders (FGIDs), and in the pathophysiology of various eating disorders. Routes of communication include: neural, immune system and hormonal system. The brain-gut axis can be compared with a complex reflex circuit of receptors, afferent fibres projecting to the integrative central areas and efferent fibres to the effector structures (smooth muscle and glands).

The conversation: levels of neural control
Communication is bi-directional when it comes to the brain (central nervous system (CNS) = main frame computer) and the digestive system (enteric nervous system (ENS) = iPAD). Neural networks for control of digestive functions are positioned in the brain, spinal cord, prevertebral sympathetic ganglia and in the walls of specialized organs. Control involves an integrated hierarchy of neural centres, which can be divided into 4 levels (Table I).

Table I: Levels of neural control

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>ENS – has local circuitry for integrative functions, independent of extrinsic nervous connections</td>
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<tr>
<td>Level 2*</td>
<td>Prevertebral sympathetic ganglia - peripheral reflex pathways are influenced by preganglionic sympathetic fibres from the spinal cord</td>
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<tr>
<td>Levels 3* and 4</td>
<td>Within the CNS</td>
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<tr>
<td>Level 3</td>
<td>Sympathetic and parasympathetic nervous system - outflow to the gut is determined, in part, by reflexes with sensory fibres that travel with the autonomic nervous system</td>
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<tr>
<td>Level 4</td>
<td>Higher brain centres - supply descending signals that are integrated with incoming sensory signals at level 3</td>
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Effector system | Muscles, mucosa and vasculature |

*The second and third levels provide input for the integration and action at the fourth level

The central nervous system includes the brain and spinal cord. The peripheral nervous system (PNS) is the nerve pathways that extend beyond the brain and spinal cord and can be divided into two parts: 1) somatic nervous system which is responsible for voluntary control of muscles and reaction to external sensations and 2) the autonomic nervous system (ANS) – responsible for the motor and sensation responses of our the viscera (Figure 1).

Overview of gut innervation
Nerve fibres occur in all the layers of the gastrointestinal tract (GIT). GIT viscera receive dual innervation via vagal and spinal primary afferents (extrinsic innervation). The GIT also has an intrinsic enteric nervous system (ENS), including the intrinsic primary afferent
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**Intrinsic innervation**

The ENS has about 100 million neurons, which is the largest accumulation of nerve cells outside the brain. It has structural and functional similarities to the brain and can be considered as the autonomic nervous system of the gut. The brain and ENS can be compared to a computer network, with the brain being the main frame computer and the ENS the laptop or iPad. The ENS (the iPad of the GIT) is a collection of neurons that constitutes “the brain of the gut”. It controls motility, regulation of fluid exchange, exocrine and endocrine secretions (gastric and pancreatic), defence actions of the GIT wall, enteric network reflex activity, neuropeptide release, microcirculation of the gut and it is also involved in the response to enterotoxins, and in the regulation of immune and inflammatory processes. It contains complete reflex circuits that detect the physiological condition of the gastrointestinal tract, integrates information about the state of the gastrointestinal tract, and controls gut movement, fluid exchange between the gut and its lumen, and local blood flow.

The ENS retains communication with the CNS (the main frame computer) through parasympathetic and sympathetic afferent and efferent neurons. The part of the nervous system that is connected with the enteric neurons is known as the central autonomic neural network. Together with these connections, the ENS provides neural control of all the functions of the GIT (Figure 2).

ENS is embedded in the wall of the digestive tract and is basically organized into two networks, the myenteric plexus (intermuscular) and submucosal plexus. The latter, the second brain (ENS), is composed of a network of different kinds of neurons, neurotransmitters and proteins that carry messages between other neurons, interneurons and immune cells.

The muscles, mucosal epithelium and vascular system are the gut’s effector systems. The behaviour of the gut, at any given moment, reflects integrated neural activity of these effector systems. The ENS is a mini brain (iPad) on which a library of programmes for different patterns of behaviour is loaded. Digestive, interdigestive and emetic patterns of intestinal behaviour reflect outputs from these three respective programmes (documents produced by the iPad).
Approximately 20 types of enteric neurons are divided into three classes according to their functions: intrinsic primary afferent neurons (IPANs), also referred to as intrinsic sensory neurons, interneurons and motor neurons.1,2

The gastrointestinal tract also has an extensive endocrine signalling system, and many gastrointestinal functions are under dual neuronal and endocrine control.2,12 Enteric neurons interact with the extensive intrinsic immune system of the gastrointestinal tract. Enteric neurons secrete a large number of neurotransmitters (Table II),1,11 In fact, 95% of the body’s serotonin is found in the ENS, along with the major cells of the immune system’s inflammatory network.1,14,16 Neuropeptides, once believed to exist exclusively in the central nervous system, are also important in regulating blood flow. The extrinsic afferents (i.e. sensory nerves) generally travel together with these efferents and they carry information about visceral stimuli to the brain.19

**Enteroenteric reflexes**

Signals between gut regions are carried both by hormones [such as cholecystokinin (CCK), gastrin and secretin] and by nerve circuits.8

**Neuroimmune interactions**

Two-way communication (another two way street) occurs between the enteric nervous system and the immune system of the gastrointestinal tract, that is, transmitters released by the terminals of enteric neurons in the mucosa influence immune-related cells, such as mast cells (MC), and the cells of the mucosa release active substances, including cytokines and mast cell tryptase, that act on enteric neurons.11,14 The inter-communication that occurs in disorders such as IBS is briefly discussed later in this article.

**Extrinsic innervation**

The ENS is well connected to the central autonomic network in the CNS through both motor and sensory pathways of the sympathetic and parasympathetic nervous system (Figure 2).4,11 The information collected by receptors is transmitted via autonomic fibres.4 In addition, the gastrointestinal tract receives a dual extrinsic innervation. The efferent nerves which can be sympathetic and/or parasympathetic fibres that modulate motor and secretory patterns programmed in the enteric nervous system. Sympathetic fibres are also important in regulating blood flow. The extrinsic afferents (i.e. sensory nerves) generally travel together with these efferents and they carry information about visceral stimuli to the brain.19

**Sensory output from the gut to the CNS**

The receptors of the gut are mostly specialized afferent neural terminations capable of directly collecting sensory information (chemical, mechanical, thermal and pain) and carries it via the vagal and splanchnic nerves to the brain.9 Primary afferents in the smooth muscle layer are sensitive to mechanical distension of the gut. They have a very low threshold and convey information about the fullness and nausea, discomfort and pain we perceive. The afferents can be activated by mechanosensitivity, chemosensitivity, sensory signal transduction and promiscuous chemosensitivity.9,20

**Mechanosensitivity**

Nerve terminals convey mechanosensory information relevant to distention and contraction of the bowel wall.9 However, the information generated at these sites and conveyed by vagal and spinal mechanosensitive afferents is very different.9 It is hypothesized that vagal afferents are involved in physiological regulation while spinal afferents are responsible for mediating pain in diseases such as IBS.9,20 Mechanosensitivity can be influenced by a wide range of chemical mediators released as a consequence of injury or inflammation.9,20

**Chemosensitivity**

Many chemical mediators are able to influence the sensitivity of visceral afferents.20 Splanchnic primary afferent neurons are

<table>
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<th>Table II: Neurotransmitters in the ENS</th>
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<tr>
<td><strong>Amines</strong></td>
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<tr>
<td>Acetylcholine</td>
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<tr>
<td>Norepinephrine</td>
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<td>Serotonin (5-hydroxytryptamine)</td>
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<td><strong>Amino acids</strong></td>
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<td>γ-Aminobutyric acid</td>
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<td><strong>Purines</strong></td>
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<td>ATP</td>
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<td><strong>Gases</strong></td>
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<tr>
<td>Nitric oxide</td>
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<tr>
<td>Carbon monoxide</td>
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<td><strong>Peptides</strong></td>
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<tr>
<td>Calciton gene–related peptide</td>
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<tr>
<td>Cholecystokinin</td>
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<tr>
<td>Galanin</td>
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<tr>
<td>Gastrin-releasing peptide</td>
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<tr>
<td>Neuromedin U</td>
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<td>Neuropeptide Y</td>
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<tr>
<td>Neurotensin</td>
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<td><strong>Opoids</strong></td>
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<tr>
<td>Dynorphin</td>
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<tr>
<td>Enkephalins</td>
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<tr>
<td>Endorphins</td>
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<tr>
<td>Peptide YY</td>
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<tr>
<td>Pituitary adenyl cyclase–activating peptide</td>
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<tr>
<td>Somatostatin</td>
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<tr>
<td>Substance P</td>
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<tr>
<td>Thyrotropin-releasing hormone</td>
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<tr>
<td>Vasoactive intestinal CONTRACTOR (an endothelin)</td>
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<tr>
<td>Vasoactive intestinal polypeptide</td>
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nociceptors, responding to high intensity stimuli, and are involved in sensing pain in the gastrointestinal tract. These mediators can influence the visceral afferents through three processes: direct activation, sensitization and through altering the phenotype of the afferent nerve. Neurotransmitters, such as calcitonin gene–related peptide and substance P may be important in visceral nociception and in the activation of nociceptive afferent neurons in conditions such as irritable bowel syndrome, as well as noncardiac chest pain, intestinal ischaemia, and inflammatory bowel disease.

**Sensory signal transduction**

Some mediators produce a direct stimulation of visceral sensory nerve endings. In this case, the afferent neurons do not respond directly to a stimulus, but after the release of a mediator from a primary sense cell. Cells that act as primary signal transducers include enterochromaffin (EC) cells which release serotonin (5-HT) and the enteroendocrine cells that release CCK both of which are thought to play a role in the pathophysiology of IBS. In order to bridge the large gap between ECs and their targets, a massive amount of neurotransmitter is released, which makes transmitter removal mechanisms critical. The ECs are particularly important in the GIT motility and IBS through 5-HT's role in signal transduction which initiates peristaltic and secretory reflexes. An overflow of 5-HT into the GIT lumen and portal circulation are thought to play a role in IBS pathophysiology.

**Promiscuous chemosensitivity**

In contrast to the specific signalling pathways that exist in vagal mucosa afferents, there are also mediators that can influence the sensitivity of spinal afferents in a more promiscuous manner. Various cells types (macrophages, MCs, muscle and neurons) can release these substances under conditions of inflammation, injury or ischaemia. Although some substances act directly on sensory nerve terminals, other substances acts indirectly, through a series of cascades.

**The implications: irritable bowel disease**

Malfunction in the brain-gut axis plays a role in satiety, obesity, glucose control and various FGIDs such as irritable bowel disease (IBS). IBS is a multidimensional symptom complex characterized by abdominal pain and discomfort, bloatedness and altered bowel habits. In addition, there is a substantial psychological co-morbidity in many patients, frequent with extra-intestinal manifestations. IBS is affected and modulated by many factors related to emotional factors, visceral function and sensation. The symptoms associated with IBS can be best explained as a dysregulation between the complex events occurring in the gut lumen, the mucosa, the ENS and the CNS, which results in alterations in sensation, motility and immune function.

**Abnormal motility**

Although initially considered the main pathophysiological cause of IBS, consistent motility abnormalities have not been demonstrated in all IBS patients. Dysmotility in the gut can develop through dysfunction in any level in the brain-gut axis. Stress causes a release of central corticotrophin-releasing factor (CRF) which accelerates colonic transit and defaecation through stimulation of vagal efferents. Inflammatory mediators, neuropeptides and other processes may directly affect muscle function or other elements in the ENS.

**Visceral hypersensitivity**

Abdominal pain, tenderness and visceral hypersensitivity are common symptoms in IBS, but the exact site of the disordered neurophysiology is not known. There are several possible locations for the sensory abnormalities in IBS such as the receptors in the gut wall, the primary sensory afferent neurons, the spinal cord and the brain itself. In addition, descending inhibitory mechanisms for the control of visceral signal transmission may be altered.

A lower threshold to discomfort and the threshold to pain during balloon distension is again a common, but not a universal, finding in patients with IBS. Visceral hypersensitivity involves both the peripheral and central nervous system. Afferents carry the message from the gut to the brain where pain is perceived and it can be amplified in the gut, spinal cord or the brain resulting in an increase in brain response. Mechanosensitive afferents may be hypersensitive to noxious stimuli and transmit erroneous information to the central nervous system. On the other hand, the information may be accurate but misinterpreted by central processing circuits responsible for visceral nociception. In some patients, derangements may exist in both brain and periphery.

Many patients report postprandial worsening of symptoms. Enhanced colonic sensitivity has been demonstrated in IBS patients after duodenal lipid administration, suggesting an exaggerated sensory component of the gastrocolonic response. 5-HT<sub>3</sub> receptor stimulation by serotonin seems to be directly related to visceral nociception in rodents, thus serotonin may modulate nociception.

**Central nervous system modulation**

Results from a recent meta-analysis documented that colonic stimulation causes a consistent activation in regions associated with visceral afferent processing (i.e. thalamus, insula, anterior cingulate) in both controls and IBS patients, but there is considerable differences in specific location of foci. IBS patients showed more consistent activation in regions associated with emotional arousal (pregenual anterior cingulated cortex, amygdale and a mid-brain cluster) and cognitive processing of sensory input and endogenous pain modulation. Reduced activation was noticed in the perigenual cortex, temporal lobe and brain stem. This data does not necessarily indicate a central aetiology for visceral hypersensitivity, but may indicate a normal cerebral response to...
heightened incoming sensory signals. IBS patients seem to fail to use central nervous system down-regulating mechanisms in response to incoming or anticipated visceral pain.

Autonomic dysfunction has also been reported in IBS, but the results are inconsistent. Increased sympathetic and decreased parasympathetic activity in IBS patients compared to control is the most common abnormalities reported.

**Stress**

Stress has always been considered as part of the pathophysiology of IBS. It has been postulated that sustained stress (central or peripheral; in predisposed individuale) can result in permanent pain increase stress responsiveness of the central stress circuits and eventually result in a vulnerability to develop functional and affective disorders. Stress is strongly associated with the onset, exacerbation and severity of IBS symptoms. In addition, IBS patients report more lifetime and daily stressful events compared to healthy individuals.

Normal people also exhibit gut function abnormalities during stress such as butterflies in the stomach before a game of sport. However, it would appear that IBS patients have a greater reactivity to stress than healthy individuals. It is also of note that IBS patients often have concurrent psychological disturbances. A proposed model in terms of stress and IBS suggests that adverse events (past or present) can influence stress responsiveness, physiological responses as well as the susceptibility to developing and exacerbating this functional disorder through amplification of brain-gut interactions.

Recent data suggest a dysregulation of adrenal activity in IBS patients. IBS patients, compared to controls, showed increased salivary cortisol levels in the morning, while they maintained the physiological circadian fluctuations. Stressors (physical and psychological) can activate the hypothalamic-pituitary-adrenal axis (HPA) as well as the sympato-adrenomedullary system, resulting in central release of CRF and consequently glucocorticoid secretion by the adrenal cortex into the circulatory system. Cortisone affects, amongst others, immune response, metabolic actions and motility in IBS.

In response to distension, central CRF can cause peripheral activation of MCs, sensitizing of the mechanoreceptors or promotion of MC degranulation in the gut. In addition CRF can be synthesized in colon mucosa cells and the local release can modulate the enteric immune system and other gut functions. CRF signalling also promotes immune response and stimulates lymphocyte proliferation through IL-2 receptor expression, which in turn enhances IL-1 and IL-2 production. CRF plays a role in endotoxin induced cytokine release, chemotaxis of mononuclear cells, induction of macrophage activation leading to local release of oxidative mediators and proinflammatory cytokines.

The HPA axis may play a role in non-standard immune activation in the gut wall. This is represented by an abnormal mucosal response to altered microbiota such as increased infiltration of mast cells, enteroneocrine cells and mononuclear cells in the colonic mucosa, without frank inflammation.

Research focusing on the role of anxiety in the exacerbation of IBS symptoms investigated the role of the limbic system and mainly that of the amygdaloid nucleus in visceral responses to stress. It would appear that descending neural pathways from the amygdale are involved in the viscotor motion, mediated by CRF-1 receptors which responsible for colonic and anxiogenic responses to stress. Endogenous serotonin peripherally released in response to stress is probably involved in central CRF-induced stimulation of colonic motility by acting in 5HT3 receptors. CRF receptors are also located peripherally on enteric smooth muscle and can be stimulated by locally produced CRF; by enteric neurons, ECs and immune cells.
administration of the probiotic *Bifidobacterium infantis* 35624 and may be related to the normalization of the cytokine ratio. Although some changes in chemokines have been reported, their role in IBS is not fully understood.29

The fact that percentage of colonic mucosa infiltrated by immune cells in IBS was between the extremes of healthy and true inflammation as in IBD, may indicate a common physiological factor triggering these disorders. Thus IBS and IBD may represent two ends of a wide spectrum of chronic inflammatory disorders.29

MC nerve interactions are involved in intestinal epithelial dysfunction and the development of stress-induced increase of colonic permeability.29 The continued activation of MC could contribute to the motility dysfunction, and be due to their proximity to neurons in the ENS, also to the visceral hypersensitivity in PI–IBS.23,29,32 Many, but not all, studies found increased numbers of MC in patients with IBS, but increased numbers of MC does not necessarily imply pathology, unless there are activated.22,32 Increased number of degranulating MC has been demonstrated in IBS patients22,23 and has been correlated with the severity and frequency of abdominal pain, bloating and is possibly with rectal hypersensitivity.22,23 The MC may also be involved in the communication with intrinsic and extrinsic nerves to modulate sensory functioning.22 Release of mediators from the MC include responses in the ENS such as visceral hyperalgesia and increased mucosal permeability, as well as the generation of symptoms such as abdominal pain and bowel habit.29

Neuropeptides

Neuropeptides plays a role in the regulation of gut motility and secretion2 and appear to modulate sensitivity.

Serotonin

Serotonin, a biogenic amine, is predominantly located in the gastrointestinal tract.3 Ninety-five per cent of serotonin is found in the GIT of which 90% is localized in the EC and 10% in enteric neurons.2,3,27 Serotonin is involved at just about every level of the bi-directional communication between gut and brain. Recent studies have implicated alterations in serotonin (5-hydroxytryptamine, 5-HT) signalling in FGIDs, such as the IBS, chronic constipation, diarrhoea, and functional dyspepsia. GIT disorders may be related to an imbalance of serotonin in the gut or a variant reaction of the GIT to chemical or mechanical stimulation and to experimental stressors.4

Serotonin can be released from enterocytes and ECs in response to chemical or mechanical stimulation and to experimental stressors.4 There are seven distinct families of 5-HT receptors, but two (5-HT5 and 5-HT3) predominate in the gut.7 Although 5-HT3 receptors are located on enteric nerves within the myenteric plexus as well as on vagal and spinal afferents, it can also be found in the brain, spinal cord and dorsal root ganglion neurons.4,15,22 Serotonin is an important mediator of peristaltic reflex4 and activation of 5-HT3 receptors is associated with enhanced GI motility, secretion, and sensation.15 The more potent effect of the 5-HT3 receptor is to activate extrinsic nerves of the gut.3

There is evidence of enhanced postprandial serotonin release in IBS patients.27 A recent study showed increased serotonin concentration in colonic mucosa of patients with constipation predominant IBS (C-IBS) compared to those with diarrhoea predominant IBS (D-IBS).20 IBS-C and IBS-D differ in terms of both number of EC and 5-HT release in most, but not all,34,35 studies.16,36,37 Both 5-HT release and EC cell population in the gut is increased in patients with IBS-D.14,16,37 whereas in some subgroups of patients with chronic constipation, there appears to be a decreased number of EC cells.14,38,37 suggesting that stimulation of the serotoninergic pathways may improve symptoms in these patients.14,16 Altered EC cells and/or 5-HT signalling can result in gastrointestinal dysmotility, visceral hypersensitivity, and secretomotor abnormalities. The body is able to regulate the availability of serotonin within the extracellular space through serotonin reuptake transporter (SERT).14 The efficacy of 5-HT3 receptor blockade in women with diarrhoea predominant IBS suggests an over-stimulation of secretomotor neurons by serotonin.

Various other mediators and transmitters are involved in the regulation of colonic motility and visceral perception such as calcitonin gene related peptide, substance P, nor-epinephrine and opiates but their role remains to be elucidated.27

Microbiota

Research is emerging showing the possible role of the gut microbiota in IBS, particular their role in the brain-gut axis conversation. Dysbiosis, including small bowel bacterial overgrowth, alterations in the quantity of microbiota as well as the composition of the microbiota is well documented in IBS as well as the role of infections and antibiotics in the pathophysiology of IBS.20 Although the mechanisms are not yet fully elucidated, it is known that the microbiota plays a role in the maintenance and function of intestinal epithelial cells which plays a central role in intestinal immunity. Evidence is also emerging for the role of the presence of inflammatory and immune components in IBS. In addition, supplementation with probiotics can alter the luminal environment or microbiota composition of the gut. Interaction between the host and the microbiota plays an important role in nociception as well as gut motility.9 Psychological stress has been shown to reduce the numbers of *Lactobacilli* and increase the growth of pathogens.9 The microbiota is able to affect sensorimotor functions of the gut in three ways through end products of bacterial fermentation and metabolism, neuroendocrine factors and immune mediators.40

The unravelling of the complexity of the brain-gut communication is beginning to afford a better understanding of the pathophysiology of IBS and further research is likely to lead to its more specific treatment.
References


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