VISCERAL PERCEPTION

Role of visceral sensitivity in the pathophysiology of irritable bowel syndrome

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Visceral hypersensitivity has been recognised as a characteristic of patients with irritable bowel syndrome (IBS). It may be involved in the pathogenesis of abdominal pain/discomfort, and seems to result from the sensitisation of nerve afferent pathways originating from the gastrointestinal tract. From a clinical point of view, hypersensitivity, although frequent, is not a constant finding among patients with IBS and cannot therefore be considered as a diagnostic marker of the condition. The advances made in understanding visceral hypersensitivity in patients with IBS are reviewed: the factors that influence abdominal distension are defined and different therapeutic perspectives are examined.

SUMMARY

Despite significant advances in the recognition of aetiological factors and pathological mechanisms, the pathophysiology of functional gastrointestinal disorders is still not fully understood. Abnormal motility patterns observed in patients with irritable bowel syndrome (IBS) are neither constant nor specific, and there is little by way of published data to show that abnormal motility is directly associated with pain. Hypersensitivity of afferent fibres is a frequent but not a constant finding, and for this reason it cannot be considered as a biological marker of the condition. Recent findings suggest that in the majority of cases the primary abnormality may be at the level of the parietal mechanoreceptors, which in some patients become sensitised by a mild post-infectious inflammatory process. Hypervigilance to abdominal events and stress are also involved in the hypersensitivity process. Imaging techniques indicate that there are differences in cortical activation induced by rectal distension between patients and controls, and between male and female patients with IBS. However, further studies are needed to confirm these observations and to define the exact roles of the peripheral and central components of visceral hypersensitivity.

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INTRODUCTION

The pathophysiology of functional gastrointestinal disorders is still not completely understood despite significant advances in the recognition of aetiological factors and pathological mechanisms. As most patients present with multiple factors, a multifactorial model seems the most appropriate way to study this condition.[1]

Abdominal pain, the symptom that constitutes the basis for the definition of IBS, has been related to the occurrence of abnormal intestinal[2] or colonic[3] contractions. This concept has led to the widespread but disappointing use of antispasmodics. Abnormal motility patterns observed in patients with IBS are neither constant nor specific, and few studies have shown a link between these patterns and pain attacks.[4] Over the last decade, attention has focused on the relationships between the brain and the gastrointestinal tract. This includes the study of the efferent pathways which coordinate motor functions, secretory functions, and process sensations originating from the gastrointestinal tract up to the central cortex.

There is general agreement that patients with IBS are more sensitive to distension of the sigmoid colon or ileum than healthy controls.[5 6] These findings were initially overlooked but considerable interest in visceral sensation has re-emerged over the last decade,[7] especially as identification of pharmacological targets on visceral afferent pathways has provided a means of tracking the development of new treatments.

This review attempts to summarise the advances made in understanding visceral hypersensitivity in patients with IBS: it defines the factors that influence abdominal distension and examines different therapeutic perspectives.

ANATOMICAL BASIS OF DIGESTIVE SENSITIVITY

Nerve pathways linking the gastrointestinal tract to the central nervous system (CNS) are organised into two parts; the enteric nervous system which provides the intrinsic innervation, and the extrinsic system, which projects along the spinal cord to the CNS. Sympathetic and parasympathetic pathways are involved in coordinating gastrointestinal motility at the periphery. The latter passes along the vagus nerves and lumbosacral plexus (fig 1).

Information sent to the CNS comes from receptors located in the intestinal wall which connect to primary afferent neurones. Electrophysiological studies have shown that activation of these receptors produces spike activity in sensory nerves.[8] Mechanical stimuli in the form of contractions, organ relaxation, or distension

Abbreviations: CNS, central nervous system; IBS, irritable bowel syndrome; NTS, nucleus of the tractus solitarius.

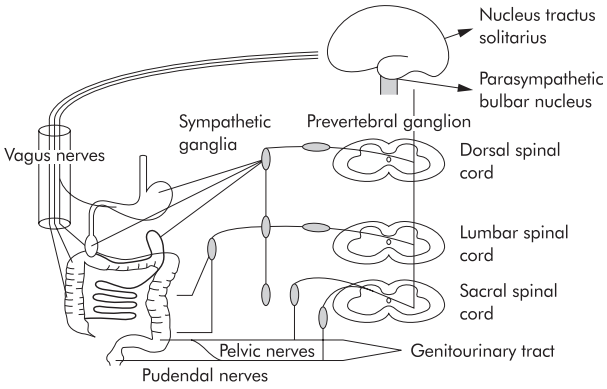

Figure 1 Schematic organisation of afferent nerve pathways originating from the gastrointestinal tract.

trigger two types of receptor activity. Slow receptors operate under physiological conditions and rapid receptors with a high response threshold respond to supraphysiological stimuli, such as large contractions.[9]

The gastrointestinal tract wall also contains polymodal nociceptors which are activated by a variety of mechanical, chemical, or osmotic stimuli and are usually involved in the recognition of painful stimuli.[10] The afferent pathways to which they link project along the same pathways as somatic pain neurones.

Studies in the cat have indicated that vagus nerves contain up to 80% of afferent fibres, originating from the upper gut, from the oesophagus, down to the jejunum. Vagal afferent neurones project to the nodose ganglion and further to the nucleus of the tractus solitarius (NTS). New functional imaging techniques of the brain have recently allowed partial identification of the brain regions that are activated by digestive stimuli.[11] Digestive sensation is thought to be integrated in the bulb and the NTS, from where impulses pass to the thalamus and cortex.

Studies in cats indicate that afferent neurones project along the vagus nerves from the oesophagus down to the jejunum. This pathway which contains up to 80% of all sensory fibres passes to the nodose ganglion and then to the NTS.[12] Sympathetic fibres pass along the splanchnic nerves to the mesenteric ganglia and connect to the prevertebral ganglia. From there, impulses are processed along the spinal cord to the NTS. Proprioceptive sensations of the anorectum are transmitted along the pudendal nerves.

NEUROMEDIATORS

Pharmacological studies have identified receptors for numerous different neuromediators which are involved in processing the information transmitted along afferent pathways.[13] The list includes biogenic amines (acetylcholine, noradrenaline), peptides (substance P, cholecystokinin, vasoactive intestinal peptide, enkephalins) purines (adenosine triphosphate, adenosine diphosphate), and nitric oxide. These neuromediators and are also found in the efferent neurones and are responsible for motor as well as sensory effects (table 1).

PHYSIOLOGICAL BASIS OF DIGESTIVE SENSITIVITY

Intrinsic afferent fibres are the primary pathways responsible for organising peristaltic reflexes. Some neurones project efferent axons directly to smooth muscle cells while others synapse with interneurones or motor neurones and are responsible for facilitating axonal reflexes.[14] These local reflexes generate motor or secretory responses in response to luminal distension and chemical stimuli. They either occur on short segments of the digestive tract or coordinate the activity over adjacent segments.

Table 1 Neurotransmitters involved in processing of digestive sensations

Level of control	Neurotransmitters
Primary afferents	SP and other tachykinins
	Histamine
	5-HT
	Cytokines
	Enkephalins
	Calcitonin gene related peptide
Myenteric plexus	SP and other tachykinins
	Histamine
	5-HT
	CCK
	Cytokines
	Enkephalins
	VIP
Spinal cord	5-HT
	CCK
	Enkephalins
	Somatostatin
	Oxytocin
CNS	5-HT
	CCK
	Calcitonin gene related peptide
	Somatostatin
	Oxytocin
	VIP

CCK, cholecystokinin; SP, substance P; VIP, vasoactive intestinal peptide; 5-HT, serotonin.

Viscero-visceral reflexes regulate the flow of luminal contents and control gastric emptying into the duodenum. Barostat studies indicate that gastric distension enhances intestinal motility,[15 16] and duodenal distension has been shown to modulate gastric emptying. Viscero-visceral reflexes may also coordinate organs distant from each other. There are a number of examples of this. The arrival of food in the stomach stimulates colonic motility[17] by activating serotonergic pathways.[18] Stimulation of a colonic distal segment usually inhibits the proximal segment and under experimental conditions injection of glycerol into the rectum inhibits tone in the left colon.[19] Moreover, voluntary suppression of defecation for one week has been shown to significantly delay gastric emptying in healthy volunteers.[20]

Stimulation of digestive afferent pathways also triggers a variety of secretory responses, including the release of adrenaline from the adrenal glands and of opiate peptides from the CNS. Integration of these various processes occurs in the NTS and the thalamus.[21]

The CNS continuously integrates incoming information from the gastrointestinal tract with information received from other organs and from the environment, in order to initiate adequate adaptive responses. Under physiological conditions, most of these processes are processed by the hypothalamus and do not reach the level of conscious perception.[22] However, sensations that trigger a particular behaviour do so via the cortex. These include hunger, satiety, need to defecate, and the physiological correlates, gastric and rectal distension.

VISCERAL HYPERSENSITIVITY AND IBS

Prompted by previous studies[5 6] there is general agreement that hypersensitivity to luminal distension is a common feature of patients with IBS.[23–25] Clinical experience shows that abdominal palpation and stretching of the colon during colonoscopy both trigger an exaggerated sensation response in patients with this condition.

Clinical characteristics of visceral hypersensitivity in IBS

Investigation of visceral perception in humans is based principally on barostat distension tests. Patients with IBS perceive the first sensation and pain at lower volumes or pressures than

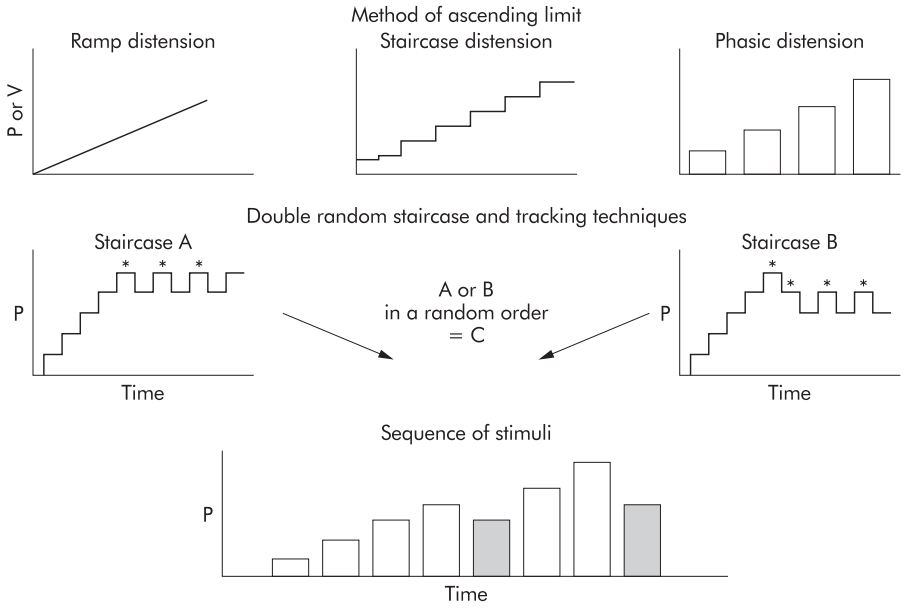

Figure 2 Various distension protocols used to measure sensory thresholds in patients with irritable bowel syndrome. With the tracking technique, subjects receive multiple distensions at around the threshold level in order to track their response. The double random staircase method uses the barostat to deliver two randomly mixed scales of impulse progression so that the stimulus cannot be predicted by the subject. *Positive response.

healthy controls.[23–25] However, compliance, which reflects the elastic properties of the smooth muscle, and wall tone are no different in patients with IBS than in control subjects.[23] It has also been shown that hypersensitivity is not limited to the expected target organs (that is, the colon and rectum in IBS) but that it also involves parts of the intestine and even the oesophagus.[26–28]

Although hypersensitivity is a frequent finding in patients with IBS, it does not appear to be a consistent indicator of the condition. In fact, some reports have estimated that only about 60% of patients are hypersensitive to distension.[28–30] One study proposed that visceral hypersensitivity may be a "biological marker" of IBS.[30] In this study, only one third of patients became hypersensitive at a second attempt to distend the rectum. In these individuals the first attempt acted as a sensitising stimulus.

Some studies have shown that patients who have IBS with diarrhoea are more hypersensitive to rectal distension than patients who have IBS with constipation, whereas other studies have failed to find this difference.[23 31] It has also been reported that hypersensitive patients frequently complain of incomplete evacuation whereas patients whose major complaint is constipation and abdominal discomfort were thought to be predominantly hyposensitive.[31] Decreases in sensory threshold were shown to be linked to the intensity of IBS related symptoms in one study,[29] but not in others.[31 32] The reasons for these differences in visceral sensitivity among patients with IBS are not known. It has been proposed that patients with normal rectal sensation are hypersensitive to jejunal distension.[28]

Methods for measuring hypersensitivity in patients with IBS

The technical conditions for performing distension tests are important as they have the potential to influence the results dramatically.[33] Distension tests are easier to perform and are reproducible if a barostat is used to inflate the bag placed in the colon or rectum. This technique allows distending pressure and volume to be measured simultaneously. Hypersensitivity is best elicited by rapid phasic distension protocols (that is, inflation of the bag at 40–60 ml/s) using distension steps of short duration (1–2 minutes), which are progressively increased until pain is induced. This technique is known as the method of ascending limits. Slow ramp distension fails to detect differences in perception between patients with IBS and healthy subjects.[24] As the patient's psychological bias may also affect the results of distension tests, complex distension protocols with repeated distensions that make the stimulus unpredictable to the subject are generally preferred (fig 2). Several studies using these protocols have confirmed that patients with IBS are hypersensitive to colonic or rectal distension.[29 31 34 35] However, recent studies have shown that sensory thresholds elicited by simple protocols of distension—that is, ascending method of limits—are not different from those recorded with protocols including repetitive distensions, both in healthy volunteers[36 37] and in IBS patients (author's unpublished data). Hypervigilance of patients for abdominal events may be the source of bias in the results of distension studies.[35] Hence Kellow *et al* showed that patients with IBS perceive more abdominal events than healthy control subjects, even when intestinal motility is normal in both.[38]

Results of distension tests are expressed either as sensory thresholds (that is, the first pressure or volume that triggers a given sensation) or in terms of the intensity of the sensation triggered by several stimuli at fixed pressure.[39 40] The use of the barostat to simultaneously measure pressure and volume during distension allows organ compliance to be calculated. Compliance is the capability of the organ to adapt to the imposed distension, expressed in ml/mm Hg. Until now, no study has shown a definitive difference in compliance between patients with IBS and healthy controls[23 41] although one study suggested that patients with diarrhoea predominant IBS may have reduced rectal wall compliance.[42]

Factors influencing the measurement of sensory thresholds

Several factors are thought to influence the perception of sensory thresholds. In general terms, older subjects appear to be less sensitive[43]; females appear to be more sensitive[44–46]; and higher sensory thresholds are recorded postprandially,[47] or when colonic motility[48] and tone[23 49 50] are enhanced. The activity of the CNS also influences perception of luminal distension, both in control subjects and in patients with IBS.

In healthy subjects, induced psychological stress (dichotomous listening) or physical stress (hand in cold water) both induce long lasting reductions in sensory thresholds.[51] The intensity of perception of rectal distension appears to be enhanced in stressed subjects.[40] On the other hand, psychological stress was found to have a distracting effect in other groups of healthy subjects, resulting in an increase in measured sensory threshold.[52 53] In one of these studies, rectal compliance was decreased after stress. This change in rectal compliance can be related to a stress induced increase in rectal motility.[54] In one of these studies the comparison of healthy subjects and IBS patients submitted to the same type of stress showed that the distracting effect of stress was not observed in IBS patients.[52]

Sensory thresholds are also influenced by the intensity of the symptoms of IBS,[29] and possibly by disturbances in bowel habits. Patients with diarrhoea predominant IBS have been shown to be more sensitive to distension than controls[55–57] but other studies suggest that patients with constipation predominant IBS are also sensitive to distension.[23 31]

Cause of visceral hypersensitivity in patients with IBS

The exact cause and mechanisms of visceral hypersensitivity in patients with IBS are not known. Comparison between the response of patients and controls to jejunal distension and electrical stimulation of primary afferents suggests that the primary abnormality may take place at the level of the mechanoreceptors.[58] It is also possible that parietal mechanoreceptors are sensitised by the mild inflammatory process that is found in a subset of patients with IBS.[59] Primary afferent nerve endings dwell in close proximity to mast cells within the intestinal submucosa, suggesting that inflammatory mediators may sensitise mechanoreceptors and nerve endings. A link between the onset of IBS and an episode of intestinal infection has already been suggested by Chaudhary and Truelove, who as long ago as 1962 were able to show that gastroenteritis preceded IBS in 30% of patients.[60] It was later observed that many patients develop IBS and complain of changes in intestinal motility and sensation after a *Salmonella* spp infection.[61] Female patients, and those with anxiety or depression, are also prone to develop IBS after an episode of gastroenteritis.[62 63]

Patients with ulcerative colitis tolerate lower volumes of distension than control subjects.[64–67] Those with more active disease tend to be more sensitive but the hypersensitivity remains, even in patients with quiescent disease.[66 67] It has been shown to be possible to sensitise healthy volunteers to rectal distension after administration of an irritant laxative, glycerol.[68]

The disorder responsible for hypersensitivity in IBS may also occur at the level of extrinsic peripheral afferent pathways. Comparison of patients with IBS to controls and patients with traumatic injury of the spinal cord suggests that sensitisation in patients with IBS occurs in splanchnic lumbar afferents.[24] Somatostatin and its analogue octreotide have been shown to increase sensory thresholds to rectal[69 70] and colonic[71] distension in patients with IBS. Conversely, somatostatin also decreases the perception of electrical stimulation of the rectum[72] and the amplitude of evoked potentials recorded at both the cortical and spinal levels. These findings imply that hypersensitivity might also result from sensitisation of peripheral afferent nerves.

The influence of the CNS on perception of luminal distension of the gastrointestinal tract has been discussed above. Hypervigilance to abdominal events has been shown to occur in patients with IBS,[35] and stress is known to sensitise healthy volunteers to distension.[40 51–53] New functional imaging techniques have shown differences between patients with IBS and controls in terms of the type of cortical activation induced by rectal distension.[12] Differences in brain activation have also been shown between male and female patients with IBS.[73] However, further research in this field is needed as at least one study has failed to show any significant difference between IBS patients and controls.[74]

CONCLUSIONS

Visceral hypersensitivity has been recognised as a characteristic of patients with IBS. It may be involved in the pathogenesis of abdominal pain/discomfort, and seems to result from the sensitisation of nerve afferent pathways originating from the gastrointestinal tract. This sensitisation is the summation of peripheral as well as central processes. The determinants of visceral hypersensitivity include the combined effects of intrinsic and environmental factors.

From a clinical point of view, hypersensitivity, although frequent, is not a constant finding among patients with IBS and cannot therefore be considered as a diagnostic marker of the condition. Future research will be needed to better understand the respective roles of peripheral and central components of visceral hypersensitivity in IBS. Meanwhile, advances in our knowledge of neurotransmitters and receptors involved in processing visceral sensation provide a major impetus for the development of new treatments of functional gastrointestinal disorders.

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