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Widespread hyperalgesia in irritable bowel syndrome is dynamically maintained by tonic visceral impulse input and placebo/nocebo factors: Evidence from human psychophysics, animal models, and neuroimaging

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Abstract

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder that is often accompanied by both visceral and somatic hyperalgesia (enhanced pain from colorectal and somatic stimuli). Neural mechanisms of both types of hyperalgesia have been analyzed by neuroimaging studies of IBS patients and animal analog studies of “IBS-like” rats with delayed rectal and somatic hypersensitivity. Results from these studies suggest that pains associated with both visceral and widespread secondary cutaneous hyperalgesia are dynamically maintained by tonic impulse input from the non-inflamed colon and/or rectum and by brain-to-spinal cord facilitation. Enhanced visceral and somatic pains are accompanied by enhanced pain-related brain activity in IBS patients as compared to normal control subjects; placebos can normalize both their hyperalgesia and enhanced brain activity. That pain in IBS which is likely to be at least partly maintained by peripheral impulse input from the colon/rectum is supported by results showing that local rectal–colonic anesthesia normalizes visceral and somatic hyperalgesia in IBS patients and visceral and somatic hypersensitivity in “IBS-like” rats. Yet these forms of hyperalgesia are also highly modifiable by placebo and nocebo factors (e.g., expectations of relief or distress, respectively). Our working hypothesis is that synergistic interactions occur between placebo/nocebo factors and enhanced afferent processing so as to enhance, maintain, or reduce hyperalgesia in IBS. This explanatory model may be relevant to other persistent pain conditions.

Keywords

Neuroimaging; Placebo analgesia; Irritable bowel syndrome; Hyperalgesia

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder wherein chronic abdominal pain is associated with an alteration in bowel habits (e.g. constipation, diarrhea), despite the apparent normality of the gastrointestinal tract (Gupta et al., 2002; Mayer and Gebhart, 1994; Naliboff et al., 1997). In this respect, IBS differs from inflammatory bowel disease. Compared to pain-free control subjects, the majority of IBS patients exhibit enhanced sensitivity to colonic or rectal distention of the rectum, as evidenced by their lowered thresholds for pain, increased intensity of sensations, and/or exaggerated viscerosomatic referral in response to rectal distension (Mertz et al., 1995; Naliboff et al., 1997; Verne et al., 2001). More recently, studies have documented widespread somatic hyperalgesia in patients with IBS (Bouin et al., 2001; Price et al., 2006; Verne et al., 2001). Here we discuss the research on the neural mechanisms that have been associated with and likely contribute to the somatic and visceral hyperalgesia in IBS patients, emphasizing the most recent studies. This discussion initially reviews experimental evidence for both visceral and secondary somatic hyperalgesia in IBS patients. We then examine the potential role of impulse input from the colon and/or rectum in the induction and maintenance of widespread somatic hyperalgesia as well as the role the central nervous system plays in the modulation of IBS-related pain. The roles of peripheral and central mechanisms are explained on the basis of psychophysical, neuropharmacological, and brain imaging experiments in humans and animal behavioral studies conducted over the last decade. Taken together, these disparate lines of research suggest that a synergistic interaction between peripheral and central mechanisms may have a significant role in IBS-related chronic pain. Our overall position is that both visceral and cutaneous hyperalgesia in IBS are sustained by peripheral and central neural mechanisms that interact at spinal cord and supraspinal levels. This model may be used to more broadly conceptualize mind–brain–body relationships in similar persistent pain conditions.

Evidence for visceral and somatic hyperalgesia in IBS patients

The first studies to investigate hyperalgesia in IBS patients concluded that their enhanced visceral sensitivity was limited to the gut (Accarino et al., 1995; Chang et al., 2000; Whitehead et al., 1990; Zighelboim et al., 1995) and that somatic sensitivity was either reduced or unaffected in patients with IBS. Whereas pain thresholds to experimentally induced rectal distension were lower in IBS patients compared to age/sex-matched control subjects, their thresholds to brief electrical, mechanical or cold stimuli were higher or not different (Accarino et al., 1995; Chang et al., 2000; Cook et al., 1987). The results of these studies are difficult to interpret and have technical problems. For example, thresholds for perception and discomfort to electrical stimulation might not have necessarily involved the stimulation of nociceptive receptors. Moreover, none of these brief tests appear to activate C-nociceptors for a sufficient time to assess neural mechanisms involving N-methyl, D-aspartate (NMDA) receptors or neuropeptides such as substance P (Price et al., 1997; 2006). Such neural mechanisms are likely to be highly relevant to widespread somatic hyperalgesia in pain conditions such as IBS, fibromyalgia, and at least some instances of neuropathic pain (Price et al., 2006).

Long duration heat stimuli that are known to activate cutaneous C-nociceptors and hence NMDA receptor mechanisms were used in several interrelated studies of IBS-related pain. Four of these studies compared the responses to both clinically relevant painful rectal distention and painful cutaneous thermal stimulation (20 s 45–47 °C temperatures to hand and foot) in IBS patients with age/sex-matched normal control subjects (Dunphy et al., 2003; Moshiree et al., 2007; Verne et al., 2001, 2003a). Large magnitudes of visceral and somatic hyperalgesia were found in the first study of female IBS patients (Verne et al., 2001). These patients gave higher pain ratings to phasic rectal distention pressures of 35 and 55 mm Hg in comparison to normal control subjects, similar to previous studies (Naliboff et al., 1997)(Fig. 1, left panel).

Heat pain sensitivity was tested in the same study 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 temperatures of 45 °C and 47 °C for 20 s. Compared to control subjects, IBS patients rated cutaneous thermal pain in the hand and the foot as much more intense and unpleasant, thereby demonstrating widespread secondary hyperalgesia (Fig. 1, right panel). Interpretation of the results of this study was limited by the fact that the results were obtained from only female IBS patients. This limitation was addressed in the second study, which primarily focused on male IBS patients (10 males, 2 females) who were veterans diagnosed with Gulf War syndrome (Dunphy et al., 2003). This second study used the same experimental methodology and design as the first study, comparing ratings of IBS patients with that of age/sex-matched control subjects. Consistent with the previous study, this second study demonstrated larger magnitudes of both visceral and cutaneous heat hyperalgesia in patients with IBS. As in the first study, the latter was larger for the foot in comparison to the hand.

A third study of female IBS patients included both pain ratings and measures of pain-related brain activity using functional magnetic resonance imaging (fMRI) (Verne et al., 2003b). In comparison with age- and sex-matched control subjects, IBS patients had both visceral and cutaneous thermal hyperalgesia, as measured by pain intensity and unpleasantness ratings, that was accompanied by corresponding increased activation of brain regions involved in pain processing, including ventroposterior lateral thalamus, somatosensory areas I and II, insular cortex, anterior cingulate cortex (ACC), and prefrontal cortical areas (Verne et al., 2003b). Thus, in comparison to age/sex-matched control subjects, IBS patients had increased pain-related activation within an entire network of brain areas, including those involved in early levels of somatosensory processing (e.g., the thalamus) (Price, 2000). This widespread pattern of increased neural activity in patients with IBS suggests but by no means proves that widespread secondary hyperalgesia is the result of central sensitization that occurs at early levels of processing, such as the spinal cord dorsal horn.

Finally, a fourth study compared visceral and somatic hyperalgesia between two patient groups, one with only IBS and the other with IBS and fibromyalgia (FM) (Moshiree et al., 2007). A pain-free control group was used to assess the magnitudes of hyperalgesia in the two patient groups. Both FM and FM + IBS groups rated rectal distension and heat stimulation as much more intense and unpleasant than the control group, consistent with the first three studies. IBS patients rated rectal distension as more painful than the FM + IBS group despite having less widespread hyperalgesia, whereas the FM + IBS group had higher pain ratings than the IBS group during heat stimulation of the foot. These results suggest that multiple peripheral sources of both cutaneous and visceral input can make separate contributions to secondary thermal hyperalgesia and that regions of primary and secondary hyperalgesia may be largely dependent on the body regions associated with the primary pain symptom.

This clear pattern of heat hyperalgesia in IBS patients, including a larger magnitude of hyperalgesia within the foot as compared to the hand, might be at least partially explained by a mechanism that partly relies on well established evidence that visceral (rectum/colon) and cutaneous (foot) nociceptive afferents converge onto common spinal lumbosacral neurons (Al Chaer et al., 2000 and references therein). Tonic activity in rectal primary afferents could sensitize the responses of these common spinal neurons to both rectal and thermal skin stimuli and many of these neurons project to pain-related brain regions. Hyperalgesia in the hand might be related to ascending propriospinal interactions between lumbosacral (foot) and cervical (hand) spinal levels. This possible mechanism is consistent with previous clinical observations showing that IBS patients often exhibit a number of extraintestinal pain symptoms such as back pain, migraine headaches, heartburn, dyspareunia, and muscle pain (Mayer and Gebhart, 1994; Mayer and Raybould, 1990). These symptoms may reflect widespread central hyperalgesic mechanisms. Similar to other pain conditions that likely depend on peripheral

impulse input, such as complex regional pain syndrome (CRPS), postherpetic neuralgia, and fibromyalgia (FM), IBS patients seem to develop widely distributed hyperalgesia, possibly related to chronic nociceptive input from the rectum and colon.

Both active facilitation and reduction in inhibition could contribute to central sensitization and secondary hyperalgesia in IBS. IBS patients have been shown to have a reduction in inhibition of evoked somatic or rectal pain that normally occurs when a noxious stimulus is simultaneously applied to another body area (King et al., 2009; Wilder-Smith et al., 2004).

Evidence from human patient studies that secondary hyperalgesia is dynamically maintained by tonic impulse input from the colon/rectum

This hypothesis about the role of tonic impulse input was tested in studies of evoked rectal and somatic pains in human IBS patients and in rat models of IBS. One strategy of testing this hypothesis was suggested by a model of neuropathic pain in which ongoing afferent input from a peripheral source maintains altered central processing that accounts for spontaneous pain, allodynia, hyperalgesia, and motor abnormalities (Gracely et al., 1992). This model was based on the observation that peripheral anesthetic blockade of nociceptive input from a few critical somatic foci whose locations varied across patients effectively abolished both spontaneous and elicited pain and cold/mechano-allodynia within widespread body regions of complex regional pain syndrome (CRPS) patients, including regions that were remote from these critical foci. A similar reversal occurred with sympathetic blocks in some CRPS patients (Price et al., 1989, 1998). Given the presence of widespread zones of hyperalgesia in neuropathic pain, fibromyalgia (FM), and IBS patients, it is possible that hyperalgesia of these patients is at least partly maintained by tonic impulse input from nociceptive and/or non-nociceptive primary afferent neurons. Considerable evidence from studies of local anesthetics on normal and abnormal ion channels shows that injured nerves or nerve terminals are blocked for a much longer time than the normal action of local anesthetics (Devor, 2006; Scholz, 2002). The normalization of secondary hyperalgesia by local anesthesia of peripheral neural generators of tonic impulse input suggests that a similar experiment could be carried out in IBS patients. Perhaps there is something abnormal about the peripheral and/or central nerve terminals of colonospinal or rectospinal afferent neurons.

The role of tonic impulse input from the rectum of IBS patients was tested by administering controlled rectal distention and cutaneous heat stimuli before and after rectal administration of lidocaine gel or saline gel in a double-blind crossover basis (Verne et al., 2003a). The comparison was ideal because it has been demonstrated that subjects cannot subjectively distinguish the two agents when applied rectally (Verne et al., 2003a). In comparison to saline placebo, lidocaine jelly completely normalized not only rectal hyperalgesia, as shown in Fig. 2 (left panel), but also hyperalgesia to thermal stimuli applied to the foot (Fig. 2, right panel). These results were not caused by systemic absorption of lidocaine because 1) the lidocaine gel was directly applied to wall of the rectum, 2) blood levels of lidocaine remained below the lower limit of detection for 50 min, and 3) most of the effects were present well before (5 min after treatment) maximum systemic absorption would have taken place even with liquid lidocaine (1–2 h after treatment) (Verne et al., 2003a). A similarly designed crossover study found that intrarectal lidocaine produced 4 to 6 h of large reductions in spontaneous pain of IBS patients (Verne et al., 2005). Thus, consistent with the role of peripheral impulse activity in some neuropathic pain conditions, tonic impulse input from a peripheral source dynamically maintains not only primary hyperalgesia from the rectum/colon but also the secondary hyperalgesia that is spatially remote (e.g. foot, hand) from the peripheral source of impulse input (i.e., rectum/colon). It also appears to maintain ongoing pain (Verne et al., 2005).

Animal models that further support the idea of a dynamic peripheral maintenance of primary and secondary hyperalgesia in IBS

Animal models have recently produced very similar behavioral results (Al Chaer et al., 2000; Lin and Al-Chaer, 2003; Zhou et al., 2007; 2008) and some of these studies have extended our understanding of neural mechanisms by providing recordings from primary afferent and dorsal horn neurons (Al Chaer et al., 2000; Lin and Al-Chaer, 2003). One animal model shows that 24% of rats initially treated with intracolonic trinitrobenzenesulfonic acid (TNBS) continue to display hypersensitivity to both rectal distension and somatic stimuli (e.g., heat stimulation of foot and tail) long after they healed from transmural TNBS-induced colitis (Zhou et al., 2008a). Thus, similar to IBS patients, mucosal and submucosal infiltration by polymorpho-nuclear leukocytes, macrophages, lymphocytes, and connective tissue mast cells (Morris et al., 1989) was no longer present in this subset of rats. Like IBS patients, the somatic hypersensitivity was largest in lumbosacral dermatomes. This combination of hypersensitivity and histologically normal colons/rectums resembles a main characteristic of IBS, a condition that develops in 25% of persons who have had infectious diarrhea (Verne et al., 2001). Similar to the study of IBS patients described above, intracolonic lidocaine administration in hypersensitive rats normalized both rectal and somatic hypersensitivity without producing detectable blood levels of lidocaine.

Another model of IBS used mustard oil injections in neonatal rats and produced delayed visceral and somatic hypersensitivity, similar to TNBS-treated rats. Oil of mustard (OM), allyl isothiocyanate, is one of the components of mustard that is an acute inflammatory stimulant of small nerve fibers. It has been used to induce acute colitis in order to study allodynia and visceral hyperalgesia in mice and rats (Al Chaer et al., 2000; Kimball et al., 2005). Intracolonic application of 0.5% mustard oil produces a visceral hyperalgesia within hours after administration. The signs of induced colitis usually disappear within 14–21 days, yet many rats continue to display visceral and somatic hypersensitivity. Rats were tested in this model during adulthood and during a time of absence of colorectal histological pathology. Compared with adult control rats treated neonatally with saline, adult rats treated neonatally with mustard oil enemas exhibited chronic visceral hypersensitivity manifested by increased contractility of abdominal muscles. These same rats also displayed hypersensitivity to cutaneous nociceptive stimulation within widespread regions but most predominantly in lumbosacral dermatomes, again similar to IBS patients and to the TNBS model.

This “mustard oil” animal model provided the opportunity to directly test the responsiveness of rectal and colonic primary afferent neurons and dorsal horn neurons on which they synapse, something which is not as yet feasible for IBS patients. In comparison to rats treated neonatally with saline instead of mustard oil, colorectal primary afferent neurons of these hypersensitive rats had higher levels of spontaneous impulse activity and much higher impulse responses to graded levels of rectal distension (Al Chaer et al., 2000; Lin and Al-Chaer, 2003). The same authors found that dorsal horn neurons receiving both rectal and somatic input had much higher levels of evoked impulse activity from both rectal distension and somatic stimuli as well as higher spontaneous activity, all in comparison to control rats (Al Chaer et al., 2000). The somatic hypersensitivity was greatest in lumbosacral dermatomes. All of these results strongly parallel those found for IBS patients and provide further evidence that both visceral and somatic hyperalgesia are dynamically maintained by increased activity in primary colorectal afferent neurons and by consequent sensitization of the dorsal horn neurons on which they synapse. These dorsal horn neurons are hyper-responsive to both visceral and somatic stimuli because they have increased excitability in general and have viscerosomatic convergence.

Unfortunately, no direct way of testing spinal cord mechanisms of hyperalgesia in IBS patients that is equivalent to that of testing rat models of IBS has been developed. However, enhanced

spinal cord processing of somatic stimuli has been examined in IBS patients through analysis of effects of rectal distensions on electro-myographic recordings of the somatic nociceptive flexion reflex (R-III) in response to painful electrical shocks within the foot area (Coffin et al., 2004). Whereas slow ramp rectal distention induced inhibition of this nociceptive reflex in 10 healthy volunteers, it facilitated this reflex in 14 IBS patients. These results provide further evidence for hyperexcitability of spinal nociceptive processing in IBS patients, evidence that is complementary to results from animal models of IBS.

Are there brain mechanisms and psychological factors that help maintain visceral and somatic hyperalgesia in IBS?

The primary afferent and dorsal horn mechanisms just described seem to be at odds with a prevailing and alternative viewpoint that numerous psychological factors contribute to and may even be the etiological origins of functional bowel disorders such as IBS (Mayer and Gebhart, 1994; Naliboff et al., 2001). These factors are integrally related to hypervigilance, level of somatic focus, or other factors related to emotional regulation. For example, the relationship of negative affect to pain conditions such as IBS is well-documented in the literature (Robinson and Riley, 1998). In nearly all published reports, the presence of negative mood is associated with higher levels of pain. Induction of negative mood has also been shown to be related to pain report and pain behavior, with some specificity to the type of emotion induced (Rhudy and Meagher, 2000, 2003; Zelman et al., 1991). Interventions or instructional sets that reduce negative emotion also reduce pain report (McCracken and Gross, 1998). IBS patients have been shown to have a propensity for hypervigilance and somatic focus and their painful symptoms may be at least partly maintained by these factors (Mayer and Gebhart, 1994; Naliboff et al., 2001). If so, then it should be possible to systematically enhance or reduce IBS pain by psychological manipulations. One way of testing this possibility has been that of modulating evoked rectal and somatic pain in IBS patients by various types of placebo/nocebo suggestions (Vase et al., 2004).

Placebo effects across two types of studies of IBS patients

Our studies of placebo effects on evoked and spontaneous pain in IBS have used two general conditions, one in which the study was conducted as a clinical trial (Verne et al., 2003a, 2005) and the other in which suggestions were given to enhance the placebo effect (Vase et al., 2003, 2004, 2005). IBS patients in two clinical trials were given an informed consent form which stated that they “may receive an active pain reducing medication or an inert placebo agent”. In one clinical trial there was a significant pain-relieving effect of rectal lidocaine as compared to rectal placebo on abdominal pain evoked by a rectal distension pressure of 35 mm Hg and there was a significant pain-relieving effect of rectal placebo as compared to the untreated baseline condition (Verne et al., 2003a) (Fig. 2, left panel). The other clinical trial found no placebo effect on ongoing abdominal pain in IBS patients and a large effect of intra-rectal lidocaine (Verne et al., 2005). Results of these two clinical trials can be compared to three studies in which IBS patients were told “the agent you have just been given is known to significantly reduce pain in some patients” at the onset of each treatment condition (Vase et al., 2003, 2005; Price et al., 2007). As shown in Fig. 3, addition of a placebo suggestion, which enhanced the expectation of less pain, resulted in a much larger placebo analgesic effect in comparison to that found in the clinical trial where no such suggestion was given. In fact, in the second type of study, the magnitude of placebo analgesia was so high that there were no longer significant differences between effects of rectal lidocaine and rectal placebo (Vase et al., 2003, 2004, 2005). The comparison between clinical trial and placebo mechanism studies indicate that by manipulating expectations through the addition of an overt suggestion for pain relief, it is possible to increase the magnitude of placebo analgesia to a level that matches that of a known active agent. It is important to recognize that these effects reflect anti-hyperalgesic

effects, because both rectal lidocaine and placebo suggestions normalized rectal hyperalgesia and did not eliminate all pain from balloon distention. Thus, pain ratings of IBS patients after placebo or lidocaine are like those of normal control subjects (Vase et al., 2003; Verne et al., 2003a). The reductions in evoked visceral pain were strongly predicted by ratings of expected pain levels and desire for relief, a prediction that follows from at least one current explanation of placebo analgesia (Price et al., 2008; Vase et al., 2004). However, placebo manipulations not only normalized visceral hyperalgesia but also somatic hyperalgesia that was tested by heat stimuli applied to the foot, despite the finding that patients did not expect this latter effect (Verne et al., 2003a).

Brain imaging tests of central modulation of pain in IBS

The results of the aforementioned studies, which show the effects of a placebo suggestion on pain evoked by visceral and somatic stimuli, provides indirect support for a brain-to-spinal cord mechanism that reverses the sensitization of dorsal horn neurons with both visceral and somatic primary afferent input. Reversal of hypersensitivity at the level of the dorsal horn should result in decreased pain-related activation at all subsequent supraspinal levels. A study tested this prediction by using the same methods of rectal distension and pain ratings scales as described above, in combination with fMRI brain imaging (Price et al., 2007). As shown in Fig. 4, a large analgesic effect was produced in IBS patients by a placebo suggestion and this effect was accompanied by large reductions in visceral-evoked neural activity (as measured by BOLD) in the thalamus, first and second somatosensory cortices (i.e., S-1 and S-2), anterior, mid-, and posterior insular cortex, and anterior cingulate cortex, all areas that are part of the pain matrix. The widespread reduction in these areas, including those at early levels of processing (e.g., thalamus, S-1), is consistent with a descending brain-to-spinal cord mechanism of pain modulation. Clearly, however, this line of evidence is indirect and more direct measures of spinal cord processing, such as the R-III reflex and even functional neuroimaging of spinal cord activity, are needed to further test this hypothesis. However, widespread reduction of neural activity throughout the “pain matrix” tends to rule out a mechanism of modulation that involves only selective effects on forebrain areas involved in cognitive processing of pain without effects at earlier stages of processing (Mayer et al., 2005; Naliboff et al., 2001; 2003; Mertz et al., 2000). Such selective effects might reflect a report bias rather than inhibition of ascending nociceptive input. For example, Mayer et al. (2005) reported that, in comparison to control subjects and ulcerative colitis patients, IBS patients exhibited greater activation in the rostroventral ACC during anticipated rectal distention.

Other brain imaging studies show placebo-induced changes in brain activity that are unlikely to be the exclusive result of decreased afferent processing of nociceptive input at spinal levels (Kong et al., 2006) alone. Additionally, one of our neuroimaging studies of IBS patients provided an opportunity to identify and analyze brain regions that were activated more during placebo analgesia than during the untreated baseline condition (Craggs et al., 2008). Some of the activated regions are known to be involved in the classic brain–spinal cord modulatory system (e.g., the rostral ACC and bilateral amygdale), thereby providing neuroimaging results that are consistent with and support the role of this classic mechanism in pain modulation (Fields and Price, 1997; Mayer and Price, 1976). Additionally, some of the placebo-activated regions are also known to be involved in emotions and emotional regulation, functions that are presently considered to be a part of the affective component of endogenous pain modulation (Petrovic and Ingvar, 2002; Petrovic et al., 2005; Price et al., 2008; Craggs et al., 2008). Moreover, increased activation also occurred in brain regions associated with other phenomena likely to be involved in the experience of pain (e.g., maintaining memory for the placebo suggestion and in developing expectations of pain reduction). For example, some placebo-activated regions were those involved in neurolinguistic processes and memory, such as the

parahippocampal gyrus, medial aspects of the left temporal lobe and left lentiform nucleus (Craggs et al., 2008). Other neuroimaging studies have identified brain regions activated by placebo that are known to comprise a neural network that is involved in associative thinking, such as the left pre-cuneus, posterior cingulate, and aspects of the temporal lobe (Bar et al., 2007). These regions, associated with cognitive and affective processes, were most active during the early part of the placebo condition (i.e., the early phase of the analgesic response), presumably at a time wherein subjects were attending to the memory of the placebo suggestions and to somatic feedback. The temporal profile of these placebo-induced brain activations is consistent with our previous explanation that the neural mechanisms of placebo analgesia produce their effect through increased involvement early in the development of placebo analgesia via self-reinforcing feedback that confirms the efficacy of the treatment (i.e., placebo suggestion). Thus, we have consistently found that placebo analgesia increases in magnitude over the first few test stimuli following the placebo suggestion (Price et al., 2007; Verne et al., 2003c; Vase et al., 2003, 2005), as shown in Figs. 2 and 3. We have interpreted this progressive increase to be the result of a kind of feedback mechanism that involves somatic focus and associative thinking (i.e., thinking that is characterized by loose and rapid associations between thoughts and images). As a result of this feedback, the placebo analgesic effect increases over time and is accompanied by increasing expectations for pain relief (Vase et al., 2005).

These feedback mechanisms need not be strictly associated with deliberate administration of a placebo or nocebo agent and are likely involved with multiple aspects of the pain experience including catastrophizing, hypervigilance and somatic focus; all of which are known to be prevalent and exacerbated among IBS patients and other types of chronic pain patients (Naliboff et al., 2001; Price et al., 2008; Robinson and Riley, 1998). Thus, searching for visceral cues that signal impending relief or worsening of symptoms could lead to a self-confirming feedback mechanism whereby increased or decreased pain leads could lead to still further changes in symptoms. Although this proposed mechanism has received some support from our behavioral and functional neuroimaging studies, its potential role in contexts where no agent is given needs to be explored. For example, expectation manipulations in non-placebo contexts have been shown to exert strong top-down inhibitory effects on sensory processing mechanisms (Koyama et al., 2005).

Finally, advanced statistical techniques have been used to investigate the neural networks involved in different facets of pain. For example, one study used structural equation modeling (SEM) and the fMRI data from an IBS and placebo study mentioned above, to characterize the effective connectivity of brain regions during baseline and placebo conditions (Craggs et al., 2007). The final model of the untreated baseline pain data (evoked by rectal distension in patients with IBS) had functional connections among brain regions that were predicted by, and consistent with an established neuroanatomical model of brain regions that interact during pain (Price, 2000). This model included the following positive connections: anterior insula–posterior insula–ACC–supplementary motor cortex as well as ACC–prefrontal cortex. The final model of placebo data revealed that, while the same brain regions were involved in both conditions, their effective connectivity changed during the experience of placebo analgesia. For example, while some of the connections were maintained during the placebo condition, the connection from the anterior insula to the ACC reversed direction during placebo and the connections from the ACC to SMA was greatly reduced (right hemisphere) or reversed (left hemisphere). Thus, the placebo suggestion resulted in changes of neural activity that are consistent with decreased anticipation of pain and a lessened demand for attention (decreased anterior insula–ACC), as well as decreased consideration of movement during pain (ACC–SMA) that should accompany a reduction in pain (i.e., placebo analgesia). These results are consistent other studies that have associated the anterior insula and ACC with the anticipation of pain (Wager et al., 2004). There was also an increased positive influence of the dorsolateral prefrontal cortex (DLPFC) on the ACC in the left hemisphere during the placebo condition,

which is also consistent with other neuroimaging and pain studies (Wager et al., 2004). Increased influence of DLPFC on the ACC may be related to a maintenance function, utilizing recall of pain in the previous baseline session and working memory of the placebo suggestions, functions that are known to be served by DLPFC (working memory) and aspects of the medial temporal lobe. This function could serve part of the foundation of a self-reinforcing feedback loop discussed above.

Given the presence of ongoing widespread somatic and visceral hyperalgesia in IBS, it is reasonable to hypothesize that induction (e.g. nocebo), maintenance, and reversal of hyperalgesia (e. g. placebo) rely on dynamic regulation by networks of brain regions. This regulation is associated with somatic focus, hypervigilance, and emotional regulation that contribute to both inhibition and facilitation of nociceptive input, depending on the context, ongoing expectations of pain, and other aspects of the psychological state of these patients. However, this central modulation seems to interact with tonic peripheral impulse input to the spinal cord, so that widespread hyperalgesia reflects a confluence of peripheral and central mechanisms.

This explanation does not exclude other models of IBS. For example, Halpert and Drossman's (2005) biopsychosocial model for irritable bowel syndrome suggests that the interaction of multiple biopsychosocial factors may determine how patients experience IBS symptoms. Their model accounts for dysregulation of the central and enteric nervous system functions in IBS. The resulting dysmotility and visceral hypersensitivity is modified by psychological factors. Thus, the explanations presented in this review are consistent with the view that IBS may result from multiple biological/neurological conditions that are modified by psychological factors.

Concluding remarks: is there a synergistic interaction between peripheral impulse input and central facilitation?

It is surprising and probably important that primary and secondary hyperalgesia can be nearly completely normalized in some IBS patients either by removing the source of tonic peripheral impulse input (i.e., local rectal anesthesia) or by providing a form of central modulation through placebo suggestions. One possible mechanism that could account for this combination of observations is that a synergistic interaction might occur between peripheral and central sources of facilitation of dorsal horn neuron responsiveness. That is, hypersensitivity of dorsal horn neurons might be dynamically maintained by impulses from visceral structures and from brain–spinal cord descending facilitation. The latter mechanism has been strongly implicated in persistent pain conditions (Gebhart, 2004; Porreca et al., 2002). If a synergistic interaction occurs between these two sources of facilitation, then removal of either source alone may be sufficient to normalize the hyperalgesia. This model is also consistent with findings that indicate that psychological factors (e.g. distress) strongly influence IBS pain. Such factors are associated with a main source of central facilitation. Of course, this hypothesis needs to be further tested. If this kind of synergistic interaction generalizes to other hyperalgesic states, it might have large implications for understanding how to assess the relative contribution of peripheral and central factors in other persistent pain conditions such as fibromyalgia and various forms of neuropathic pain.

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Fig. 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 foot (right panel). Note that patients with IBS rate pain intensity from rectal distention and cutaneous heat stimuli ($P<0.001$). Values are represented as means $\pm$ standard deviation, $n=12$ IBS patients, 17 controls. Based on data from Verne GN, Robinson ME, Price DD: Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. *Pain* 93:7–14, 2001.

Fig. 2.

(Left panel) VAS pain intensity ratings during rectal distention (35 mm Hg). Three separate trials were performed: baseline or natural history (natural), rectal placebo, and rectal lidocaine. This study was conducted with a standard clinical trial design without suggestions for analgesia (10 IBS patients). (Right panel) VAS pain intensity ratings of cutaneous heat pain in the same IBS patients, showing a similar reversal of heat hyperalgesia by lidocaine.

Fig. 3.

Comparison of the placebo effect of a clinical trial and that of a second study wherein a verbal suggestion for analgesia was added. Note the larger placebo effect for the latter. Based on data from Vase L, Robinson ME, Verne GN, Price DD: The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients: An empirical investigation. *Pain* 105:17–25, 2003.34

Fig. 4.

In a fMRI study, brain activity of irritable bowel syndrome (IBS) patients was measured in response to rectal distension by a balloon barostat (Price et al., 2007). A large placebo effect was produced by suggestions and accompanied by large reductions in neural activity in known pain-related areas, such as thalamus, S-1, S-2, insula, and anterior cingulate cortex (ACC). These large reductions occurred during the period of stimulation and well before subjects provided pain ratings, thereby reflecting effects unlikely to result from report biases. Based on data from Price, D.D., Craggs, J.G., Verne, G.N., Perlstein, W.M., Robinson, M.E., 2007. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients, *Pain* 127, 63–72.