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Effects of the N-methyl-D-aspartate Receptor on Temporal Summation of Second Pain (Wind-up) in Irritable Bowel Syndrome

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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 not well understood. IBS patients frequently complain of pain in body regions somatotopically distinct from the gut, suggesting that central hyperalgesic mechanisms may be involved. In the current study, during the wind-up testing session, a series of 6 heat pulses were presented with an inter-stimulus interval (ISI) of 3 seconds. Following the 1st, 3rd, and 6th thermal stimuli, subjects were asked to rate the late thermal sensation or second pain. IBS patients who demonstrated temporal summation of pain (TSSP) then received dextromethorphan and placebo in a randomized, double-blind, fashion to block wind-up. The results showed: (1) a subset of IBS patients, but not controls, showed TSSP in response to a series of noxious heat pulses (2) TSSP was blocked by administration of dextromethorphan, an NMDA receptor antagonist. In summary, these findings further elucidate mechanisms of somatic hypersensitivity in a subset of IBS patients. Our results also support an etiologic basis for abnormal NMDA receptor mechanisms in some IBS patients. Future studies are needed to determine if NMDA receptor antagonists may be used to treat IBS patients.

Keywords

Irritable bowel syndrome (IBS); visceral and thermal hypersensitivity; wind-up; temporal summation of second pain (TSSP); repetitive afferent barrage; nociceptive stimuli; central sensitization

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1. INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that is estimated to affect up to 20% of the U.S. population.²⁸ Even though the pathophysiology of IBS is unclear, visceral and somatic hypersensitivity to nociceptive stimuli have been shown to be present in a subset of IBS patients.^{15,16,38,39} The pathophysiological mechanisms of the pain and hypersensitivity in this IBS subset are also not well understood. Many patients with IBS frequently complain of pain body regions somatotopically distinct from the gut, suggesting that central hyperalgesic mechanisms may be involved.^{9,10,19,30} Previously, hypersensitivity was thought to be limited to the gut. However, numerous studies have recently shown that some IBS patients exhibit hyperalgesia to nociceptive stimuli applied to the extremities.^{2, 38} These studies suggest that processing of visceral and somatic stimuli overlap as a result of viscerosomatic convergence of neural input in the lumbosacral spinal cord. Thus, chronic nociceptive input from the colon/rectum may sensitize spinal cord neurons that also receive somatic input from other lumbosacral tissues. We have shown that a subset of IBS patients has greater somatic sensitivity than control subjects and this hypersensitivity is somatotopically organized.⁴⁴ Thus, lumbosacral spinal segments that share primary afferent input from the colon/rectum and from lumbosacral dermatomes display the greatest sensitivity.¹⁹

Do these pathophysiological mechanisms reflect enhancement of normal pain processing?

Because our goal here was to better understand the above hypersensitivity, we considered several possible mechanisms. There are forms of brief experimental pain-causing stimuli that can reliably evoke perceptions of first and second pain when applied to the hand or foot.^{17,18,33,34} Second pain, which results from impulse conduction in peripheral C (unmyelinated) afferent axons, progressively increases in intensity when such stimuli are applied more often than once every 3 seconds and this summation at least partly results from a central N-methyl-D-aspartate (NMDA) receptor mechanism within the dorsal horn. Thus, dorsal horn nociceptive neurons also show temporal summation in response to repeated C-fiber stimulation, termed 'wind-up'. There is increasing evidence that pathophysiologic mechanisms of pain include enhancements of this spinal NMDA receptor mechanism as well as reductions in inhibitory mechanisms that normally serve to limit pain.^{6,18}

The critical frequency for 'windup' mimics the natural frequency of peripheral C nociceptors that discharge every 2–3 seconds at stimulus intensities likely to be minimally painful.²⁷ Tonic impulse input control over C nociceptor afferents is critical for inducing and maintaining central hyperalgesic states associated with chronic pain (e.g., neuropathic pain). Psychophysical tests demonstrate temporal summation of second pain (TSSP) in response to noxious heat pulses in pain free subjects and TSSP is a correlate of spinal 'windup'.²² TSSP is enhanced or abnormally triggered by non-nociceptive afferent neurons in chronic pain disorders such as post-herpetic neuralgia, temporomandibular joint disease, fibromyalgia, and complex regional pain disorder (CRPS) thereby reflecting pathophysiological expressions of mechanisms that already exist in healthy pain-free subjects.^{7,14,23,25}

Rationale for study

Recently, a very sensitive test of TSSP, heat pulses generating skin temperatures of 47° C, showed greatly enhanced TSSP in chronic pain patients that were receiving opioid therapy.³ By systemically applying a battery of psychophysical and pharmacologic tests to IBS patients and controls, including heat pulses similar to those used by Chen et al., we tested the following general hypotheses about these mechanisms: (1) Somatic hypersensitivity IBS

patients partially results from an exaggeration and/or an abnormal triggering of NMDA receptor mechanisms, reflected in enhanced TSSP; (2) The enhanced TSSP in IBS patients is NMDA receptor mediated and hence, like spinal 'windup', will be reversed by Dextromethorphan, an NMDA receptor antagonist.

2. METHODS

2.1 Participants

The study was approved by the University and Veterans Administration Institutional Review Boards and all subjects signed informed consent forms prior to the start of the study. All IBS patients that were recruited had IBS-related gastrointestinal symptoms for at least 5 years and had upper endoscopy and colonoscopy with biopsies which were normal. The diagnosis of IBS was made by an experienced gastroenterologist who based the diagnosis on the ROME III criteria and exclusion of organic disease.¹³ Fibromyalgia syndrome (FMS) was excluded in all participants using the 1990 American College of Rheumatology criteria for FMS.¹⁰ The diagnostic criteria for FMS is the presence of ≥ 11 tender points and wide spread body pain. Tender points are discrete areas of allodynia and/or hyperalgesia where the application of a localized pressure of ≤ 4 kg will elicit pain. 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.

Study participants were asked to stop narcotic agents for 4 weeks and serotonin antagonists, serotonin uptake inhibitors, tricyclic antidepressants, non-steroidal anti-inflammatory drugs, and acetaminophen at least 1 week prior to the study. If participants were unable to stop these medications due to underlying medical conditions, they were excluded from participation in the study. 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.

2.2 Beck Depression and State Trait Anxiety Inventory

All study participants completed the Beck Depression Inventory and the State Trait Anxiety Inventory.^{1,24} Depressive and anxiety disorders were exclusionary criteria if they were severe enough to interfere with the individual's ability to participate in the study. Therefore, study subjects who scored 29 or higher on the Beck Depression Inventory and/or 45 or higher on the State Trait Anxiety Inventory, were excluded. Such scores are approximately one standard deviation above the mean for general medical patients.

2.3 Response Measures

The protocol was thoroughly explained in detail to all of the study participants. The thermal testing procedure along with the method of responding was discussed. They were instructed to attend to both first (first pain) and late thermal sensations (second pain or wind-up) that were produced by the heated thermode strapped to the plantar aspect of their right foot. An explanation and diagram of the expected time-course of the sensory experiences were presented. The numerical rating scale used was explained to all of the subjects.^{20,21} The scale ranged from 0 to 100, in increments of 5, with verbal descriptors at intervals of 10: 10=warm, 20=a barely painful sensation, 30=very weak pain, 40=weak pain, 50=moderate pain, 60=slightly strong pain, 70=strong pain, 80=very strong pain, 90=nearly intolerable pain, and 100=intolerable pain as previously described.²⁵ Previous experience with the scale has shown that increments of 5 provide appropriate resolution for the discriminable steps in late sensation intensity from threshold to nearly intolerable levels.¹⁸

All participants underwent a training session prior to the start of the study so that they could more easily differentiate between first and second pain. Subjects were instructed that the thermal sensation could increase, decrease, or stay the same with stimulus repetition and that they should remove their foot from the thermode at the point at which the pain becomes intolerable. Participants were also told that they may or may not feel sensations of heat pain during each pulse and that a late sensation of heat or second pain would likely be perceived 1–2s after each heat pulse.

2.4 First Pain

All thermal stimuli were delivered using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel), which is a peltier-element-based stimulator. Temperature levels were monitored by a contactor-contained thermistor, and returned to a preset baseline of 39°C by active cooling at a rate of 1.5°C/s. Thermal stimuli were delivered to a premarked spot on the planter aspect of the right foot with a large thermode (3×3 cm). This site was chosen because it represents a body site that shows spinal segmental convergence with the colon (planter aspect of the foot). The trial consisted of a 5-second adapting temperature of 39 °C, followed by a 3-second pulse at 47°C. This was followed by an 80 second inter-stimulus interval (ISI) and a total of 4 heat pulses. The percent maximum response to each successive heat pulse was recorded for each individual. First pain is related to impulse input from A-delta nociceptive afferents that are sensitive to noxious heat stimuli.²² Thus, this test served to determine whether IBS patients were hypersensitive to impulse input from these types of primary nociceptive afferent neurons.

2.5 Temporal Summation of Second Pain (TSSP)

Approximately 10 minutes following the thermal testing for first pain (see above), all subjects underwent repetitive thermal stimulation to induce TSSP. For the wind-up testing session, a series of 6 heat pulses were presented with an interstimulus interval of 3 seconds. The trial consisted of a 5-second adapting temperature of 39 °C, followed by a 3-second thermal pulse at 47°C. This was followed by a 3 second inter-stimulus interval (ISI). Following the 1st, 3rd, and 6th thermal stimuli, subjects were asked to rate the late thermal sensation or second pain (1–2 seconds following the heat pulse) using the numerical rating scale described above. The percent maximum response to each successive heat pulse was recorded for each individual. The train of 6 heat pulses was repeated 2 additional times following 10 minute rest periods and the means for the trials were recorded.

2.6 Dextromethorphan

We next performed a double-blind, placebo controlled, crossover study using Dextromethorphan and placebo (Bendryl). Following first and second pain testing, those IBS patients (10 of the 27) who demonstrated significant TSSP, 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. Because of a slow onset and long time-course of action, TSSP testing was started 45 minutes after ingestion of the experimental agents. Randomization was counterbalanced such that all 10 IBS patients received both placebo and Dextromethorphan on two different days. Following administration of either placebo or Dextromethorphan on the first day, IBS patients underwent a 3 day washout period prior to returning for the 2nd day of testing.

2.7 Statistical Analysis

Statistical analyses were done using SAS software, Version 9.1.3 of SAS system Copyright © 2003 SAS institute Inc. and Prism version 6. The analysis involved one between- and two within-subject variables, and consequently, the repeated measures command within the

General Linear model module of SPSS was used. ANOVA was used to analyze the pain testing data. Values are expressed as means $\pm$ standard deviation (SD)

3. RESULTS

3.1 Subjects

A total of 42 participants were studied. This included 27 IBS patients (27 females, mean age 28.6 ± 3.2 years) and 15 control subjects (15 females, mean age 27.9 ± 2.7 years). There were no significant differences between these groups (controls, IBS) in age or sex. All of the IBS patients had diarrhea-predominant IBS and met the Rome III criteria for irritable bowel syndrome. There were no significant between group differences on the Beck Depression Inventory and the State Trait Anxiety Inventory between the IBS patients and controls.

3.2 Thermal Stimuli: First Pain

As shown in Fig. 1, the perceived intensity of first pain decreased markedly in percent maximum response with each successive heat pulse with ISIs of 80 sec. This decrease occurred in all normal controls and 63% (17/27) of IBS patients as illustrated by their decreasing ratings of % maximal response of 1st pain. The decrease in magnitude of first pain in response to trains of 4 consecutive heat pulses, were statistically significant by ANOVA analysis ($p < 0.001$). Suppression of first pain with subsequent heat pulses has been previously reported.^{17,18} Interestingly, in 37% of IBS patients (10/27), there was no significant suppression of first pain with consecutive heat pulses (Fig.1, circled groups of open triangles).

3.4 Temporal Summation: Second Pain

All subjects were asked to respond to the windup protocol at the 1st, 3rd, and 6th heat pulses of the TSSP protocol (Figure 2 lower panel). Overall, IBS patients exhibited increased temporal summation to second pain, however, this did not reach statistical significance ($p = 0.6$) compared to controls (Figure 2A). There was no summation of second pain reported in either controls or IBS patients who exhibited suppression of first pain. However, the perceived intensity of second pain (wind-up) markedly increased with each successive heat pulse in the same subset of IBS patients that did not show suppression of first pain (Figure 2B) (** $p < 0.001$).

The neural mechanisms critical for wind-up and temporal summation of second pain exist at the level of synaptic interactions between C-polymodal nociceptive afferents and dorsal horn neurons. These synaptic interactions are known to involve long-duration excitatory processes related to the release of neurotransmitters, such as glutamate, and neuromodulators such as, substance P that activate NMDA receptors and lead to central sensitization.^{18,19} Thus, if windup is mediated by the NMDA receptors, then NMDA antagonists should block windup in this subset of IBS patients.

3.5 Effects Dextromethorphan on windup in IBS patients

IBS patients that exhibited TSSP were included in the following trial. Following administration of oral NMDA receptor antagonist Dextromethorphan (60 mg), TSSP was nearly completely blocked in IBS patients compared to administration of placebo (* $p < 0.01$; ** $p < 0.001$) (Figure 3). Similar doses of Dextromethorphan decreased wind-up in fibromyalgia patients.²⁶

4. DISCUSSION

This study is the first to demonstrate three original findings concerning abnormal NMDA receptor mechanisms in IBS patients. First, a subset of IBS patients but not normal control subjects showed marked TSSP in response to a series of noxious heat pulses with a low peak intensity (i.e., 47° C). Second, further analysis showed that this TSSP only occurred in a subset of IBS patients that did *not* display temporal suppression of first pain. Finally, TSSP was blocked by administration of the NMDA antagonist dextromethorphan at a dose shown to attenuate TSSP in fibromyalgia patients. These findings further elucidate mechanisms of somatic hypersensitivity in IBS patients. Our results also support a previous study that demonstrates that a similar stimulus paradigm of TSSP is a sensitive quantitative test of enhanced NMDA receptor mechanisms.³

The presence of “subsets” within IBS groups is consistent with previous results

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.^{42,44} The latter may generate more tonic peripheral impulse input, thereby making some IBS patients especially vulnerable to central sensitization. Work by our laboratory and others suggests that specific subsets of patients with functional pain disorders such as IBS may be characterized by abnormalities in both peripheral and central pain processing mechanisms.^{16,19} 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.^{19,30}

Enhanced TSSP in IBS patients corroborates other evidence for abnormal NMDA mechanisms in IBS

Wind-up has been regarded as instrumental in the induction and/or maintenance of chronic disorders involving allodynia and hyperalgesia.⁴ 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.¹⁷ One way to determine whether temporal summation and NMDA receptor activation are involved is to fully characterize wind-up of second pain in normal individuals and in chronic pain patients such as those with IBS. 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). Dextromethorphan may also activate opioid receptors and block certain nicotinic receptors at the doses we used in this study. Thus, effects at receptors other than the NMDA receptor may also contribute to our current findings.

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.^{35–37,40, 43} In this model, NMDA NR1 subunit expression was greater in the spinal cord of rats with an IBS-like syndrome compared to control rats. 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.²⁹ Also, our current study further supports the study by Chen et al., 2009 that also depicts similar wind-up characteristics in patients with chronic pain.³

Abnormal central sensitization may at least partly explain the chronic pain present in some IBS patients. This central pathophysiological process in IBS patients is similar to processes in other chronic pain conditions without identifiable peripheral sources of nociceptive input.

⁴ 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 hyperalgesia. In particular, temporal summation of pain was assessed, using brief repetitive stimulation of the glabrous skin of the foot. This method selectively activates unmyelinated C nociceptors in contrast to commonly used methods of ramp-and-hold thermal stimulation that evoke sensations dominated by input from myelinated nociceptors.^{33,34} Unmyelinated nociceptors are strongly implicated as a source of chronic pain because of a ubiquitous distribution and a propensity for prolonged discharges in response to chemical and other forms of stimulation.^{5, 11, 27}

What is the mechanism for lack of first pain suppression and is it related to enhanced TSSP? (Could it be lack of central inhibitory mechanisms?)

The demonstration of psychophysical differences between IBS patients and controls in the present study is consistent with other observations of low pain thresholds in IBS patients.^{19,38} Enhanced wind-up could be related to sensitized NMDA receptors on central neurons and hence to a maintained central mechanism of allodynia/hyperalgesia.³² This possibility is supported by evidence that wind-up and central sensitization share common mechanisms.^{17–19} A study that examined the relationships between central sensitization and wind-up showed that once wind-up was produced in wide dynamic range spinal neurons by repetitive C-fiber stimulation, the enhanced C fiber-mediated responses could subsequently be maintained by a very low frequency of C fiber stimulation—one stimulus every 10 seconds.¹² This result suggests that once wind-up occurs, a sensitized state can be maintained by extremely low frequencies of tonic peripheral input from nociceptors. Local anesthetic blockade of this input in IBS patients and in “IBS-like” rats completely normalizes somatic and visceral hypersensitivity.^{31,41}

Summary

The results of our present study suggest that enhanced temporal summation and central sensitization are chronically present in a subset of IBS patients and that both the summation and the sensitization are blocked by administration of dextromethorphan. Psychophysical testing using brief thermal stimuli applied to the skin can reveal these abnormalities and may be characteristic of IBS patients as well as 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 maintains hyperalgesia, central sensitization, and enhances wind-up/TSSP. 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.

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Figure 1.

Scatter plot of numerical ratings for the percent maximum response for first pain for a total of 4 pulses for each study subject. Values are means $\pm$ standard deviation. Closed circles represent controls and open triangles represent IBS patients.

Figure 2A

Figure 2B

Figure 2.

A. Numerical ratings for the percent maximum response of second pain (wind-up) for the 1st, 3rd, and 6th. Values are means $\pm$ standard deviation. Closed circles represent controls and closed triangles represent IBS patients.

B. Numerical ratings for the percent maximum response of second pain (wind-up) for the 1st, 3rd, and 6th. Values are means $\pm$ standard deviation. Closed circles represent controls; open circles represent IBS patients who had suppression of first pain; filled squares represents IBS patients who did not have suppression of first pain.

Dextromethorphan and Wind-Up

Figure 3. Numerical ratings for the percent maximum response of second pain (wind-up) for the 1st, 3rd, and 6th in IBS patients who exhibited wind-up. Values are means $\pm$ standard deviation. Open squares represent baseline; closed circles represent the placebo condition; open circles represent the trial with Dextromethorphan.