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Viscerosomatic Facilitation in a Subset of IBS Patients, an Effect Mediated by N-Methyl-D-Aspartate Receptors

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Abstract

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder in which the pathophysiological mechanisms of the pain and hypersensitivity are incompletely understood. IBS patients frequently complain of pain in body regions somatotopically distinct from the gut, suggesting involvement of central hyperalgesic mechanisms. We tested the role of tonic peripheral impulse input by using both repetitive thermal stimuli to the leg and repetitive stimuli to the rectum. Changes in thermal/visceral pain sensitivity after nociceptive thermal/visceral repetitive stimulation were determined. A subset of IBS patients showed enhanced rectal/thermal pain sensitivity after repetitive thermal/rectal stimulation respectively. IBS patients then received 60 mg dextromethorphan and placebo (Benadryl) in a randomized, double-blind, crossover trial. The results showed: (1) a subset of IBS patients had increased visceral/cutaneous hypersensitivity following a series of repetitive nociceptive stimuli (2) This increased pain sensitivity was blocked by administration of dextromethorphan. This is the first human study that indicates repetitive stimulation enhances a bidirectional mechanism of secondary hyperalgesia due to viscerosomatic facilitation in IBS patients. These unique findings elucidate mechanisms of somatic hypersensitivity in IBS patients and support an etiologic basis for abnormal NMDA receptor mechanisms that may be the target of future therapies for IBS.

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Keywords

Irritable bowel syndrome (IBS); visceral and thermal hypersensitivity; repetitive afferent barrage; dextromethorphan; NMDA receptor; viscerosomatic facilitation

1. INTRODUCTION

Many patients with IBS frequently complain of pain body regions somatotopically distinct from the gut, suggesting that central hyperalgesic mechanisms may be involved.¹⁶ Previously, hypersensitivity was thought to be limited to the gut.^{13,31} However, several recent studies have shown that some IBS patients demonstrate hyperalgesia to nociceptive stimuli applied to the extremities.^{2,21,26} These studies suggest that processing of visceral and somatic stimuli may overlap as a result of viscerosomatic convergence-facilitation in the lumbosacral distribution.^{12,17} Thus, chronic afferent nociceptive input from the gut may sensitize spinal cord neurons that exhibit somatotopic overlap with the gut. We have previously shown that a subset of IBS patients have greater somatic hypersensitivity than controls and this somatic hypersensitivity is somatotopically organized in that the lower extremities that share viscerosomatic convergence with the colon demonstrate the greatest hypersensitivity.^{21,26} Pain in IBS patients is likely to be a partly maintained by peripheral impulse input from the colon/rectum because several studies show that local rectal—colonic anesthesia normalizes visceral and somatic hyperalgesia in IBS patients and in “IBS-like” rats.^{22,29} Yet these forms of hypersensitivity are also highly modifiable by placebo and nocebo factors (e.g., expectations of relief or distress, respectively). Our working hypothesis is that both central sensitization and enhanced afferent processing produces and maintains hyperalgesia in IBS. This explanatory model may be relevant to other persistent pain conditions.

To further test the role of tonic impulse activity and central sensitization in IBS, we measured pain sensitivity following nociceptive repetitive thermal stimulation of the calf and visceral stimulation of the colon (rectal distension). Noxious repetitive thermal stimulation was used to determine if afferent impulse input from somatic tissues can facilitate nociception from visceral stimulation. Similarly, noxious repetitive visceral stimulation was used to determine if visceral impulse input can facilitate cutaneous heat nociception. Our overall hypothesis is that visceral and somatic hypersensitivity in IBS patients is sustained by both central and peripheral neural mechanisms that interact at spinal cord and supraspinal levels.¹⁸

In the current study, we sought to obtain psychophysical evidence for or against the possibility that input to central nociceptive pathways is abnormally processed in a subset of IBS patients with longstanding thermal and visceral hyperalgesia. In particular, we tested the convergence facilitation theory^{11,12} by using repetitive stimulation of rectal and somatic tissues to induce central sensitization and then used an NMDA receptor antagonist to block facilitation.²⁷ Thus, the aims of this study were to: 1, evaluate visceral and somatic pain sensitivity in IBS patients compared to controls; 2, determine if repetitive nociceptive thermal stimulation increases visceral hypersensitivity; 3, determine if repetitive nociceptive rectal distension increases thermal hypersensitivity; 4, determine whether increased visceral and heat pain sensitivity following repetitive stimulation can be reversed by Dextromethorphan, an NMDA receptor antagonist.

2. MATERIALS AND METHODS

2.1 Participants

The study was approved by both University of Florida, North Florida/South Georgia Veterans Administration, and the Ohio State University Institutional Review Boards and all subjects signed informed consent prior to the start of the study. All IBS patients that were recruited had gastrointestinal symptoms for at least 5 years and had upper endoscopy and colonoscopy with biopsies which were normal. We used only a homogenous group of diarrhea-predominant IBS patients in this study as our previous studies have focused on this group of IBS patients who have evidence of visceral and somatic hypersensitivity. The diagnosis of IBS was made by an experienced gastroenterologist who based the diagnosis on the ROME III criteria and exclusion of organic disease.¹⁰ Fibromyalgia (FM) was excluded in all IBS patients and controls using the 1990 American College of Rheumatology criteria for FM.⁶ The controls that were recruited were free of any evidence of acute and/or chronic somatic/abdominal pain based on a complete history and physical exam by an experienced gastroenterologist. In addition, all controls were screened for any systemic conditions that could affect sensory responses.

None of the participants were on serotonin antagonists, pain medications, serotonin uptake inhibitors, or tricyclic antidepressants for at least 1 month prior to the study. Subjects were instructed to refrain from use of any analgesic medication or caffeine for 48 hours before their sessions. All sessions were conducted between 10 AM and 6 PM to control for circadian rhythm effects. Female subjects were tested during the follicular phase and were not tested during active menstruation. This reduced the influence of enhanced clinical symptoms during active menses during which IBS patients may exhibit enhanced rectal sensitivity. The protocol was thoroughly explained in detail to all of the study participants.

2.2 Beck Depression and State Trait Anxiety Inventory

All study participants completed the Beck Depression Inventory and the State Trait Anxiety Inventory.^{4,9} Depressive and anxiety disorders were exclusions if they were severe enough to interfere with the individual's ability to participate in the study. Therefore, study subjects who scored 30 or higher on the Beck Depression Inventory and/or 53 or higher on the State Trait Anxiety Inventory, were excluded. Such scores would be approximately one standard deviation above the mean for general medical patients.

2.3 Response Measures

A mechanical visual analogue scale (M-VAS) was used to measure perceived pain intensity in all subjects following the experimental pain stimuli.¹⁵ The M-VAS is anchored by the descriptors "no pain sensation" and "the most intense pain sensation imaginable" at 10, respectively. Standard written instructions and practice in rating painful stimuli was given to all subjects. All subjects rated their current clinical pain intensity on the M-VAS scale during the day of each testing session.

On the first day of the study, all participants either underwent baseline visceral or thermal pain testing. The order of the baseline testing was randomized and counterbalanced across groups to prevent any order effects. The participants who underwent baseline visceral pain testing on the first day also had repetitive thermal stimulation of the left calf. Alternatively, the participants who underwent baseline thermal testing on the 1st day had repetitive visceral stimulation performed on the same day.

2.4 Baseline Visceral Pain Testing

A 500 ml polyethylene bag was used for rectal distension (Zinetics Medical, Inc., Salt Lake City, UT). The lubricated balloon was placed into the rectum so that the attached end of the bag was 1 cm from the anal sphincter. A barostat (IsoBar 3: G & J Electronics Corp., Willowdale, Ontario) was used to inflate (phasic distension, 870 mL/min) the rectal balloon to a pressure plateau of 35 mmHg for 5 seconds each followed by a 2 minute inter-stimulus rest (resting pressure of 5 mmHg). Following the visceral stimulus, the subject was asked to rate the perceived pain intensity using the M-VAS scale. The trial was repeated and mean pain intensity was recorded for each subject.

2.5 Baseline Thermal Pain Testing

All thermal stimuli were delivered using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel). Thermal stimuli were delivered to a premarked spot on the left calf with a large thermode (3×3 cm) as previously described. Each trial consisted of a 5-second adapting temperature of 32°C, followed by a 5-second pulse at 47°C. This was followed by a 60-second inter-stimulus rest. Following the stimulus, the subject was asked to rate the perceived pain intensity using the M-VAS scale. The trial was repeated and the mean pain intensity was recorded for each subject.

2.6 Repetitive Nociceptive Stimulation

Immediately following the baseline visceral and thermal pain testing above, all subjects underwent repetitive thermal (calf) or repetitive visceral stimulation (rectal distension). The order of testing (i.e. repetitive rectal distension vs. repetitive thermal) was randomized and counterbalanced across groups to prevent order effects. Following the repetitive thermal or visceral stimulation respectively, all subjects were allowed to rest and returned within 7 days to complete the other repetitive stimulation paradigm.

Thermal stimuli were delivered to the same premarked spot used in the baseline testing on the left calf with the large thermode (3×3 cm). A total of thirty 5 second 47°C heat pulses with a 5 second interstimulus interval were performed at each site (Figure 1A). Study subjects were randomized to receive thermal stimulation of the calf. Immediately following repetitive thermal stimulation of the calf, rectal distension testing was repeated exactly as outlined above in the baseline visceral pain testing. The change from the baseline VAS pain rating to rectal distension was recorded for each subject. After a 30 minute rest, each subject underwent repetitive thermal stimulation of the calf again. The change from baseline in the VAS pain rating to rectal distension was again recorded for each subject.

The rectal balloon was inflated to a pressure plateau of 35 mmHg for 30 seconds each followed by a 30-second inter-stimulus rest (resting pressure of 5 mmHg). This was repeated 12 times (Figure 1B). Immediately following the visceral stimuli, ratings of suprathreshold temperatures were measured on the left calf as outlined above in the baseline thermal pain testing. The change from the baseline VAS pain rating to thermal stimulation was recorded for each subject. After a 30 minute rest, each subject underwent repetitive rectal distension again. The change from the baseline VAS pain rating to thermal stimulation was recorded for each subject again.

2.7 Dextromethorphan

We next performed a double-blind, placebo controlled, crossover study using Dextromethorphan and placebo (Bendryl). The subset of IBS patients (33%) that demonstrated increased pain report to repetitive nociceptive stimulation (visceral and thermal), were randomized to receive identical-appearing capsules (along with 300 cc of water) containing either 60 mg of Dextromethorphan or 50 mg of Benadryl as a placebo.

The dose of 60 mg of Dextromethorphan was used because it was shown to be effective in our previous study reversing hyperalgesia in IBS patients.²⁷ Benadryl was used as a placebo for several reasons. First, we used it successfully as a placebo in our earlier study and when asked, patients did not know whether they received placebo (Benadryl) or dextromethorphan. Second, Benadryl has similar side effects as Dextromethorphan; however, it does not have any analgesic actions. Because of a slow onset and long time-course of action, repeat repetitive stimulation testing was started 45 minutes after ingestion of the experimental agents. Randomization was counterbalanced such that all (33%) IBS patients received both placebo and Dextromethorphan on two different days. Following administration of either placebo or Dextromethorphan on the first day, all patients underwent a 7 day washout period prior to returning for the 2nd day of testing.

2.8 Statistical Analysis

The statistical analysis was performed using SAS software, Version 9.1.3 of SAS system Copyright © 2003 SAS institute Inc. and Prism version 6. Frequency distribution was used to classify the IBS patients based on pain thresholds on the individual tests and to classify the groups of patients based on changes in visceral and thermal perception thresholds following repetitive nociceptive stimulation. IBS patients were separated into two distinct subsets based on the distribution and range of the MVAS ratings for the thermal and visceral nociceptive stimuli. The hypersensitive group of IBS patients was defined as those IBS patients with pain sensitivity ratings that fell out of the total range in normal controls. Values are expressed as means $\pm$ standard deviation (SD). The changes in pain intensity ratings between baseline visceral/thermal pain testing following repetitive thermal/visceral pain stimuli respectively were assessed with a one-sample t-test comparing the sample mean at less than 0.05 level.

3. RESULTS

3.1 Subjects

A total of 69 participants were studied that included 45 patients (28 Females, 17 Males; mean age 27.3 ± 4.2 years) with diarrhea-predominant IBS (IBS); and 24 control subjects (14 Females, 10 Males; mean age 29.0 ± 3.1 years). There was no difference in age or sex between the groups (controls, IBS). There were no group differences on the State Trait Anxiety Inventory (STAI) or on the Beck Depression Inventory (BDI). All of the IBS patients had diarrhea-predominant (IBS) for at least 5 years and met the Rome III criteria for irritable bowel syndrome.¹⁰

3.2 Baseline Visceral/Thermal Pain Testing

Frequency distribution analysis was used to cluster the IBS patients into 2 groups based on the range of reported values for visceral and thermal sensation respectively. One group of IBS patients (67%) had a similar range of MVAS ratings to visceral and thermal stimulation as the control group respectively (Figure 2). Using cluster analysis a subset of IBS patients (33%), termed hypersensitivity IBS patients (H-IBS), demonstrated hypersensitivity to both visceral and thermal stimuli respectively as demonstrated by much higher ranges of ratings compared to controls and the normosensitive group of IBS patients (N-IBS).

3.3 Repetitive Visceral/Thermal Stimulation

All study subjects rated mean pain intensity to thermal stimulation of the left calf following repetitive rectal distension. Changes in the mean pain ratings compared to baseline thermal stimulation were recorded for each subject. Interestingly, the H-IBS patients (33% of IBS patients), but neither the N-IBS patients (67%) nor controls, demonstrated a significant

increase in ratings to thermal stimuli after repetitive visceral stimulation (Figure 3). Due to the complexities of the stimulus response paradigm, we were not able to ask our subjects to rate VAS scores during repetitive heat stimulation.

Following repetitive thermal stimulation of the calf, all study subjects rated mean pain intensity to visceral stimulation (rectal distension). The changes in the mean pain ratings to visceral stimulation were recorded. H-IBS patients, but neither the N-IBS patients nor controls, demonstrated a significant increase in ratings to visceral stimuli (Figure 4). Thus, only IBS patients who showed increased baseline visceral and heat pain sensitivity also showed enhancement of these forms of hypersensitivity in response to repetitive stimulation. It is important to recognize that these enhancements were the result of stimulation of another tissue source (i.e., enhanced heat pain sensitivity in response to repetitive rectal stimuli and enhanced rectal pain sensitivity in response to repetitive heat stimulation). Due to the complexities of the stimulus response paradigm, we were not able to ask our subjects to rate VAS scores during repetitive visceral stimulation.

3.4 Effects of Dextromethorphan on Enhanced Pain Sensitivity from Repetitive Stimulation

H-IBS patients that exhibited increased baseline and hypersensitivity to repetitive nociceptive stimulation were included in the following trial. Following administration of oral NMDA receptor antagonist Dextromethorphan (60 mg), increased mean MVAS ratings to thermal/rectal distension following repetitive visceral/thermal stimulation were nearly completely blocked compared to administration of placebo (* $p < 0.01$) (Figures 5 & 6). There were no changes with placebo or control condition.

4. DISCUSSION

The results support and extend a convergence-facilitation mechanism of IBS in which tonic impulses from the colon and rectum induce and maintain central sensitization of lumbosacral spinal cord neurons that receive convergent input from both visceral and somatic tissues. In addition to well established principles of viscerosomatic convergence, two types of evidence support convergence-facilitation in IBS.^{1,8,11-14,24,32} The first is the demonstration of increased sensitivity to rectal distension and cutaneous heat stimulation in human IBS patients and rat IBS models.^{15,26} The second is that of reversing this hypersensitivity in both IBS patients and animal IBS models by means of local anesthesia (i.e. rectal/colonic application of lidocaine).^{22,29}

4.1 Repetitive stimulation enhances a bidirectional mechanism of secondary hyperalgesia in subset IBS patients

The present study provides a further line of evidence for this mechanism by showing that experimentally induced tonic impulse input from the rectum (repetitive rectal distension) increases heat pain sensitivity within the calf and that repetitively induced nociceptive input from the calf increases pain sensitivity from rectal distension. Thus, this viscerosomatic convergence-facilitation mechanism operates in both directions. This bidirectionality of this mechanism adds a principle to the convergence-facilitation theory first proposed by MacKenzie.^{11,12} Moreover, both types of central facilitatory effects are based on NMDA receptor mediated signaling because they both can be blocked by dextromethorphan, an NMDA receptor antagonist. However, a peripheral site of action of dextromethorphan cannot be completely excluded. This pathophysiological mechanism occurs in a distinct subset of H-IBS patients and not in other N-IBS or normal control subjects. Another important finding of our study is that counter-irritation did not produce pain inhibition. This can occur especially if the nociceptive stimuli are delivered simultaneously to produce

diffuse noxious inhibitory controls (DNIC). This did not occur in our present study as the thermal and visceral noxious stimuli were given at different time points.

These results extend our previous work by providing evidence that increasing tonic impulse input through repetitive stimulation of one tissue source, such as the rectum, enhances heat pain sensitivity related to another tissue in a subset of IBS patients have evidence of somatic hypersensitivity that is somatotopically organized such that the lower dermatomes (i.e. calf) that share viscerosomatic convergence with the colon demonstrate the greatest hypersensitivity.¹⁶ A unique finding of the current study was that the somatic and visceral hypersensitivity that was present could be enhanced by repetitive nociceptive stimulation. These findings suggest that patients with IBS and visceral hypersensitivity may develop somatic hypersensitivity as a result of tonic facilitation by visceral impulse input and viscerosomatic convergence onto common spinal cord neurons^{1, 11-14}. This spinal sensitization in IBS patients may be induced and/or maintained by tonic impulse input from the colon to the spinal cord.

The pattern of thermal hypersensitivity seen in IBS patients might at least be partially explained by the likelihood that visceral (colon) and somatic (calf) nociceptive afferents converge onto common spinal lumbosacral neurons^{1, 11-14}. The chronic visceral nociceptive input from the colon may sensitize the responses of these common spinal neurons to nociceptive somatic stimuli. Work by our laboratory and others suggests that patients with functional pain disorders such as IBS may be characterized by abnormalities in both peripheral and central pain processing mechanisms.^{2,5,16} Similar to IBS, patients with other chronic pain disorders such as temporomandibular disorders have been shown to have widespread hyperalgesia.¹⁹

4.2 A role of NMDA receptors in bidirectional facilitation and hyperalgesia

The results of our present study further support that enhanced afferent barrage and central sensitization are chronically present in a subset of IBS patients and that the thermal and visceral sensitization is blocked by administration of dextromethorphan. Psychophysical testing using thermal and visceral stimuli can reveal these abnormalities that distinctly characterize a subset of IBS patients. These abnormalities may exist in some patients with other chronic pain conditions. Although there have been no characteristic gastrointestinal and/or peripheral pathophysiologic abnormalities demonstrated in IBS patients, a chronic, nociceptive drive from the colon may lead to tonic impulse input over nociceptive afferents that enhances wind-up, maintains central sensitization and therefore hyperalgesia.. Further prospective studies are now needed in IBS patients to further characterize the etiological basis for abnormal NMDA receptor mechanisms in at least some IBS patients.

Human Studies Supporting Viscerosomatic Convergence-facilitation: Several earlier studies in IBS patients found that enhanced visceral sensitivity was limited to the gut and that somatic hypersensitivity was either reduced or unaffected.³¹ Some of the likely reasons for the findings of these studies is that the brief stimuli that were used may not activated a sufficient number of C-nociceptors for a long enough time to assess neural mechanisms involving N-methyl, D-aspartate (NMDA) receptors.¹⁷ These neural mechanisms may be highly relevant to widespread somatic hyperalgesia as well as neuropathic pain in IBS and fibromyalgia.¹⁶

4.3 The etiology of peripheral and central pathophysiological mechanisms in subset IBS patients

The dichotomy between IBS patients who display these mechanistic abnormalities versus those who don't may be related to recent findings of heat hyperalgesia in those IBS patients

who have increased intestinal permeability.³⁰ The latter may generate more tonic peripheral impulse input, thereby making some IBS patients especially vulnerable to central sensitization. Many patients with IBS exhibit a wide variety of somatic symptoms including back pain, migraine headaches, heartburn, dyspareunia, and muscle pain. Collectively, these somatic symptoms suggest that a subset of IBS patients may also suffer from central hyperalgesic dysfunction.¹⁶

Several recent studies in IBS patients have used long duration heat stimuli that are known to activate C-fibers and NMDA receptors.^{21,25-28} These studies compared the responses to clinically relevant rectal and thermal stimulation in the colon and hand/foot in IBS patients. These studies concluded that a subset of IBS patients have both visceral and thermal hypersensitivity to nociceptive visceral and thermal stimuli. The thermal hypersensitivity is in a gradient in which the greatest hypersensitivity is the lower extremity which shares the greatest viscerosomatic convergence with the colon.^{26,30} Tonic activity in primary rectal afferents could sensitize the responses of common spinal neurons to both thermal and rectal stimuli. Hyperalgesia in the upper extremity might be related to ascending propriospinal interactions between cervical (upper extremity) and lumbosacral (foot) spinal levels. This is consistent with previous observations that IBS patients demonstrate a number of extraintestinal symptoms such as headaches, muscle pain, and back pain.²⁶ Thus, these symptoms suggest widespread central hyperalgesic mechanisms.

One validated model of neuropathic pain exists in complex regional pain syndrome in which ongoing afferent input from a peripheral source maintains altered central processing that accounts for hyperalgesia.⁷ Peripheral anesthetic blockade of nociceptive input from somatic foci eliminated both spontaneous and elicited pain within widespread body regions in patients with complex regional pain syndrome (CRPS). A similar reversal of both thermal and visceral pain occurred with the rectal administration of lidocaine jelly in IBS patients.²² In comparison to saline placebo, lidocaine jelly completely normalized not only rectal hyperalgesia, but also hyperalgesia to thermal stimuli applied to the right foot. Similarly, a crossover study done demonstrated that intrarectal lidocaine produced 4-6 hours of large reductions in spontaneous pain of IBS patients.²³ Thus, tonic impulse input from a peripheral source dynamically maintains not only primary hyperalgesia from the colon, but also the secondary hyperalgesia that is spatially remote (lower extremity) from the peripheral source of impulse input (colon). This is consistent with the role of peripheral impulse activity in some neuropathic pain conditions such as CRPS.⁷

We have recently shown that a subset of IBS patients exhibit wind-up, temporal summation of "second pain," in response to a series of brief 47°C heat pulses.²⁷ Interestingly, similar doses of Dextromethorphan decreased wind-up in fibromyalgia patients.²⁰ Wind-up is instrumental in the induction and/or maintenance of chronic disorders involving allodynia and hyperalgesia.³ Thus, tonic or chronic pain can result from a process of temporal summation via excessive activation of NMDA receptors, either as a result of abnormally high levels of short-term nociceptive input or because of continual input from C nociceptors. The enhanced wind-up of thermal pain in IBS subjects may be related to an ongoing peripheral input from C nociceptors that sensitize NMDA receptors on central nociceptive neurons (with or without tonic peripheral drive). Several recent studies by our group using an IBS-like animal model of visceral and somatic hypersensitivity further supports NMDA mechanisms in the pain of IBS patients.^{25,27-28} Another mechanism that may explain the enhanced wind-up in IBS patients is abnormal processing at supraspinal levels. We have previously shown enhanced activation of cerebral structures using fMRI in IBS patients compared to controls.²¹

4.4 Summary

The results of our present study further support a convergence-facilitation mechanism in a subset of IBS patients that display enhanced pain sensitivity to rectal and cutaneous heat stimulation (Fig 2). Both forms of enhanced pain sensitivity can be increased still further by repetitive visceral and cutaneous nociceptive stimulation (Figs 3-4) and these increases were nearly completely prevented by administration of dextromethorphan, an NMDA receptor antagonist (Figs 5-6). Taken together, these results provide further evidence for central sensitization that is dynamically induced and maintained by peripheral input from the colon/rectum. Using quantitative thermal and visceral stimuli, evidence for this mechanism was provided by analysis of hyperalgesic responses in combination with pharmacological manipulation of NMDA receptor mechanisms related to central sensitization. Similar pathophysiological NMDA receptor mechanisms may extend across this subset of IBS patients and patients with other chronic pain conditions. Although there have been no characteristic gastrointestinal and/or peripheral pathophysiologic abnormalities demonstrated in IBS patients, a chronic, nociceptive drive from the colon may lead to tonic impulse input over nociceptive afferents that enhances windup/TSSP, central sensitization, and consequently secondary hyperalgesia. Further prospective studies are now needed in IBS patients to determine the etiological basis for abnormal NMDA receptor mechanisms in at least some IBS patients. The implications of our current findings could have a major impact on the way patients with functional gastrointestinal disorders like IBS are diagnosed and treated.

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PERSPECTIVE

Repetitive stimulation enhances a bidirectional mechanism of secondary hyperalgesia due to viscerosomatic convergence in IBS patients. The findings elucidate unique mechanisms of somatic/visceral hypersensitivity in a subset of IBS patients and further support an etiologic basis for abnormal NMDA receptor mechanisms that may be future targets of therapies for IBS.

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Figure 1A.

Paradigm for repetitive thermal stimulation of the calf. A total of thirty 5 second pulses of 47°C with a 5 second interstimulus interval were given following baseline visceral pain testing. Visceral pain testing was repeated following the repetitive thermal stimuli.

Figure 1B.

Paradigm for repetitive visceral stimulation of the rectum. A total of twelve 30 second pulses of 35mmHg with a 30 second interstimulus interval were given following baseline thermal pain testing. Thermal pain testing was repeated following the repetitive visceral stimuli.

Figure 2.

The results of the baseline visceral and thermal pain testing for IBS patients and controls are illustrated (filled circles: controls; open triangles: IBS patients). Frequency distribution of VAS scores for visceral and thermal sensitivity in controls and IBS patients. There is a subset IBS patient with higher VAS readings to visceral and thermal stimuli (~ 33% of IBS patients; red dash circle).

Figure 3.

This figure compares responses to visceral and thermal stimulation for the percent maximum VAS scores for thermal sensitivity following repetitive visceral stimulation in controls and IBS patients. Closed circles represent controls; open circles represent IBS patients with baseline thermal hypersensitivity; filled squares represent IBS patients who did not have baseline thermal hypersensitivity. Values are means $\pm$ standard deviation.

Figure 4.

This figure compares responses to visceral and thermal stimulation Numerical ratings for the percent maximum VAS scores for visceral sensitivity following repetitive thermal stimulation in controls and IBS patients. Closed circles represent controls; open circles represent IBS patients with baseline thermal hypersensitivity; filled squares represent IBS patients who did not have baseline thermal hypersensitivity. Values are means $\pm$ standard deviation.

Figure 5.

This figure compares responses to visceral and thermal stimulation for the percent maximum VAS scores for thermal sensitivity following repetitive visceral stimulation in controls and IBS patients. Open squares represent baseline; closed circles represent the placebo condition; open circles represent the trial with Dextromethorphan. Values are means $\pm$ standard deviation.

Figure 6.

This figure compares responses to visceral and thermal stimulation for the percent maximum VAS scores for visceral sensitivity following repetitive thermal stimulation in controls and IBS patients. Open squares represent baseline; closed circles represent the placebo condition; open circles represent the trial with Dextromethorphan. Values are means $\pm$ standard deviation.