Brain–gut interaction in irritable bowel syndrome

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Abdominal pain occurs commonly in irritable bowel syndrome. The mechanism of pain is likely to be either peripheral or central sensitization of gut nerves or aberrant brain processing. Functional brain techniques are now allowing the study of brain–gut interactions.

Functional gastrointestinal disorders are conditions that are primarily characterized by chronic abdominal pain or discomfort often associated with dysregulation of gut function in the absence of any detectable organic disease (Thompson et al, 1999). In clinical practice, functional gastrointestinal disorders are further categorized by primary symptom characteristics; for example, irritable bowel syndrome (IBS) is classified as a functional gastrointestinal disorder because the symptoms are attributable to the mid or lower gastrointestinal tract.

DIAGNOSTIC CRITERIA FOR IBS

One of the difficulties in dealing with patients with suspected IBS is the uncertainty associated with establishing a diagnosis. There is presently no established biological marker for IBS, so Thompson et al (1999) suggested that the diagnosis of IBS can be made if during at least 12 weeks (which need not be consecutive) in the preceding 12 months of abdominal discomfort or pain two or more of the following three features are present:

- Pain relieved with defecation
- Onset of pain associated with a change in frequency of stool
- Onset of pain associated with a change in form (appearance) of stool.

EXTENT OF CLINICAL PROBLEM

IBS is a disturbingly common functional gastrointestinal disorder, with GP-based surveys revealing that 30% of their patients suffering a gastrointestinal complaint have IBS (using both the Rome (Vanner et al, 1999) or Manning (Manning et al, 1978) criteria), with an unexplained female preponderance (Thompson et al, 2000). This distressing condition presents a major challenge for gastrointestinal health-care professionals, while concomitantly placing significant demands on health budgets (Talley et al, 1995). More indirect costs include work absenteeism and an impaired quality of life (Drossman, 1999). Despite these facts, the pathophysiology of this disorder remains unclear.

Previously consigned to the realm of the unimportant and psychosomatic, research is now beginning to define specific mechanisms of IBS. A convergence of evidence from human and animal studies now sustain the theory that IBS results from a combination of altered gastrointestinal motility (Mayer et al, 2001), deranged gut epithelial function (Barbara et al, 2002) and visceral hypersensitivity (Chan et al, 2001). It is the latter topic that this article will focus on, providing a brief overview of the complexity of this major clinical problem while outlining the proposed interaction of the brain and gut in IBS and describing the current research methods available for investigating this brain–gut interaction.

BRAIN–GUT INTERACTION IN HEALTH

The neural regulation of gut function is complex and mainly under autonomic control, with the proximal end of the oesophagus and the external anal sphincter being the exception. The muscles in this anal region consist of striated fibres that are predominantly under voluntary control. The rest of gut function is modulated by a complex integration of efferent and afferent pathways consisting of the enteric nervous system, which is a group of nerve cells in the gut wall, and the autonomic nervous system, comprising sympathetic and parasympathetic nerves (Aziz and Thompson, 1998) (*Figure 1*). These are further subdivided into intrinsic and extrinsic components.

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Intrinsic components

Intrinsic components are provided by the enteric nervous system and consist of neurons of the myenteric plexus (Auerbach's plexus) and submucosal plexus (Meissner's plexus), forming a complex internal regulator for the modification of gastrointestinal motility. The enteric nervous system receives afferent signals directly from the gut and can rapidly respond with or without involving the autonomic nervous system. (For a more extensive review see Costa and Brookes (1994).)

Extrinsic components

Extrinsic components consist of either somatic motor nerves (striated muscles in the pharynx are innervated by lower cranial nerves, while the anal canal is innervated by the pudendal nerve) or the autonomic nervous system nerves (splanchnic are sympathetic and vagal/sacral are parasympathetic). The sympathetic nervous system acts mainly to decrease gastrointestinal activity, and the parasympathetic nervous system stimulates gastrointestinal motility. Stimuli within the gut are detected by vagal and spinal afferents. Each have a different function, and are therefore considered to have different roles in mediating sensation.

Vagal afferents: These are responsible for low-threshold activity, and predominantly convey physiological information. They are probably involved in behavioural and emotional aspects of pain, rather than cognition.

Spinal afferents: These are able to encode noxious events and provide the main pathway for pain perception (Grundy, 2002).

BRAIN–GUT INTERACTION IN DISEASE

Patients with IBS often complain of recurrent episodes of lower abdominal pain, altered frequency of defecation and a feeling of abdominal distension. A large proportion of patients with IBS also suffer depression, hysteria and obsessive–compulsive traits, with psychological stress often triggering an exacerbation of symptoms (Ringel, 2001). A characteristic pathophysiological abnormality found in association with most of these symptoms is a heightened perception of visceral sensation (hypersensitivity). This has been widely demonstrated in IBS, with patients demonstrating lower pain thresholds to visceral distension than controls (Mertz et al, 1995).

Various hypotheses have been proposed to explain the aetiology of visceral hypersensitivity:

- Sensitized gut afferent nerves, such as the vagus, splanchnic and pelvic nerves (peripheral sensitization)
- Sensitized spinal cord neurones (central sensitization)
- Aberrant brain processing of a visceral sensation.

Peripheral sensitization

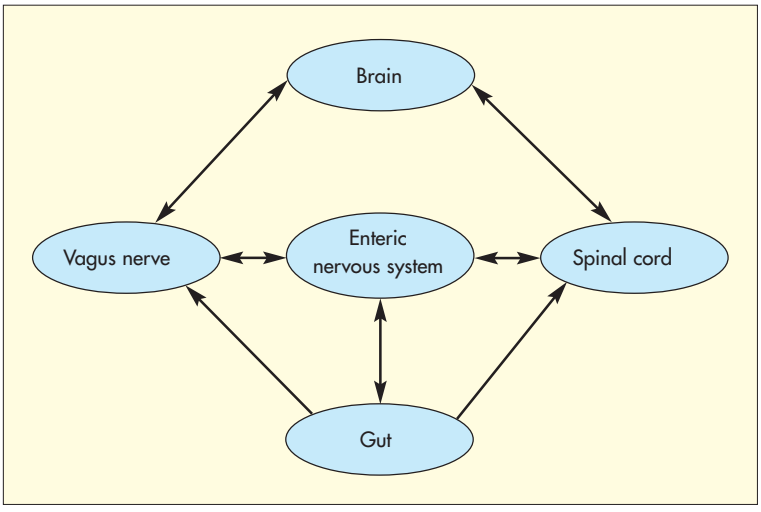
Similar to other organs within the body the gut may become damaged by trauma, surgery and bacterial or viral invasion. This triggers a rapid reaction in the tissue local to the site of injury, causing temporary alteration in the gut epithelium with associated inflammation. Prompt medical or surgical intervention relieves the immediate problem, but many patients develop prolonged symptoms of pain after the original insult has passed. This persistence of pain is thought to be caused by the presence of a range of inflammatory mediators at the site of injury (bradykinin, prostaglandin, adenosine, 5-hydroxytryptamine and nerve growth factors), which activate and sensitize nociceptive afferent nerves.

In patients who develop post-infective IBS it is postulated that an inappropriate learned response has occurred as a result of the modulation of the sensory nerve endings, causing changes in gut regulation. Biopsies taken from patients with chronic visceral hypersensitivity without evidence of overt inflammation have shown demonstrable cellular changes indicative of peripheral sensitization (Lowe et al, 1997). It is therefore considered that in patients with IBS peripheral sensitization plays a part in visceral hypersensitivity.

Central sensitization

A secondary consequence of sensitized gut afferent nerves is the development of an area of hypersensitivity in the healthy, undamaged tissue surrounding the site of injury. Repetitive dis-

Figure 1. Schematic representation of the innervation of the gut.



charge from the nociceptive gut afferents (C-fibres) caused by local injury or inflammation may result in an alteration of pain processing within the dorsal horn of the spinal cord or within the CNS. This increased afferent fibre excitability causes the release of glutamate, which causes the activation of the spinal N-methyl-D-aspartate (NMDA) receptors.

Prolonged activation of the NMDA receptors changes the receptive fields of the spinal neurones at the site at which visceral and somatic nerves converge on second-order afferent neurones. This results in recruitment and amplification of both non-nociceptive and nociceptive inputs from healthy gut tissue adjacent to the primary site of inflammation (Woolf, 1995; Woolf and Salter, 2000). The effect of this is that a physiological stimulus that was previously painless is now perceived as painful (allodynia), while a painful stimulus is perceived even more intensely (hyperalgesia).

This phenomenon has been particularly well studied in somatic tissue, revealing that the sensitization can persist long after the original damage has recovered. It is likely that a similar mechanism is responsible for the hypersensitivity observed in some patients with IBS. Indeed, it is known that patients with IBS demonstrate both allodynia and hyperalgesia and also have a greater somatic radiation of pain when their gut is stimulated in comparison with healthy subjects, suggesting that sensitization of converging viscerosomatic spinal neurones plays a role (Moriarty and Dawson, 1982).

Human models of peripheral and central sensitization

Until recently the role of peripheral and central sensitization in mediating visceral hypersensitivity was unclear owing to a lack of experimental models and non-invasive neurophysiological techniques assessing visceral afferent pathways. The first consistent model for human visceral hypersensitivity has now been developed (Sarkar et al, 2000). Sarkar et al demonstrated that the infusion of hydrochloric acid into a healthy oesophagus reduces the pain threshold, not only in the acid-exposed region (primary hyperalgesia) but also in the adjacent, unexposed region (secondary hyperalgesia).

Studies on somatic pain models suggest that primary hyperalgesia is caused by peripheral sensitization, and secondary hyperalgesia is caused by central sensitization. This suggests that gut injury can lead to both peripheral and central sensitization, and could be in part the pathophysiological basis for visceral hypersensitivity seen in patients with IBS. This is supported by studies suggesting that patients with IBS demonstrate greater rectal secondary hyperalgesia in response to experimental distension of the sigmoid colon in comparison with healthy controls (Munakata et al, 1997).

Aberrant brain processing of a visceral sensation

The brain is important for both receiving and processing ascending pain signals in addition to controlling the descending antinociceptive system designed to inhibit the transmission of pain. Any alteration in the cerebral processing of these signals may alter the sensation of pain experienced. The role of cognitive influences such as anticipation, fear and hypervigilance (excessive attention to a painful stimulus) on the perception of visceral sensation is considered of great significance.

The manipulation of attention and changes in arousal level produced by stress and relaxation have been shown to alter the perceived intensity of gut distension-related sensations (Accarino et al, 1997). Patients with functional gastrointestinal disorders often selectively attend to sensations that arise from the gut (Whitehead and Palsson, 1998), which may be an important factor in sustaining symptoms and contributing to the development of visceral hypersensitivity in IBS.

TECHNIQUES FOR MEASURING BRAIN–GUT PATHWAYS

Standard measurements of visceral sensation rely on descriptive methods of reporting pain. While great care is taken to eliminate subjective factors from introducing response bias, it remains difficult to objectively measure sensation with these techniques.

The development of non-invasive techniques such as cortical-evoked potentials, functional magnetic resonance imaging, positron emission tomography and, more recently, magnetoencephalography now enable detailed investigation of the human brain processing of visceral sensation. In addition they allow for the identification of brain modulation involved in association with cognitive factors such as attention (Jovicich et al, 2001). Each of these measurements rely on the principle that as activation occurs within the body, the part of the brain associated with the functioning organ has an increase in neuronal activation with concomitant increase in metabolic activity and augmentation of local blood flow. It is the ability to

measure these individual parameters that differentiates the type of test used.

Cortical-evoked potentials: These are measurements of the electrical potentials generated by cortical neurons in response to a series of repeated sensory stimuli. Measurement is non-invasive and involves the recording of the electroencephalogram via surface electrodes placed on the scalp. Cortical-evoked potentials can now be successfully recorded from multiple sites within the gut and be used to investigate the integrity and physiological characteristics of visceral afferent pathways (Hobday et al, 2002).

Functional magnetic resonance imaging: This measures the magnetic signal provided by the change in oxyhaemoglobin levels in capillaries adjacent to active brain tissue. Studies in patients with IBS have demonstrated that activation of the anterior cingulated cortex (CNS pain centre) occurs in response to rectal stimulation to a greater extent than in controls (Mertz et al, 2000), suggesting heightened pain sensitivity of the brain–gut axis in this group.

Positron emission tomography: This measures cerebral blood flow or tissue metabolic activity following systemic injection of a radioisotope, such as labelled water ($H_2{}^{15}0$) or a glucose analogue (^{18}F-fluorodeoxyglucose). However, the use of a radioisotope precludes the use of positron emission tomography in repeated studies. Positron emission tomography has shown that the perception of acute rectal pain is associated with activation of the anterior cingulated cortex in healthy subjects, and patients with IBS show an aberrant brain activation pattern during both noxious rectal distension and the anticipation of rectal pain (Silverman et al, 1997).

Magnetoencephalography: This is a technique that enables the detection of minute magnetic fields generated by active groups of cortical neurons. Magnetoencephalography has comparable spatial resolution to positron emission tomography and functional magnetic resonance imaging, but directly reflects changes in neuronal activity on a millisecond-by-millisecond basis. Recent advances in magnetoencephalography analysis have made it feasible to study the visceral–cortical pain matrix in real time, which may enable us to identify the sequence of activation of individual cortical regions. This temporal information will ultimately provide the opportunity to identify specific neurophysiological abnormalities present in individual patients with IBS (Aziz et al, 2000).

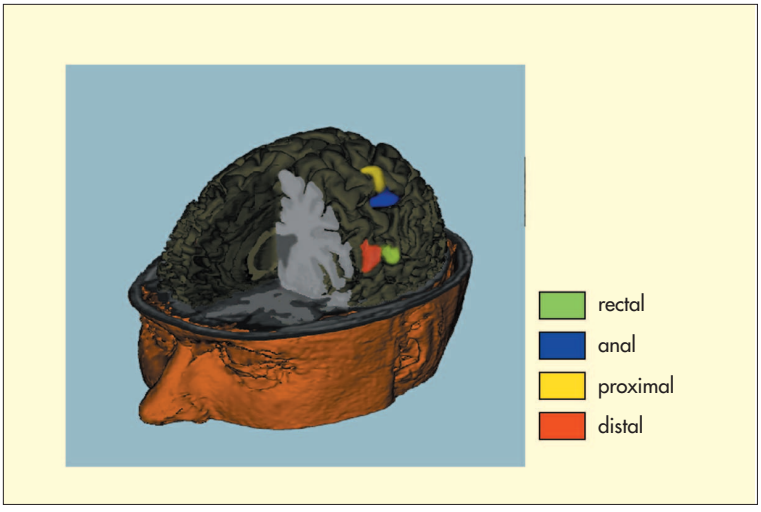
LITERATURE ON THE BRAIN PROCESSING OF VISCERAL SENSATION

Studies using functional brain-imaging techniques have provided insight into the role that cognitive and emotional factors play in modulating the brain processing of somatic sensation (Derbyshire et al, 1998; Ploghaus et al, 1999; Peyron et al, 2000). These studies highlight the importance of the neural network, which integrates cognitive and sensory information.

Functional brain-imaging techniques have also been used to identify brain areas that process human visceral sensation (*Figure 2*) (Aziz et al, 1997, 2000; Furlong et al, 1998; Hobson et al, 2000). These studies show that the cortical processing of visceral sensation involves initial processing in the primary and secondary somatosensory cortices for sensory discrimination, with subsequent involvement of the anterior cingulated cortex and pre-frontal cortices for affect and cognition respectively. This indicates that humans are not only able to localize the site of gut sensation, but are also able to assign emotional valence to it.

Recent studies (Phillips et al, 2003) that have examined the influence of emotional context on the cerebral processing of oesophageal sensation have demonstrated that visceral sensation is modulated by the emotional context in which it is perceived, and that the dorsal anterior cingulate gyrus and anterior insula integrate emotionally salient and gut-sensory information.

Figure 2. Results of a functional magnetic resonance imaging study, demonstrating the cortical representation of the proximal (striated muscle) and the distal (smooth muscle) oesophagus in comparison with that of the anal canal or the rectum. The smooth muscle regions of the proximal and distal gut have a representation on the caudal part of the primary sensory cortex, whereas the striated muscle regions are represented on the more rostral parts of the primary sensory cortex.



Experiments involving viewing of faces depicting progressively more fearful expressions have shown that as context becomes more negative, there is an amplification of sensory input such that a non-painful visceral stimulus is interpreted as more noxious (Phillips et al, 2003). This work has significant clinical relevance with regard to understanding of unexplained functional gut pain, where negative emotional states may contribute towards visceral hyperalgesia in functional gastrointestinal patients, so that non-noxious sensation is perceived as noxious. Therefore, the treatment of emotional disturbances may be useful in managing visceral hyperalgesia in patients with a functional gastrointestinal disorder.

CRITICISM OF STUDIES

A multiplicity of studies have been performed investigating the pathophysiology of IBS. Results have been variable, probably because of the mixed groups of patients studied. For instance, Silverman et al (1997) showed that while healthy subjects show activation of the anterior cingulated cortex to painful and anticipated rectal stimulation, patients with IBS do not show this activation but instead show activation in the frontal cortex. Mertz et al (2000) showed that while both patients with IBS and healthy volunteers show activation of the anterior cingulated cortex in response to progressive, increasing rectal stimulation intensities, the activation in this region was stronger in patients with IBS in comparison with controls. This variation in results is probably because patients with IBS represent a heterogeneous group with many different mechanisms being responsible for visceral hypersensitivity. Studying these patients as a unified group is likely to give variable results.

KEY POINTS

- Abdominal pain in patients with irritable bowel syndrome is the commonest symptom and the most difficult to treat.
- Visceral hypersensitivity is characteristic in irritable bowel syndrome patients with abdominal pain and may be the result of either peripheral/central sensitization of aberrant brain processing.
- Peripheral/central sensitization may result from gut inflammation or injury while aberrant brain processing may be the result of emotional or cognitive problems.
- Functional brain imaging techniques allow the study of the neuroanatomy of the brain.
- Studies using imaging techniques are now providing information on the differential pattern of brain activation in visceral hypersensitivity states caused by peripheral and central factors.

FUTURE WORK

Future work aimed at subgrouping patients with a functional gastrointestinal disorder on the basis of their physiological, psychological and neurophysiological profiles will help in further elucidating the mechanisms of hypersensitivity in these patients, and will enable specific hypothesis-testing experiments to be performed. This will help to confirm whether visceral hypersensitivity is caused by peripheral or central sensitization, or by aberrant brain processing. This will enable therapy to be specifically targetted at the mechanisms involved in generating symptoms.

CONCLUSION

The ultimate aim of research into functional gastrointestinal disorders is to identify the pathophysiological processes involved in the development of IBS. This will enable therapeutic strategies to be piloted, and will provide a clearer picture of how to clinically manage this disorder. Understanding brain–gut interaction and the contribution that central and peripheral sensitization and cognitive factors play in the aetiology of visceral hypersensitivity is integral to this process. If cognitive and emotional biasing is responsible for the symptoms reported by patients, suitable psychological treatment strategies could be targeted at alleviating symptom severity.

Equally, if central or peripheral sensitization is found to be the route cause of visceral hypersensitivity in IBS, therapeutic interventions may be trialed. For example, pharmacological agents with selective NMDA-receptor antagonistic properties, which are currently in development, may be used for the treatment of pain of visceral origin. However, it is likely that visceral hypersensitivity is a combination of peripheral/central sensitization and emotional/cognitive problems; if this is the case, a multidimensional treatment strategy for IBS will be required. HM

Conflict of interest: none.

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