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World J Gastroenterol 2007 July 21; 13(27): 3699-3704
World Journal of Gastroenterology ISSN 1007-9327

BASIC RESEARCH

Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome

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Received: 2007-02-19 Accepted: 2007-04-11

Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World J Gastroenterol* 2007; 13(27): 3699-3704

http://www.wjgnet.com/1007-9327/13/3699.asp

Abstract

AIM: To investigate the role of endogenous pain modulatory mechanisms in the central sensitization implicated by the visceral hypersensitivity demonstrated in patients with irritable bowel syndrome (IBS). Dysfunction of modulatory mechanisms would be expected to also result in changes of somatic sensory function.

METHODS: Endogenous pain modulatory mechanisms were assessed using heterotopic stimulation and somatic and visceral sensory testing in IBS. Pain intensities (visual analogue scale, VAS 0-100) during suprathreshold rectal distension with a barostat, cold pressor stimulation of the foot and during both stimuli simultaneously (heterotopic stimulation) were recorded in 40 female patients with IBS and 20 female healthy controls.

RESULTS: Rectal hypersensitivity (defined by 95% CI of controls) was seen in 21 (53%), somatic hypersensitivity in 22 (55%) and both rectal and somatic hypersensitivity in 14 of these IBS patients. Heterotopic stimulation decreased rectal pain intensity by 6 (-11 to -1) in controls, but increased rectal pain by 2 (-3 to +6) in all IBS patients ($P < 0.05$) and by 8 (-2 to +19) in IBS patients with somatic and visceral hypersensitivity ($P < 0.02$).

CONCLUSION: A majority of IBS patients had abnormal endogenous pain modulation and somatic hypersensitivity as evidence of central sensitization.

Key words: Diffuse noxious inhibitory controls; Endogenous pain modulation; Hypersensitivity; Irritable Bowel Syndrome; Quantitative sensory testing; Visceral pain; Sensitization

INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by abdominal discomfort or pain accompanied by changes in gastrointestinal motility. Peripheral and central nervous system sensitization have been proposed as an underlying mechanism in IBS[1]. Persistent or altered peripheral input secondary to divers insults is likely to lead to central changes in nociception and sensory perception. Previous brain imaging studies have demonstrated differences in the central processing of visceral nociceptive input between patients with IBS and healthy controls, mainly in the centers dealing with secondary pain processing and the assigning of affective content[2,3]. Nociceptive input to the brain is subject to endogenous modulation by brainstem and cortical pathways, including the periaqueductal gray (PAG)-rostroventral medulla (RVM) network, spino-bulbo-spinal diffuse noxious inhibitory controls (DNIC) and the frontal lobe[4,5].

Functional assessment of the endogenous pain modulatory pathways has been extensively validated in humans using heterotopic stimulation ("counterirritation")[6-11]. DNIC has been shown to be abnormal in fibromyalgia and in a pilot study in IBS using heterotopic stimulation[12,13]. Altered somatic as well as visceral sensory function would be expected as a consequence of central sensitization or abnormal endogenous modulation. Visceral sensitization has been demonstrated in a majority of patients with IBS, but the studies examining somatic sensory function have yielded equivocal results[14-20].

In the current study, we investigated central sensitization in IBS by testing endogenous pain modulatory pathways and visceral and somatic sensory function in matched patients and healthy controls. Our study hypotheses were, firstly, that IBS patients demonstrate deficient endogenous pain modulation in the form of inadequate pain inhibition during heterotopic stimulation and, secondly, that IBS patients with visceral hypersensitivity are also hypersensitive to suprathreshold somatic stimulation.

MATERIALS AND METHODS

Patients

Forty female IBS patients and 20 female healthy subjects were recruited by advertisements and through the Gastrointestinal Unit. Equal numbers of diarrhea and constipation predominant IBS patients, as defined by the Rome 2 criteria, were included and none had any evidence of organic gastrointestinal pathology after gastrointestinal workup, including endoscopy, stool and blood tests, and H_2-breath test for lactose intolerance[21]. IBS patients were required to have an average abdominal pain intensity of at least 30 on the 0-100 VAS in the two weeks before study inclusion. IBS and control subjects between 18 and 60 years of age were recruited. Controls had no gastrointestinal symptoms or evidence of chronic diseases. Main exclusion criteria in all groups were bowel resections (except appendectomy), major abdominal operations, treatment with tricyclic antidepressants, selective serotonin reuptake inhibitors, gastrointestinal prokinetics, anticholinergics, antispasmodics or analgesics in the last 14 d, and chronic pain apart from IBS-especially fibromyalgia. Institutional Ethics Committee approval was given for the study and all subjects gave their written informed consent to participation. Patients were familiarized with the study procedures on a separate day before the start of the actual testing day. The same investigator performed all tests.

Rectal distension thresholds

On the morning of the study day subjects were asked to attempt defecation and a warm water enema (300 mL) was administered to empty the rectum before rectal insertion of the lubricated, flaccid and oversized 600 mL polyethylene bag on the end of a catheter. Leakage of the rectal bag was excluded by distension with air under water before insertion and after removal at the end of the study. The bag was inflated and then pulled outwards until slight resistance was felt. The catheter was taped to the buttocks, the bag deflated and subjects positioned in a relaxed supine position. The catheter was attached to a G&J Distender® barostat (Toronto, Canada) set at an inflation rate of 27 mL/s and a safety cut-off threshold of 60 mmHg. After a resting period of 20 min the minimum distending pressure was determined and the rectal pain threshold titrated using an ascending methods of limits (AML) paradigm with 5 mmHg increments of 30 s duration followed by a decrease to baseline for 30 s until the Pain threshold ("first feeling of pain") was reached. Subsequently, the following tests were performed in randomized sequence with a break of 30 min between tests.

Tonic rectal stimulation

Pain intensity was rated on a 100 mm anchored horizontal VAS after constant distension at the individually determined pain threshold pressure plus 20% for 120 s. This suprathreshold stimulation was chosen to induce moderate pain (visual analogue scale VAS score between 30 and 40, where 0 = no pain, 100 = unbearable pain) and was based on data from our own pilot studies.

Table 1 Characteristics of IBS patients and healthy controls. Means and 95% confidence intervals are shown

	IBS n = 40	Healthy controls n = 20
Age (yr)	39 (36-42)	41 (37-45)
Height (cm)	166 (164-168)	168 (163-173)
Weight (kg)	69 (65-73)	75 (67-84)
Years with IBS	6 (3-12)	Not applicable
n with diarrhea-/constipation-predominant IBS	20/20	0/0
Luteal phase/non-menstruating	19/13	11/9

Somatic stimulation: cold pressor test

Pain intensity was rated by VAS after immersion of the left foot up to the calf in a circular flow ice-water bath maintained at 4℃ for 120 s. Care was taken to position the foot comfortably in the water bath, with the calf padded by cushions.

Heterotopic stimulation

The above rectal and somatic stimuli were applied concomitantly; rectal pain was rated on the VAS after 120 s. During all tests subjects were instructed to rate only their rectal pain.

Rectal compliance was calculated from the slope of the linear portion of the volume-pressure curve from each inflation sequence.

Statistical analysis

All continuous group data were calculated as means and 95% confidence intervals. Threshold values reaching cut-off were recorded as the maximum possible value. Analysis of variance (ANOVA) testing for group differences in somatic and visceral pain ratings and for changes in ratings during heterotopic stimulation was predefined, with post-hoc testing performed by Tukey's Test in case of significance (Statistica 7.1, StatSoft Inc., Tulsa, USA). For secondary analysis IBS patients were classified as hypersensitive or non-hypersensitive based on their titrated rectal distension pressures and their somatic and rectal pain ratings using the 95% confidence intervals of healthy controls as the threshold limits for hypersensitivity, as suggested in the literature[22,23]. Correlations were assessed using multiple regression analysis with Bonferroni correction for multiple testing. A significance level of $P < 0.05$ was applied.

RESULTS

Patient characteristics are shown in Table 1. The subject groups were well matched, with no significant differences in demographics. All subjects completed the entire test series. The phase in the menstrual cycle was recorded for all subjects and there were no differences between the subject groups in the numbers of patients in the luteal phase or in those post-menopausal or post-hysterectomy.

Rectal pain thresholds and compliance

The mean pain pressure thresholds were 42 (38-46) mm

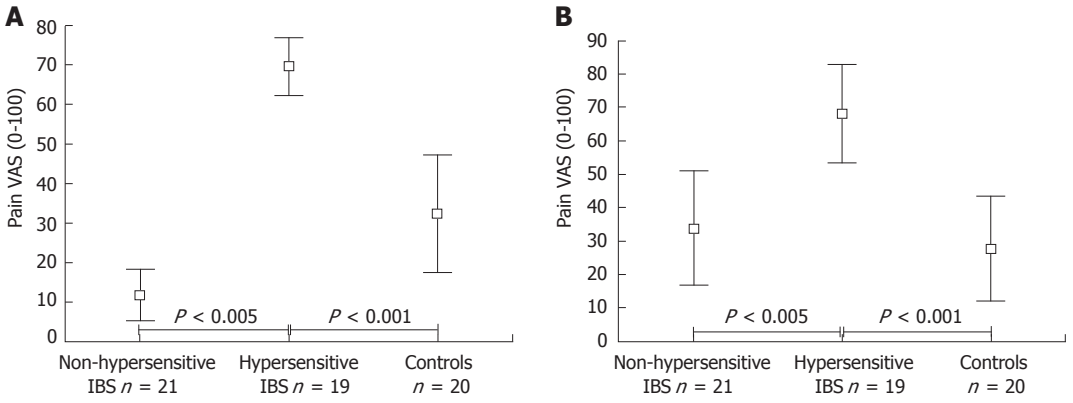

Figure 1 Pain intensity ratings (100 mm VAS) during tonic rectal (**A**) and tonic somatic (**B**) stimulation in non-hypersensitive and hypersensitive IBS patients and in healthy controls. Hypersensitivity is defined by the 95% confidence interval of healthy controls. Means (symbol), 95% confidence intervals (whisker) are shown.

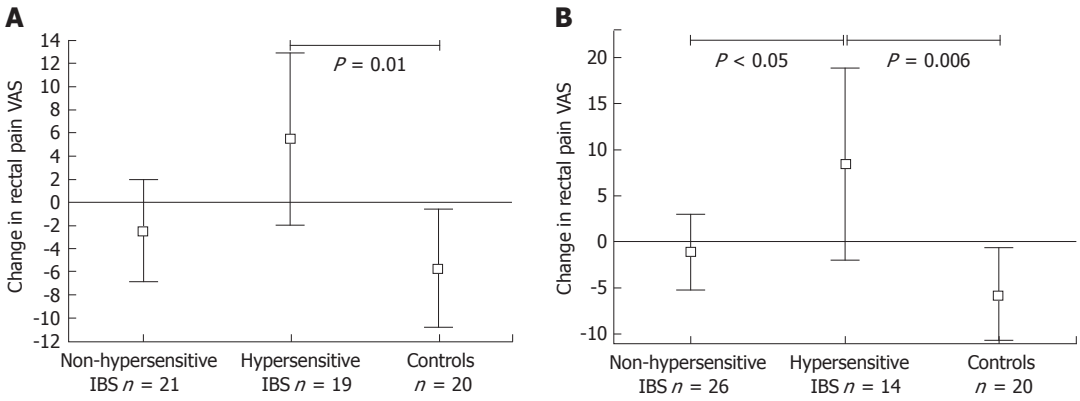

Figure 2 Change in rectal pain intensity scored on a VAS 0-100 during heterotopic stimulation in IBS subgroups and controls. Means (symbol), 95% confidence intervals (whisker) are shown in patients hypersensitive or not to tonic rectal (**A**) and both tonic rectal and somatic (**B**) stimulation. Hypersensitivity is defined by the 95% confidence interval of healthy controls.

Hg in healthy controls and 37 (34-40) mm Hg in IBS patients ($P = 0.05$). Mean rectal compliance values were 5.7 (4.6-6.9) mL/mmHg in controls and 6.9 (5.4-8.5) mL/mmHg in IBS patients, with no significant differences between IBS subgroups or to controls.

Rectal distension stimulation

Pain intensity VAS ratings during rectal tonic suprathreshold stimulation at pain threshold +20% pressures were 39 (23-54) in controls and 42 (24-52) in IBS patients (not significant). Twenty-one (53%) of all 40 IBS patients, 16 of 20 (80%) diarrhea-predominant IBS and 5 of 20 (25%) constipation-predominant IBS patients were hypersensitive compared to controls (see Methods for definition). The threshold for rectal hypersensitivity was 47 mmHg. Figure 1A illustrates the pain ratings in hypersensitive and non-hypersensitive IBS groups and in controls during tonic rectal distension. There was no difference in body weight in the hypersensitive versus non-hypersensitive groups (66 (56-76) kg and 71 (57-84) kg, respectively). Their respective rectal compliance was 4.9 (4.5-5.9) and 6.1 (4.7-7.5) (no significant difference).

Somatic stimulation

Pain intensity VAS ratings during somatic stimulation were 27 (12-43) in controls and 51 (39-64) in all IBS patients ($P = 0.02$). Premature withdrawal from the ice water due to strong pain occurred in 2 IBS patients and in one control. The maximum pain intensity score of 100 was accorded in these cases. Twenty-two of all 40 (55%) IBS patients, 14 of the 20 (70%) diarrhea-predominant and 8 of the 20 (40%) constipation-predominant IBS patients showed somatic hypersensitivity. The threshold for somatic hypersensitivity was 43 on the pain VAS.

Overlap somatic and visceral hypersensitivity

Fourteen of the 22 patients hypersensitive to the somatic stimulus were also viscerally hypersensitive. Somatic pain scores were 68 (53-83) in IBS patients hypersensitive to rectal stimulation and 32 (21-43) in IBS patients without rectal hypersensitivity ($P < 0.001$ versus controls and non-hypersensitive IBS) (Figure 1B). Visceral and somatic hypersensitivity correlated significantly in IBS patients ($r = 0.82$, $P < 0.000001$).

Heterotopic stimulation

When somatic stimulation was applied during rectal stimulation, mean group rectal pain scores *decreased* by 6 (-11 to -1) (mean change -16% from baseline) in healthy controls, *increased* by 2 (-3 to +6) (mean change +2%) in all IBS patients ($P < 0.05$ *vs* controls) and *increased* by 8 (-2 to +19) (mean change +12%) in IBS patients with both somatic and visceral hypersensitivity ($P = 0.006$ *vs* controls) (Figure 2). There was no significant correlation between somatic pain levels and the change in rectal pain scores during heterotopic stimulation. During heterotopic stimulation rectal pain changed by +2 (-4 to 9) in diarrhea-predominant IBS and by +1 (-6 to 7) in constipation-predominant IBS (not significant).

DISCUSSION

A majority of IBS patients, mainly from the IBS-D

subgroup, demonstrated either visceral or somatic hypersensitivity, with substantial but incomplete overlap of hypersensitivity to visceral and somatic stimuli. The visceral and somatic hypersensitivity states correlated significantly. While rectal hypersensitivity has previously been shown in a majority of IBS patients using various study endpoints, the few studies relating to somatic sensory dysfunction in IBS have yielded controversial results showing either somatic hypo- or hypersensitivity[14,16-20,22,24-28]. This discrepancy is probably best explained by the choice of different stimulation intensities, i.e suprathreshold versus threshold and painful versus non-painful, and to a lesser degree also by the selection of stimulation techniques, such as thermal versus pressure or electrical. In the current study we used painful, suprathreshold, tonic stimulation over a larger skin surface area as high-intensity and tonic stimulation have demonstrated sensitization consistently[29-34].

Central sensitization is a possible mechanism underlying the somatic and visceral hypersensitivity. In the current study endogenous pain modulation, one of the major mechanisms contributing to central sensitization, was shown to function as expected in healthy controls, but malfunctioned in a majority of patients with IBS. Previously, heterotopic somatic stimulation has not only been shown to reduce somatic pain intensity in healthy controls, but also discomfort or pain thresholds to gastric, duodenal and rectal distension[35,36]. Little previous data exist on endogenous pain modulation in IBS. Coffin *et al*[35] demonstrated hyperexcitability of spinal sensory modulation in IBS using a somatic nociceptive flexion reflex (R-Ⅲ reflex) and concomitant rectal distension. Wilder-Smith *et al*[13,37]. in two previous studies showed abnormal endogenous pain modulation and central pain processing by functional brain MRI in IBS. The current study extends this data by determining somatic as well as visceral sensory function in a larger and balanced group of IBS patients and correlating generalized sensory hypersensitivity with dysfunctional endogenous pain modulation. Hypersensitive IBS patients had evidence of endogenous pain facilitation rather than inhibition during heterotopic stimulation. Dysfunctional endogenous pain modulation is likely to reflect an imbalance between pain facilitatory and inhibitory systems and has been found in fibromyalgia and interstitial cystitis, both of which are associated with IBS[4,15,36,38,39].

The design of the current study with heterotopic stimulation only at a lower body site does not allow the distinction between localized, lumbosacral somatic hypersensitivity possibly involving convergence, and widespread sensitization. However, a recent study by Rodrigues *et al*[17] clearly demonstrated uniform somatic hypersensitivity from the face to the calf in IBS, rendering localized hypersensitivity in IBS unlikely.

Throughout this study hypersensitivity and abnormal endogenous pain modulation were more common in diarrhea-predominant than in constipation-predominant IBS patients, although the mean group changes in rectal pain during heterotopic stimulation were similar. Differences between IBS subgroups in sensory function and in fMRI brain activity during visceral pain have been observed in earlier studies[13,40]. This study was not powered for subgroup comparison, but this comparison deserves further investigation in larger patient groups.

Dysfunctional pain modulation is an attractive mechanistic hypothesis within the biopsychophysical model of functional bowel disease, as endogenous pain modulation acts as a central filter for extraction and amplification of noxious input, providing a possible unifying concept for both the "top-down" psychological and the "bottom-up" peripheral insult etiological postulates[1,41-45]. Endogenous pain modulation plays a central role in the neuromatrix integrating cognitive, emotional, autonomic and effector responses to pain[17]. Interestingly, the activity of the pain modulatory pathways differs between men and women, possibly explaining some of the gender differences in the incidence of IBS[12,36,38]. Nonetheless, it should be pointed out approximately one quarter of IBS patients did not have evidence of any hypersensitivity with the tests applied. It would therefore at present be inappropriate to label the described sensory dysfunction as a disease marker. However, further refinement of technique and improved exclusion of other differential diagnoses may lead to better discrimination.

Attentional effects represent a potential confounding and overlapping factor in the study of descending pain modulation pathways, as cognition feeds into the same neural pathways. A recent fMRI study clearly demonstrated distinct effects due to attention and DNIC on pain pathways, with minor functional anatomical overlap[37]. Potential weaknesses of this study are, firstly, the absence of psychological and emotional correlational data in our subjects. These factors are known to influence pain perception, but are likely to exert much of their influence via the studied endogenous pain modulatory mechanisms. Secondly, the intensity of the somatic, heterotopic stimulus was not individually titrated, hence introducing a potential stimulation bias as IBS patients rated this stimulus as more intense than controls.. There was, however, no significant correlation between somatic stimulation intensity and the change in rectal pain scores during heterotopic stimulation. Additionally, recent data has confirmed that endogenous modulation effects do not depend on the intensity of the conditioning stimulus[46,47].

In conclusion, a majority of IBS patients demonstrated evidence for central sensitization, with visceral and somatic hypersensitivity associated with abnormal function of endogenous pain modulation and pain facilitation.

COMMENTS

Background

IBS is a very common syndrome characterized by abdominal discomfort or pain accompanied by changes in gastrointestinal motility. Peripheral and central nervous system sensitization have been proposed as an underlying mechanism in IBS. Previous brain imaging studies have demonstrated differences in the central processing of visceral nociceptive input between patients with IBS and healthy controls, mainly in the centers dealing with secondary pain processing and the assigning of affective content. Input regarding pain to the brain is subject to extensive endogenous modulation by brainstem and cortical pathways. Altered somatic as well as visceral sensory function would be expected as a consequence of central sensitization or abnormal endogenous modulation. We have previously shown abnormal endogenous modulation of visceral pain in IBS, but there is no data on modulation of somatic pain or sensory input.

Research frontiers

Brain imaging and new sensory testing techniques are enabling the redefining and detailed examination of brain function and pain processing in health and disease.

Innovations and breakthroughs

The above techniques are demonstrating abnormal processing of sensory and pain information in the brain in somatic and visceral pain disorders and are revealing an intricate functional integration of cognitive, emotional, homeostatic, motor and sensory brain centres. Understanding dysregulation in this neuromatrix, with a central role for endogenous modulation, is providing us with a new, holistic understanding of hitherto difficult to understand diseases, such as so-called 'functional' syndromes.

Applications

This and previous related publications demonstrate malfunction in one of the brain's central regulatory mechanisms, endogenous pain modulation, in IBS. Because of the manifold connections between many major brain centres and this modulatory network, potential exist for manipulation via several avenues, including psychological, pharmaceutical as well as physical therapy. These research data can and will be applied to other related chronic pain syndromes.

Peer review

This is a study of 20 healthy female controls, 20 IBS-D, and 20 IBS-C women to try to further examine rectal hypersensitivity and somatic hypersensativity using a cold pressor test of the foot. It's an excellent work, very timely and interesting.

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