LEADING ARTICLE

Central sensitisation in visceral pain disorders

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The concepts of visceral hyperalgesia and visceral hypersensitivity have been examined in a variety of functional gastrointestinal disorders (FGIDs). Although the pathophysiological mechanisms of pain and hypersensitivity in these disorders are still not well understood, exciting new developments in research have been made in the study of the brain-gut interactions involved in the FGIDs

The concept of visceral hyperalgesia has been examined in a variety of functional gastrointestinal disorders (FGIDs), including oesophagitis, gastro-oesophageal reflux disease, non-ulcer dyspepsia, gastroparesis, and irritable bowel syndrome (IBS). Visceral hypersensitivity has also been demonstrated in non-gastrointestinal disorders such as interstitial cystitis and ureteric colic.¹ Although the pathophysiological mechanisms of pain and hypersensitivity in these disorders are still not well understood, exciting new developments in research have been made in the study of the brain-gut interactions involved in the FGIDs.

In this issue of *Gut*, Sarkar and colleagues² address the phenomenon of temporal summation of pain, termed "wind-up", and its relationship to central sensitisation and secondary visceral pain hyperalgesia caused by acidification of the oesophagus (see page 920). Also in this issue of *Gut*, Drewes and colleagues³ examine peripheral and central sensitisation using both mechanical and thermal stimuli in patients with oesophagitis compared with control subjects (see page 926). They found that in patients with oesophagitis, the interaction between central and peripheral nociceptive input may help explain patient symptoms. Understanding the implications of these two studies requires examining the concept of central sensitisation in visceral pain disorders. Both of these studies have important clinical and research ramifications for the study of FGIDs.

GENERAL MECHANISMS OF VISCERAL HYPERALGESIA

Prior to discussing the mechanisms of hyperalgesia in the FGIDs, some definitions need to be clarified. Hyperalgesia is the term used to refer to a reduced pain threshold and/or an exaggerated response to a painful stimulus. The two components of hyperalgesia include primary (at the site of tissue injury/inflammation) and secondary. Allodynia however refers to a prior non-painful stimulus which now evokes pain. Visceral hypersensitivity is defined as the increased

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intensity of sensations and the lowered thresholds for visceral pain seen in patients with FGIDs. No pathological basis has been found for these disorders. The concept of central sensitisation involves the development of secondary hyperalgesia/allodynia resulting from altered afferent input to the spinal cord dorsal horn. As a result of sensitisation of the peripheral primary afferents, increased synaptic activity is seen at the dorsal horn of the spinal cord leading to changes in their excitability. This outlasts the original injury at the primary afferents leading to central sensitisation. Examples of central sensitisation will be discussed later in the text.

Several potential mechanisms exist for visceral hypersensitivity:

- (1) Sensitisation of primary afferent neurones innervating the gastrointestinal tract.
- (2) Spinal sensitisation due to tonic impulse input from these primary afferent neurones and/or
- (3) Descending facilitation from the brain to the spinal cord and/or gut.
- (4) Selective alteration in cerebral cortical processing of ascending afferent input.

Some of the above mentioned mechanisms will be discussed with respect to the most common FGID, IBS.

NEUROBIOLOGY OF PRIMARY VISCERAL AFFERENTS

The mechanisms of chronic visceral hyperalgesia are not as well studied as those which contribute to somatic hyperalgesia, and little is known about the specific peripheral and central afferents that are sensitised and lead to chronic visceral hypersensitivity. Understanding of the physiology of primary visceral afferents has led to better insight into the mechanisms leading to chronic altered sensations from the viscera, as seen in patients with FGIDs. IBS comprises 50% of referrals to gastroenterologists and affects up to 20% of the US population.^{4–5} Research into this common disorder has provided the opportunity to study central pain mechanisms in FGIDs. The first studies investigating visceral hypersensitivity in IBS concluded that the enhanced sensitivity was limited to the gut.^{6–9} Several studies since have demonstrated enhanced perceptual responses to distension of the gut (visceral hypersensitivity) in patients with IBS.^{10–11} In IBS, the primary visceral afferents and their receptors are found in the serosa, muscle, and

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Abbreviations: FGIDs, functional gastrointestinal disorders; IBS, irritable bowel syndrome; FM, fibromyalgia

mucosa of the gut and respond to mechanical (distension) stimuli and local luminal and chemical stimuli. In response to a triggering event such as inflammation, environmental stress, psychological stress, or trauma, the gut becomes sensitised to luminal distension, resulting in visceral hypersensitivity.¹²

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Although primary visceral afferents play a role in persistent and acute visceral pain, other silent nociceptors also exist which are mechanically insensitive until tissue injury occurs and which then develop spontaneous activity and mechanosensitivity.¹³ For example, acute instillation of bile salts into the colon significantly increases the activity of mechanosensitive colonic afferents in response to colonic distension.¹² These activated silent nociceptors may then contribute to chronic visceral hypersensitivity through both peripheral and central nervous system mechanisms.

Studies in IBS patients have shown that both primary and secondary hyperalgesia can be normalised by removing either the peripheral impulse input or central nervous system facilitation which is associated with anticipation and other psychological factors.¹⁴⁻¹⁵ One study done by our group involved performing rectal distension and thermal stimulation before and after administration of rectal lidocaine jelly or saline jelly. In comparison with saline placebo, lidocaine jelly normalised both rectal hyperalgesia and also thermal hyperalgesia at the foot. Interventions reducing negative emotion have also been found to reduce first and second pain.¹⁴⁻¹⁶ A similar reversal of hyperalgesia can occur in response to placebo and was shown to be related to changes in expectations of pain and the desire for pain relief.¹⁴ Since either a peripheral treatment or a central modulation (that is, placebo) completely normalises hyperalgesia, it is possible that a synergistic interaction may occur between the peripheral and central mechanisms of pain modulation in IBS.

EVIDENCE FOR CENTRAL SENSITISATION

Hyperalgesia includes both central and peripheral nervous system components and may be maintained by either.¹⁷ Prior work from our group has shown that hypersensitivity in IBS patients is not just limited to the gut and that more widespread alterations in central pain processing may be involved in this chronic pain disorder.¹⁸⁻¹⁹ Other studies have supported widespread somatic hyperalgesia associated with IBS.²⁰ Moreover, IBS patients exhibit a wide variety of extraintestinal symptoms, including back pain, migraine headaches, heartburn, dyspareunia, and muscle pain. These extraintestinal manifestations are consistent with the possibility that patients with IBS may also have central hyperalgesic dysfunction.²¹ Supporting evidence has similarly been seen in patients with other chronic pain disorders, such as temporomandibular disorder in which generalised hyperalgesia is also present.²²

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Recently, an animal model for IBS has been developed in which colonic irritation in neonatal, but not adult, rats leads to chronic visceral hypersensitivity with characteristics of allodynia and hyperalgesia associated with central

sensitisation.²³ This chronic visceral hypersensitivity persists through adulthood despite the absence of any identifiable histopathology. In this study, rats treated with mustard oil enemas displayed chronic visceral hypersensitivity which was manifested by increased contractility of the abdominal musculature and hyperexcitability of the viscerosensitive neurones in the lumbosacral spinal cord (L6–S1) in response to colorectal distension. These rats also displayed hypersensitivity to cutaneous nociceptive stimuli with increased responses of these neurones to pinching and deep tissue stimulation demonstrating secondary hyperalgesia with visceral afferents sensitising the somatic nociceptives at the same level of the spinal cord. This transient colonic irritation therefore resulted in chronic visceral and somatic hypersensitivity which persisted through their adulthood despite the removal of the stimulus. Several other studies have also shown that salmonella infection of the gut can cause persistent sensitisation of the gut long after clearing of the infection leading to IBS.²⁴⁻²⁵

EXPERIMENTAL STUDIES

The first study to show large magnitudes of thermal hyperalgesia in IBS patients compared with controls was done by our laboratory showing that patients with IBS also display somatic hypersensitivity in response to experimental thermal pain stimuli which extends to the cervical spinal levels, albeit at a lower magnitude than that exhibited at the lumbosacral levels.¹⁴⁻¹⁵⁻¹⁸⁻²⁶ As patients with IBS do not report cutaneous pain, thermal hypersensitivity in these patients is a reflection of secondary hyperalgesia and central sensitisation. Secondary hyperalgesia may then be the result of anatomical convergence from visceral and somatic nociceptive afferents onto a common pool of spinal dorsal horn neurones at the lumbosacral level with sensitisation of central neurones by tonic impulse activity in the visceral primary afferents in the gut.¹⁵ The most pronounced hyperalgesia appears to occur at the lumbosacral level at which colon and lower extremity nociceptive afferents are likely to converge onto common spinal segments, explaining why patients had higher thermal hypersensitivity in the foot than in the hand (see fig 1).¹⁴⁻¹⁵⁻¹⁹

Further evidence on central sensitisation has been shown by functional magnetic resonance imaging done in patients with IBS. In comparison with pain free control subjects, IBS patients also demonstrated visceral and thermal hyperalgesia that was accompanied by corresponding increases in stimulus induced activation of brain regions involved in pain processing.¹⁵ Brain regions activated included the thalamus,

Figure 1 Synaptic convergence from both colonic and cutaneous nociceptive afferent neurones onto a common dorsal horn neurone. This then transmits via the spinothalamic tract to the brainstem and then the brain. Somatovisceral convergence is well established for spinothalamic tract neurones and neurones of other ascending pathways to the brain.

somatosensory areas I and II, insular cortex, prefrontal cortical areas, and the anterior cingulate cortex.

"Fibromyalgia is a chronic pain disorder which demonstrates widespread body areas associated with abnormalities in pain sensitivity diagnosed by eliciting local pain at standard tender points"

Similar to IBS, fibromyalgia (FM) is a chronic pain disorder which demonstrates widespread body areas associated with abnormalities in pain sensitivity diagnosed by eliciting local pain at standard tender points. In another study performed by our laboratory, we compared the magnitude of visceral and thermal hypersensitivity in IBS patients with and without fibromyalgia to healthy controls.²⁷ We found that IBS patients rated rectal distension as more painful than patients with IBS and FM (FMS+IBS) for the high intensity stimulus (55 mm Hg rectal balloon distension) ($p < 0.004$) but the FMS+IBS group rated hot water immersion of the foot as more painful than IBS patients ($P = 0.027$). Interestingly, foot stimulation was perceived as more painful than the hand for both IBS and FMS+IBS groups. These findings have been supported by other studies which show that patients with both FM and IBS have enhanced somatic pain perception compared with patients with only IBS²⁸ and others showing enhanced thermal pain sensitivity in FM patients compared with control subjects.^{29–30}

DISCUSSION OF THE PRESENT STUDIES

Given this background on central sensitisation in visceral pain disorders, the results of the studies by Sarkar and colleagues² and Drewes and colleagues³ in this issue of *Gut* can be put into greater focus. Sarkar and colleagues² investigated the relationship between "wind-up" or temporal summation and visceral pain in the oesophagus. They evaluated perception at pain threshold in eight healthy controls in which they applied 20 electrical stimuli to the hand and upper oesophagus at 0.1 Hz (non-wind up frequency) or 2 Hz (wind-up frequency) both before and one hour after infusion of acid and/or saline for 30 minutes into the lower oesophagus. In both the hand and upper oesophagus, "wind-up" only occurred with the 2 Hz frequency. Following infusion of acid into the lower oesophagus, the pain threshold decreased in the upper oesophagus, indicative of secondary hyperalgesia. Interestingly, wind-up to the 2 Hz train increased in the upper oesophagus but not in the hand.

The results of Sarkar and colleagues² demonstrate that oesophageal acidification does in fact lead to secondary hyperalgesia, as measured by increased "wind-up". This strongly suggests that central sensitisation and central neuronal plasticity may be present following acid infusion. Similar to other visceral pain disorders discussed in this article, secondary hyperalgesia developed following a nociceptive stimulus (acid) to a visceral structure (oesophagus). It is interesting that the hand did not develop secondary hyperalgesia, as was seen in the oesophagus. This may be explained by the fact that sensory testing with "wind-up" was performed only one hour following the nociceptive stimulus. Central sensitisation with further involvement of spinal segments (that is, hand) may very well have occurred if sensory testing was performed over a longer period of time following the nociceptive stimulus. For example, central sensitisation and widespread secondary hyperalgesia seen in IBS patients may be dynamically maintained by a tonic nociceptive impulse drive from the gut to the spinal cord. Unlike chronic impulse input that occurs with inflammation, this impulse input may be neurogenic and not associated

with signs of tissue injury. Widespread hyperalgesia is also found in animal models of IBS³¹ and in animal models of chronic pain such as the CCI rat model. Interestingly, spatially extensive increases in neural activity are found in the spinal cords³¹ and brains of CCI rats,³² consistent with widespread hyperalgesia found in IBS patients, FMS patients, and some patients with complex regional pain syndrome.^{19–30}

"Central sensitisation and widespread secondary hyperalgesia seen in IBS patients may be dynamically maintained by a tonic nociceptive impulse drive from the gut to the spinal cord"

The study by Drewes and colleagues³ supports earlier findings of Sarkar and colleagues³³ which showed that acid infused into the lower oesophagus induces hypersensitivity to pain in the non-acid exposed upper oesophagus, thereby demonstrating the contribution of central sensitisation in oesophageal hypersensitivity. In this current study, Drewes and colleagues³ studied 11 patients with grade B oesophagitis compared with controls. Nociceptive mechanical distensions and thermal stimulation (water in distension bag heated to 60°C) were applied to the lower oesophagus in both groups of patients before and after the smooth muscle relaxant butylscopolamine was given. Neither patients with oesophagitis nor controls were sensitive to mechanical distension of the oesophagus. In contrast, following administration of butylscopolamine, patients with oesophagitis were more sensitive and had a larger pain referral area to mechanical stimulation compared with controls. Patients with oesophagitis were also more sensitive to thermal stimulation of the oesophagus compared with controls.

"The findings of central neuroplastic changes in visceral pain disorders could have important implications in the treatment of these disorders"

These findings by Drewes and colleagues³ compliment the findings by Sarkar and colleagues² and others, and suggest that peripheral sensitisation may lead to and facilitate central pain mechanisms. Thus chronic longstanding acid exposure of the oesophagus and the resulting visceral pain may lead to sensitisation of both peripheral nerves (heat sensitive VR1 receptors) and the central nervous system. This may lead to chronic neuroplastic changes in the spinal cord that could result in central sensitisation and a larger secondary pain referral area. Taken together, the findings of central neuroplastic changes in visceral pain disorders could have important implications in the treatment of these disorders.

CONCLUSION

Central sensitisation, viscerosomatic convergence, and rostral-caudal spread of spinal hyperexcitability all may play major roles in the pathophysiology of FGIDs. The degree of secondary hyperalgesia may also be further enhanced by additional input from deep tissues. This widespread hyperalgesia which results from the primary visceral afferents in these disorders may provide a source of chronic tonic input which in turn leads to the development of other chronic pain syndromes. Future research needs to address the mechanisms of somatic hypersensitivity in visceral pain disorders.

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REFERENCES

- Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994;**107**:271–93.
- Sarkar S, Woolf CJ, Hobson AR, et al. Perceptual wind-up in the human oesophagus is enhanced by central sensitisation. *Gut* 2006;**55**:920–5.
- Drewes AM, Reddy H, Pedersen J, et al. Multimodal pain stimulations in patients with grade B oesophagitis. *Gut* 2006;**55**:926–32.
- Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology* 1990;**99**:409–15.
- Verne GN, Cerda JJ. Irritable bowel syndrome. Streamlining the diagnosis. *Postgrad Med J*, 1997;**102**:197–4.
- Accarino AM, Azpiroz F, Malagelada JR. Selective dysfunction of mechanosensitive intestinal afferents in irritable bowel syndrome. *Gastroenterology* 1995;**108**:636–43.
- Cook LJ, van Eeden A, Collins SM. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. *Gastroenterology* 1987;**93**:727–33.
- Whitehead WE, Holtkotter B, Enck P, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology* 1990;**98**:1187–92.
- Zigheboim J, Talley NJ, Phillips SF, et al. Visceral perception in irritable bowel syndrome. Rectal and gastric responses to distension and serotonin type 3 antagonism. *Dig Dis Sci* 1995;**40**:819–27.
- Mertz H, Naliboff B, Munakata J, et al. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology* 1995;**109**:40–52.
- Naliboff BD, Munakata J, Fullerton S, et al. Evidence for two distinct perceptual alterations in irritable bowel syndrome. *Gut* 1997;**41**:505–12.
- Gebhart GF. Pathobiology of visceral pain: molecular mechanisms and therapeutic implications IV. Visceral afferent contributions to the pathobiology of visceral pain. *Am J Physiol Gastrointest Liver Physiol* 2000;**278**:G834–8.
- Su X, Wachtel RE, Gebhart GF. Inhibition of calcium currents in rat colon sensory neurons by K⁺ but not mu- or delta-opioids. *J Neurophysiol* 1998;**80**:3112–19.
- Vase L, Robinson ME, Verne GN, et al. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. *Pain* 2003;**105**:17–25.
- Verne GN, Robinson ME, Vase L, et al. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. *Pain* 2003;**105**:223–30.
- McCracken LM, Gross RT. The role of pain-related anxiety reduction in the outcome of multidisciplinary treatment for chronic low back pain: preliminary results. *J Occup Rehabil* 1998;**8**:179–89.
- Greenspan JD. Quantitative assessment of neuropathic pain. *Curr Pain Headache Rep* 2001;**5**:107–13.
- Verne GN, Robinson ME, Price DD. Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. *Pain* 2001;**93**:7–14.
- Verne GN, Price DD. Irritable bowel syndrome as a common precipitant of central sensitization. *Curr Rheumatol Rep* 2002;**4**:322–8.
- Bouin M, Meunier P, Riberdy-Poitras M, et al. Pain hypersensitivity in patients with functional gastrointestinal disorders: a gastrointestinal-specific defect or a general systemic condition? *Dig Dis Sci* 2001;**46**:2542–8.
- Mayer EA, Raybould HE. Role of visceral afferent mechanisms in functional bowel disorders. *Gastroenterology* 1990;**99**:1688–704.
- Sarlani E, Greenspan JD. Evidence for generalized hyperalgesia in temporomandibular disorders patients. *Pain* 2003;**102**:221–6.
- Al Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 2000;**119**:1276–85.
- Gwee KA, Leong YL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;**44**:400–6.
- McKendrick MW, Read NW. Irritable bowel syndrome—post salmonella infection. *J Infect* 1994;**29**:1–3.
- Verne GN, Himes NC, Robinson ME, et al. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. *Pain* 2003;**103**:99–110.
- Moshiree B, Gupta V, Gaible R, et al. Thermal and visceral hypersensitivity in irritable bowel syndrome patients with and without fibromyalgia. *J Pain* 2005;**6**:S6.
- Chang L, Mayer EA, Johnson T, et al. Differences in somatic perception in female patients with irritable bowel syndrome with and without fibromyalgia. *Pain* 2000;**84**:297–307.
- Price DD, Staud R, Robinson ME, et al. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain* 2002;**99**:49–59.
- Staud R, Vierck CJ, Cannon RL, et al. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 2001;**91**:165–75.
- Mao J, Price DD, Coghill RC, et al. Spatial patterns of spinal cord [14C]-2-deoxyglucose metabolic activity in a rat model of painful peripheral mononeuropathy. *Pain* 1992;**50**:89–100.
- Mao J, Mayer DJ, Price DD. Patterns of increased brain activity indicative of pain in a rat model of peripheral mononeuropathy. *J Neurosci* 1993;**13**:2689–702.
- Sarkar S, Aziz QA, Woolf CJ, et al. Contribution of central sensitization to the development of noncardiac chest pain. *Lancet* 2000;**356**:1154–9.