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CRITICAL REVIEW

Peripheral and Central Contributions to Hyperalgesia in Irritable Bowel Syndrome

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Abstract: **Irritable bowel syndrome (IBS) is a common gastrointestinal disorder seen by gastroenterologists. We discuss some recent evidence for potential neural mechanisms that could contribute to somatic and visceral hyperalgesia in IBS patients. The combination of research studies of human IBS patients and studies of rats with delayed rectal hypersensitivity after recovery from experimentally induced neonatal colitis strongly suggests a mechanism wherein both primary visceral hyperalgesia and secondary widespread cutaneous hyperalgesia are dynamically maintained by tonic impulse input from the noninflamed colon and/or rectum. The secondary hyperalgesia is likely to be at least partly related to sensitization of spinal cord dorsal horn neurons and in this respect might be similar to other persistent pain conditions such as fibromyalgia and complex regional pain syndrome.**

Perspective: ***Pain in irritable bowel syndrome is likely to be at least partly maintained by peripheral impulse input from the colon/rectum and central sensitization, yet it is also highly modifiable by psychological factors such as nocebo and placebo effects. A synergistic interaction might occur between psychological factors and abnormal afferent processing.***

Key words: *Psychophysics, hyperalgesia, allodynia, temporal summation, placebo, visceral hypersensitivity, irritable bowel syndrome, fibromyalgia.*

Hyperalgesia in Irritable Bowel Syndrome Patients

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder seen by gastroenterologists. Patients classically present with chronic abdominal pain associated with an alteration in bowel habits. It is presently accepted that the majority of IBS patients exhibit enhanced sensitivity to balloon distention of the rectum (Fig 1, left panel). This visceral hypersensitivity is manifested by lowered thresholds for visceral pain, increased intensity of sensations, and/or exaggerated viscerosomatic referral in comparison to control subjects.[17,23,37] More recently, studies have provided evidence for widespread somatic hyperalgesia in IBS.[4,37] Here we discuss this more recent evidence in the context of potential neural mechanisms that could contribute to somatic and visceral hyperalgesia in IBS patients. Our overall position is that both visceral and cutaneous hyperalgesia in IBS are sustained by peripheral and central neural mechanisms, and understanding these mechanisms has the potential for improving therapy for IBS.

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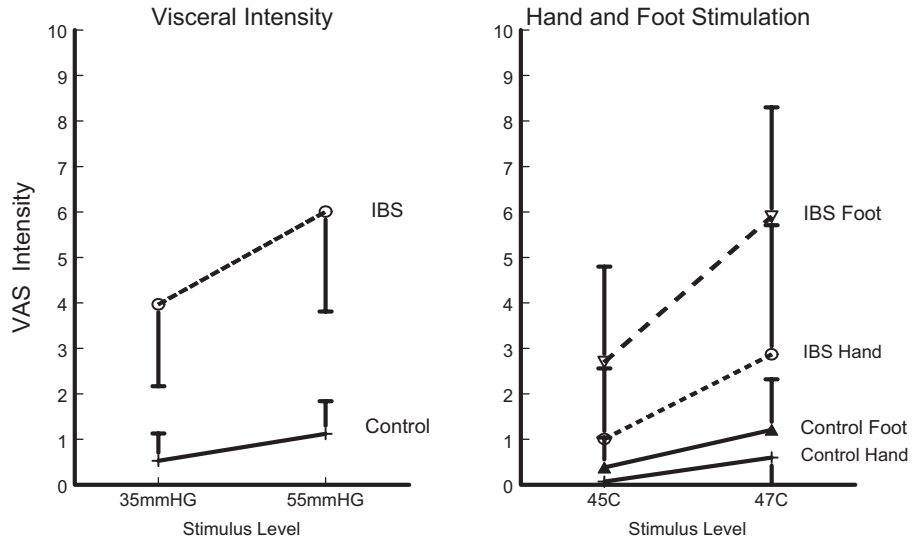

Figure 1. IBS patients' and normal control subjects' VAS pain intensity ratings of rectal distention pressures of 35 and 55 mm Hg (left panel) and of thermal stimulation of the hand and foot (right panel). Note that patients with IBS rate pain intensity much higher than controls ($P < .001$) at both temperatures and skin sites. Values are represented as means ± standard deviation, n = 12 IBS patients, 17 controls. Ratings of normal subjects were somewhat lower than those reported elsewhere[21,23] but are typical across our own published studies.[34,35,37,38] Reprinted with permission from Verne GN, Robinson ME, Price DD: Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. Pain 93:7-14, 2001.[37]

Is Hyperalgesia Limited to the Gut in IBS?

The first studies to investigate visceral sensitivity in IBS concluded that enhanced sensitivity in IBS was limited to the gut.[1,7,40,43] Interestingly, 2 prior studies have examined cutaneous pain in IBS patients by using electrocutaneous stimulation.[1,7] In one study, 13 patients with Crohn's disease, 13 control subjects, and 12 patients with IBS had electrodes positioned on the skin of their hands.[7] Touch threshold, defined as the current just detectable by the subject, and pain threshold, defined as the current at which the subject first described the stimulus as painful, were significantly higher in both IBS and Crohn's disease compared with normal subjects. A later study compared somatic transcutaneous electrical nerve stimulation in 17 patients with IBS and 15 healthy controls.[1] The perception threshold and threshold for discomfort were both higher in the IBS subjects than in controls. A possible limitation common to both studies is that the thresholds for perception and discomfort to electrical stimulation might not have necessarily involved stimulation of nociceptive receptors. Thresholds for detection of electric shock and discomfort thresholds might be below those required to activate nociceptive receptors.[25] Furthermore, it has been shown that tactile input and touch perception can be inhibited by nociceptive input.[3] This mechanism might account for higher tactile thresholds in IBS patients if, unlike control subjects, they have ongoing visceral nociceptive input.

Thus, less agreement has been reached with regard to secondary cutaneous hyperalgesia in IBS patients.[4,5,8,11,20,35,37] One study suggested that IBS patients exhibit cutaneous hypersensitivity only when they have fibromyalgia (FM) as a comorbid condition.[5] However, some investigators have acquired evidence that patients with IBS but without other chronic pain conditions including FM have both visceral and cutaneous hypersensitivity in response to experimental stimuli.[4,35,37] A number of these studies have compared results of both clinically relevant painful rectal distention and painful cutaneous thermal stimulation in IBS patients with age/sex-matched normal control subjects.[8,35,37]

Evidence of Thermal Hyperalgesia in IBS

The first study to show large magnitudes of thermal hyperalgesia in IBS patients compared visual analogue scale (VAS) ratings of pain intensity and unpleasantness in response to rectal distention and cutaneous thermal stimuli in 12 patients with IBS but without FM and 17 healthy controls.[37] With methods similar to those of other investigators,[17,23] phasic distention of the rectum (870 mL/min) to constant pressure plateaus of 35 and 55 mm Hg for 30 seconds each were performed, followed by a 60-second interstimulus rest at a resting pressure of 5 mm Hg. Cutaneous (thermal) sensitivity was tested by asking each subject to immerse his/her right hand (up to the level of the wrist) or right foot (up to the level of the right malleolus) in a circulating, heated, water bath at random temperatures of 45°C and 47°C for 20 seconds each with a 5-minute rest between each stimulus.

Similar to previous studies,[17,23,40] Verne et al[37] showed that, in comparison with normal control subjects, IBS patients with alternating bowel habits gave higher pain ratings to phasic rectal distention. IBS patients rated rectal distention pressures of 35 and 55 mm Hg as more intense and unpleasant in comparison with controls (Fig 1, left panel). They also rated cutaneous thermal pain in the foot as much more intense and unpleasant in comparison with control subjects, thereby demonstrating